Chapter 4

GPR119 Agonists: A Novel Strategy for Type 2 Diabetes Treatment

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1. Introduction

Type 2 diabetes (T2DM), also known as non-insulin-dependent diabetes mellitus (NIDDM), manifests with an inability to adequately regulate blood-glucose levels. T2DM may be characterized by a defect in insulin secretion or by insulin resistance, namely those that suffer from T2DM have too little insulin or cannot use insulin effectively. Insulin resistance which refers to the inability of body tissues to respond properly to endogenous insulin develops because of multiple factors, including genetics, obesity, increasing age, and having high blood sugar over long periods of time[1].

Current therapies for diabetes mellitus include: glucose-lowering effectors, such as metformin which reduces glucose production from the liver; insulin; insulin secretagogues, such as sulphonylureas, which increase insulin production from pancreatic β-cells; activators of the peroxisome proliferator-activated receptor-γ (PPAR-γ), such as the thiazolidinediones, which enhance insulin action; and α-glucosidase inhibitors which interfere with gut glucose production. There are, however, deficiencies associated with currently available treatments, including hypoglycemicepisodes, weight gain, loss in responsiveness to therapy over time, gastrointestinal problems, and edema[2]. Glucagon-like peptide 1 (GLP-1) analogs and dipeptidyl peptidase 4 (DPP-4) inhibitors are also widely used in clinical therapy for T2DM. GLP-1 analogs, which require parenteral administration, appear not to be associated with hypoglycemia but cause a relatively high frequency of gastrointestinal side effects[3]. Small molecule DPP-4 inhibitors enhance glucose-dependent insulin release by inhibiting the degradation of endogenous GLP-1[4]. Several nonpeptide, except DPP-4 inhibitors, binding G protein-coupled receptors (GPCRs) have been deorphanized recently and are currently being evaluated as candidate GLP-1 secretagogues for T2DM[5, 6]. Among these, the G protein-coupled receptor 119 (GPR119) has received considerable attention from the pharmaceutical industry in recent years. GPR119 may

present an attractive drug target for treating T2DM, and its agonists may therefore represent potential new insulin secretagogues free of the risk of causing hypoglycemia.

GPR119 has been described as a class A (rhodopsin-type) orphan GPCR without close primary sequence relative in the human genome[7]. The activation of GPR119 increases the intracellular accumulation of cAMP, leading to enhanced glucose-dependent insulin secretion from pancreatic β-cells and increased release of the gut peptides GLP-1 (glucagon-like peptide 1), GIP (glucose-dependent insulinotropic peptide) and PYY (polypeptide YY)[8]. Preclinical and clinical studies with GPR119 agonists in type 2 diabetes support that GPR119 agonists have been proposed as a novel therapeutic strategy for diabetes. These investigations indicate that orally available, potent, selective, synthetic GPR119 agonists: a) lower blood glucose without hypoglycemia; b) slow diabetes progression; and c) reduce food intake and body weight. This review provides an overview of the recent progress made in the discovery of orally active GPR119 agonists[9], and outlines the current clinical trial landscape and paints a detailed illustration of the key structural information realized from GPR119 agonist campaigns.

2. GPR119: A historical perspective

2.1. Discovery and characteristics of GPR119

After the discovery of GPR119 in 1999 using data afforded by the Human Genome Project, it was subsequently described in the peer-reviewed literature as a Class A receptor with no close relatives. Independently, this receptor has been studied and described in the literature under various synonyms, including SNORF25 [10, 11], RUP3 [12], GPCR2 [13] , 19AJ [14] , OSGPR116 [15], MGC119957, HGPCR2 and glucose-dependent insulinotropic receptor (GDIR) [9]. This potentially confusing nomenclature has now been largely rationalized in favor of the designation “GPR119”.

The human receptor is encoded by a single exon with introns located on the short arm of X-chromosome (Xp26.1) (Figure 1). GPR119 homologs have been identified in several vertebrate species, including the rat, mice, hamster, chimpanzee, rhesus monkey, cattle and dog[14]. Fredriksson et al. (2003) report the rat isoform of GPR119 (accession number AY288429) as being 133 amino acids longer than the mouse and human receptors (468 vs. 335 amino acids)[16]. In contrast, Bonini et al. (accession number AR240217) and Ohishi et al. give identical sequences for the rat receptor, which are 335 amino acids in length and have 96% amino-acid identity with mouse GPR119[10, 11, 17].

2.2. GPR119 Receptor Expression

Using methods to detect receptor GPR119 mRNA, it has been proposed that, in human tissues, the pancreas and foetal liver have been consistently identified as major sites of GPR119 mRNA expression, with high expression also being noted in the gastrointestinal tract in several studies, while, in rodents, mRNA was detected in most of the tissues examined [9-11] , with the pancreas [12, 18] and gastrointestinal tract, in particular the colon

and small intestine, again appearing as major sites of expression. GPR119 expression has also been described in certain regions of the rat brain.

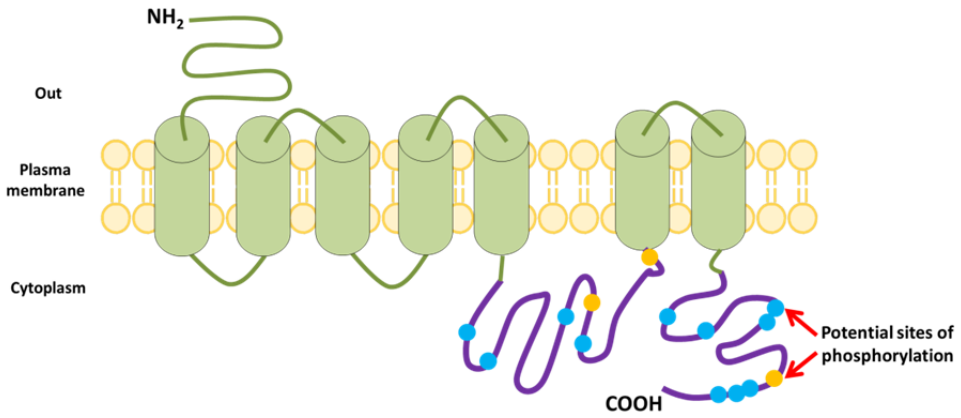

Figure 1. Schematic summary of Human GPR119 membrane topology model. Clusters of serine (S) and threonine (T) residues are highlighted in blue orange circles in the third intracellular loop and the C-terminus domain, and could represent potential sites of phosphorylation.

In situ reveals that pancreatic β cells are the main site of GPR119 expression in pancreatic islets[19]. High expression levels in pancreatic β cell lines NIT-1, MIN6 and RIN5 supports this observation[18, 20, 21]. Consistent with its expression in gut tissues, GPR119 mRNA was strongly expressed in several rodent GLP-1 secreting L-cell lines-including STC-1, FRIC, Hnci-h716 and GLUTag line[21, 22]. GPR119 mRNA has also been found in glucose-dependent insulinotropic peptide (GIP)-producing murine intestinal K cells[23].

2.3. GPR119 signaling and de-orphanization

High-level expression of GPR119 in transfected HEK293 cells led to an increase in intracellular cAMP levels via activation of adenylate cyclase [10, 11, 19], indicating that this receptor couples efficiently to $G\alpha_s$. In support of these data, potential endogenous ligands and synthetic small molecule agonists of GPR119 have been shown to increase cAMP levels (Figure 2).

Lysophosphatidylcholine (LPC, Figure 3, **1**) was the first proposed endogenous ligand for GPR119, based on its ability to stimulate glucose-dependent insulin release and increase cAMP in GPR119-transfected cells. Overton et al. have reported that the fatty-acid amide oleoylethanolamide (OEA, Figure 3, **2**) promotes a concentration-dependent increase in cAMP levels in stably transfected and endogenous GPR119-expressing cell lines with potency that was greater than LPC[24]. The identification of OEA as a potential endogenous ligand for GPR119 was of particular interest, since this compound has been reported to produce a number of pharmacological effects in rodent studies[25], including: a) reducing food intake and body weight gain through interacting with the nuclear receptor peroxisome proliferator-

activated receptor α (PPAR-α)[16, 26]; b) increasing fatty acid uptake by adipocytes and enterocytes through increased fatty acid translocase expression[27]; and c) altering feeding behaviour and motor activity through activation of an ion channel, the transient receptor potential channel, subfamily V, member 1 (TRPV1)[28]. The endovanilloid compounds *N*-oleoyl dopamine (OLDA, Figure 3, **3**) and olvanil have recently been described as GPR119 agonists with in vitro potencies similar to that of OEA. Moreover, in vivo studies demonstrated that oral administration of OLDA (100 mg/kg) increased GIP release and improved oral glucose tolerance in mice; these effects were absent or attenuated in GPR119 null mice. These fatty acid amides, OEA and OLDA, represent the best candidates for endogenous ligands, although they are less potent and selective than the natural ligands identified for many other GPCRs. Nonetheless, this work raises the possibility that other lipid amides may play a physiological role via GPR119 signaling[23, 25].

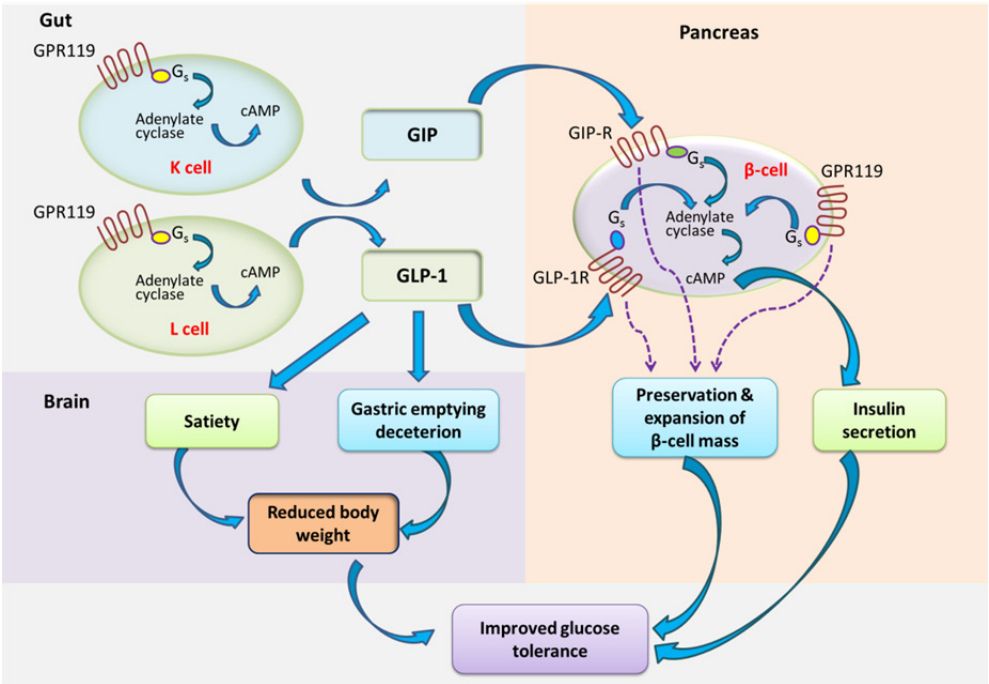

Figure 2. Schematic diagram illustrating the possible actions of GPR119 agonists[23]. GPR119 is expressed on certain enteroendocrine cells (L and K cells) in the small intestine and by β-cells within the islets of Langerhans of the pancreas. In all three cell types, ligation of GPR119 by an agonist leads to the activation of adenylate cyclase and a rise in cAMP. This triggers the release of glucagon-like peptide 1 (GLP-1), and glucose-dependent isulinotropic peptide (GIP) or insulin from L, K and β-cells, respectively. Addtitionally, GLP-1 and GIP can both interact with their cognate receptors on the β-cell to elicit insulin secretion. Thus, GPR119 agonists lead to a rise in insulin release by both direct mechanisms. Since GLP-1 (and probably GIP) also promotes β-cell viability, it is possible that orally acting GPR119 agonists may influence both the secretory activity and the viability of β-cells, leading to improved glucose homeosetasis in patients with T2DM.

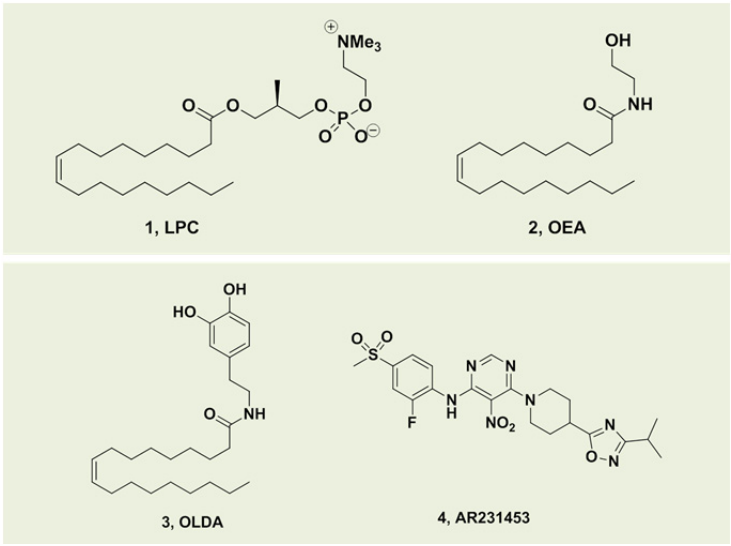

Figure 3. Proposed ligands of GPR119.

3. GPR119 regulation of insulin and incretin secretion

3.1. GPR119 regulation of insulin secretion

Based on the expression profile and coupling properties of GPR119, it stands to reason that activation of the receptor in pancreatic β cells might lead to enhanced glucose-dependent insulin release. Although the mechanism by which insulin secretion is increase following the activation of GPR119 involves a rise in cAMP, Ning et al. have demonstrated that potentiation of insulin secretion is also dependent on the closure of ATP-sensitive K^+ channels and the consequent gating of voltage sensitive calcium channels[29]. The potent, selective GPR119 agonist discovered at Arena Pharmaceuticals, Inc., AR231453 (Figure 3, 4), significantly increased insulin release in HIT-T15 cells (a hamster insulinoma-derived line with robust GPR119 expression) and in rodent islets. By contrast, no effect of this compound could be seen in islets isolated from GPR119-deficient mice, confirming that its effects were indeed mediated by GPR119[25].

3.2. GPR119 regulation of incretin secretion

GPR119 stimulates the release of GIP, GLP-1 and at least one other L-cell peptide, peptide YY (3-36) (PYY)[30]. GPR119 mRNA was found to be expressed at significant levels in intestinal sub-regions that produce GIP and GLP-1. Cellular expression studies have extended these observations by showing that most GLP-1 producing L cells in the ileum and colon also contain GPR119 [30]. This is consistent with data showing high GPR119 expression in most *in vitro* L-cell models[30, 31]. GIP, the other major insulinotropic hormone of the gut, is produced primarily in the duodenal K cells (Figure 2).

In considering the actions of GPR119 agonists as pontential mediators of GLP-1 and GIP secretion, and the potential beneficial actions that derive from this, it should not be overlooked that the enteroendocrine cells from which these incretins are released, also secrete a range of additional products, including GLP-2, oxyntomodulin (OXM), cholecystokinin, and PYY from L cells, as well as xenin from K cells. So far, very little attention has been paid to these additional intestinal peptides during analysis of GPR119-mediated responses *in vivo*, but it is clear that their actions may be important in determining of the overall profile of metabolic responses following administration of GPR119 agonists. The role of these additional hormonal agents will required to clarify in the further study[23].

4. GPR119 Agonists: Medicinal chemistry

4.1. Clinical trial status and future prospects

It is hardly surprising that, based on the strong biological proof of concept generated using the potent, selective agonist molecule 4[19, 30, 32]. In recent years, numerous patents describing GPR119 agonists have been disclosed, and several companies have advanced GPR119 agonists into the clinic for the treatment of type 2 diabetes (Table 1, Figure 4): Ortho-McNeil/Arena (APD-668 and APD-597; both discontinued), Sanofi-Aventis/Metabolex (SAR-260093/MBX-2982; Phase 2), Glaxo-SmithKline (GSK-1292263; Phase 2), Astellas/Prosidion (PSN-821; Phase 2) and Bristol-Meyers Squibb (Phase 1). The following sections provide an overview of the multiple classes of GPR119 agonists, along with the available biological data, reported by various pharmaceutical organizations. Each section is categorized according to applicant.

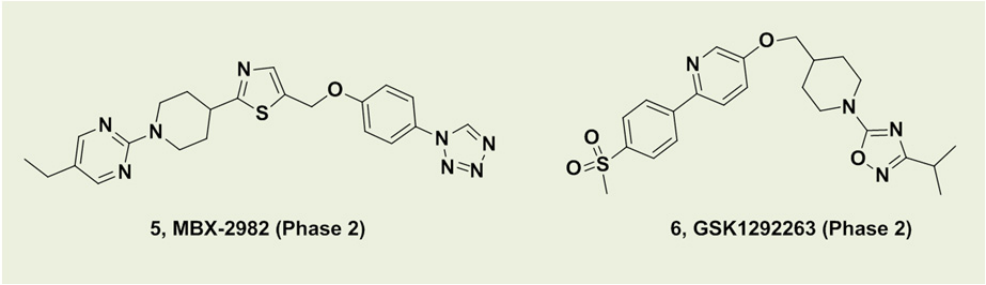

Figure 4. Structures of GPR119 agonists (MBX-2982 [5] and GSK1292263 [6]).

Drug	Company	Highest development status	ClinicalTrials.gov identifier
SAR-260093 /MBX-2982	Sanofi-Aventis /Metabolex	Phase 2	NCT01035879
GSK-1292263	GlaxoSmithKline	Phase 2	NCT01119846, NCT01218204, NCT01128621, NCT00783549, NCT01101568
PSN-821	Astellas/Prosidion	Phase 2	NCT01386099
APD-668	Ortho-McNeil/Arena	Discontinued	
APD-597	Ortho-McNeil/Arena	Discontinued	

Table 1. GPR119 agonists currently in development.

4.2. Available structures of GPR119 agonists

4.2.1. Arena pharmaceuticals

Arena Pharmaceuticals has been actively pursuing two GPR119 modulators, derived from 4 that were both considered for progression into human clinical, studies as potential drug candidates after the discovery and validation of this receptor as a viable target for the treatment of metabolic disorders. In December 2004, Arena announced a collaboration agreement with Ortho-McNeil Pharmaceutical, Inc., under which two Arena-discovered GPR119 agonists were selected for preclinical development (Arena Pharmaceuticals, Inc., Press Release, December 23, 2004, http://arna.client.shareholder.com/releasedetail.cfm?ReleaseID=320778). The first compound, APD668 (also known as JNJ28630355), displayed high GPR119 potency across various species (hEC50 = 0.47 nM, mEC50 = 0.98 nM, rEC50 = 2.51 nM; melanophore dispersion assay) and demonstrated good in vivo activity (3–30 mg/kg, p.o.) in rat and mouse oGTT studies. Compared to a known DPP-IV inhibitor, APD668 (Figure 5, **7**) was found to be more potent at a dose of 30 mg/kg. In addition to delaying the onset of hyperglycemia, APD668 delayed elevation of HbA1c and also decreased the levels of triglycerides and free fatty acids. Furthermore, APD668 demonstrated a reduction in food intake (30mg/kg) causing a slight decrease in body weight[8, 33]. However, APD668 was a potent inhibitor of CYP2C9 (IC50 = 0.1 μM), a hydroxylated metabolite **8** (Figure 5) was shown to accumulate to a much greater extent than was expected based on observations in preclinical species that showed such accumulation only at very high doses (>300 mg/kg). Though **8** showed only 80–90% of the exposure of **7** after 24 h, as a result of its significantly longer half-life (41–50 h) compared to **7** this ratio was increased to 4.3- to 5.1-fold after 14 days of dosing. Although this metabolite did not have significant activity at the target receptor (either in agonist or antagonist assays), the high concentration and long half-life were considered a potential liability for the further development of APD668 (Arena Pharmaceuticals, Inc., Press Release, January 07, 2008; http://arna.client.shareholder.com/releasedetail.cfm?ReleaseID=320208).

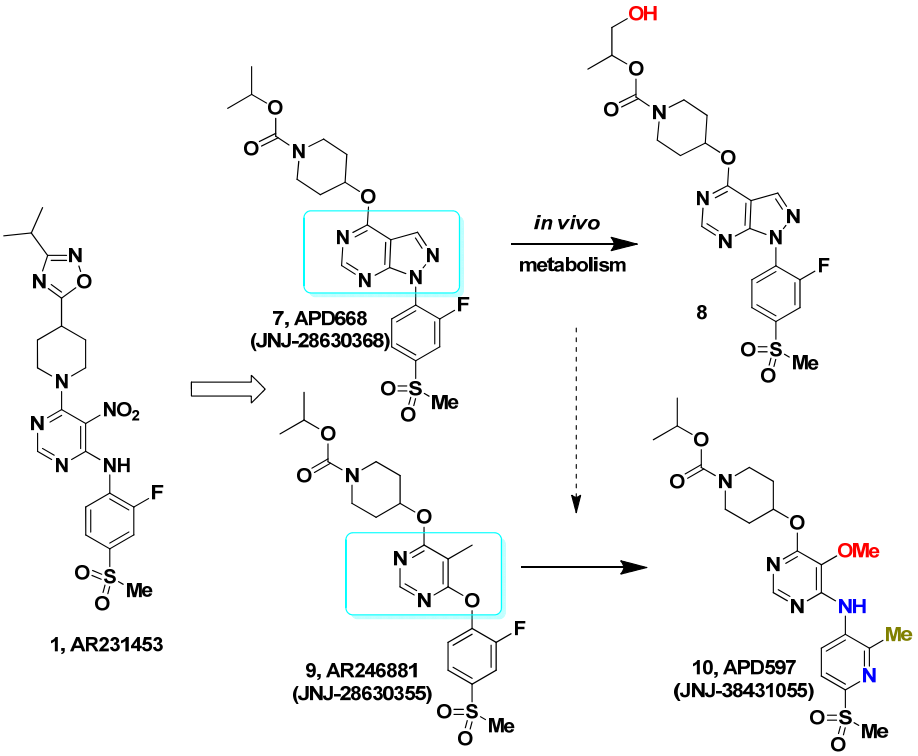

Figure 5. Early clinical candidates for GPR119 derived from the tool compound AR231453 and the structure of the major hydroxylated metabolite of APD668[34].

To tackle the CYP2C9 inhibition we elected to focus primarily on our alternative scaffold, as exemplified by **9** (Figure 5), which generally had significantly lower CYP2C9 inhibition than the pyrazolopyrimidine series (CYP2C9 IC50 for 9 = 5.3 μM) without bringing other obvious liabilities into play[34]. Therefore, they were encouraged that switching to this scaffold may also be the best approach to try to increase the range of possible sites of metabolism, without greatly increasing clearance. Then APD597 (JNJ-38431055, Figure 5, **10**) was then developed, which described the second generation trisubstituted pyrimidine agonists with improved solubility, pharmacokinetic and metabolism characteristics and excellent in vivo activity. In the anesthetized Guinea Pig, treatment with APD597 (hGPR119 EC50 = 46 nM) did not produce any dose-related, statistically significant effects on mean arterial blood pressure (MAP), heart rate (HR) or on the electrocardiogram (ECG) at cumulative doses up to 5 mg/kg IV, when compared to vehicle controls. Preliminary safety studies in rat (14-day) and dog (7-day) revealed no obvious liabilities that would prevent further development[34]. In December 2008, Ortho-McNeil–Janssen Pharmaceuticals, Inc., put APD668 on hold to initiated phase 1 clinical trials of the second Arena-discovered GPR119 agonist, APD597 for the treatment of T2DM (Arena Pharmaceuticals, Inc., Press Release, December 15, 2008; http://arna.client.shareholder.com/releasedetail.cfm?ReleaseID=354391).

4.2.2. Astellas

Compounds effective in stimulating insulin secretion and inhibiting the increase of blood sugar levels have been reported by Astellas. These were derived from a bicyclic scaffold in which a pyrimidine ring was fused to an aromatic (e.g., thiophene, thiazole, and pyridine) or a nonaromatic (e.g., dihydrothiophene, dihydrofuran, and cycloalkyls) heterocycle[8]. Detailed pharmacological data on two disclosed GPR119 agonists from Astellas have been presented. The first generation analog, AS1535907 (Figure 6, **11**), increased intracellular cAMP levels in GPR119 transfected HEK293 cells (EC50 = 1.5 μM) and enhanced insulin secretion in the mouse NIT-1 pancreatic β-cell line and rat perfused pancreas. *In vivo* studies in normal and *db*/*db* mice suggested improved glucose tolerance following oral treatment with this compound (10 mg/kg). Gene expression studies also revealed that AS1535907 upregulated PC-1 mRNA, thus suggesting possible involvement in insulin biosynthesis[8, 35].

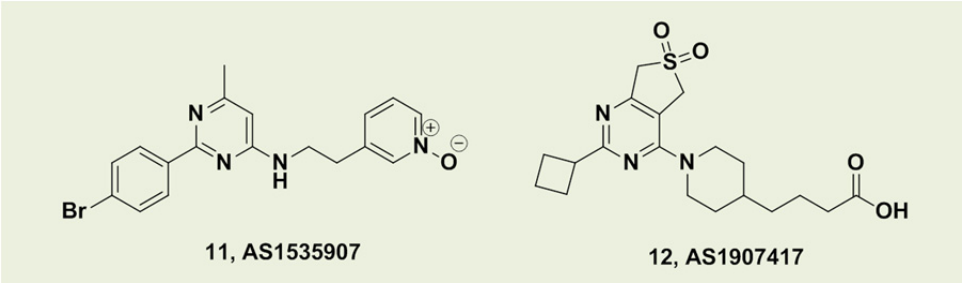

Figure 6. Compounds AS1535907 and AS1907417 from Astellas.

Further SAR optimization resulted in the second generation compound, AS1907417 (hEC50 = 1.1 μM, Figure 6, **12**), which improved upon the metabolism and efficacy liabilities associated with AS1535907, AS1907417 effectively reduced glucose levels in normal and diabetic mice. Significant increases in insulin secretion, were observed in vitro at concentrations of 0.3μM and in vivo after oral administration at doses of 3 mg/kg. The potential long term pharmacological efficacy of AS1907417 for preserving pancreatic β-cell function and insulin production was suggested by the reduction of plasma TG and NEFA levels in several diabetic animal models[8, 36].

4.2.3. Biovitrum

Biovitrum has several published patent applications identifying GPR119 agonists which differ in the nature of the central aromatic ring (compounds 13–15)[8, 32]. The central heterocyclic ring consisted of a pyridine[37], pyradazine[38], pyrimidine[39], or pyrazine[40] nucleus, which was connected to the piperidine ring via an optionally substituted amino methylene (e.g., Figure 7, **13**) or an oxymethylene linker. Compounds 13, 14, and 15 (Figure 7) were reported to have EC50 values of 22, 46, and 14 nM, respectively, in a human GPR119 cAMP HTRF (homogenous timeresolved fluorescence) assay.

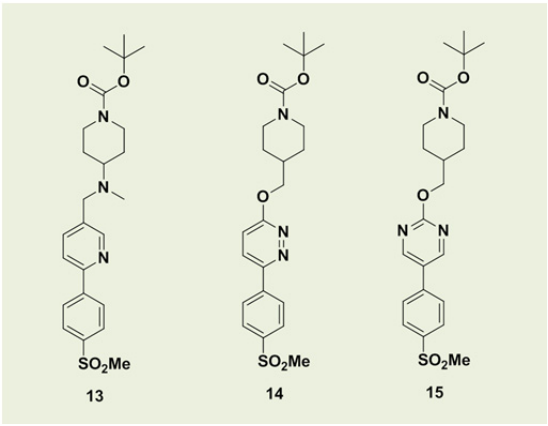

Figure 7. Compounds 13-15 from Biovitrum.

4.2.4. Bristol-Myers squibb

The first series of GPR119 agonists reported by Bristol–Myers Squibb featured a [6,5], [6,6], or [6,7] bicyclic central core[41, 42]. Representative examples containing pyrimidine-fused pyrrazole, triazole, and morpholine ring systems are shown in Figure 8. The second BMS series featured a pyridone central core that was N-substituted with the aryl motif and linked to the piperidine motif at the 4-position through an oxygen linker (Figure 8, 19, 20;); pyridazone analogs have also been claimed as GPR119 modulators[43, 44]

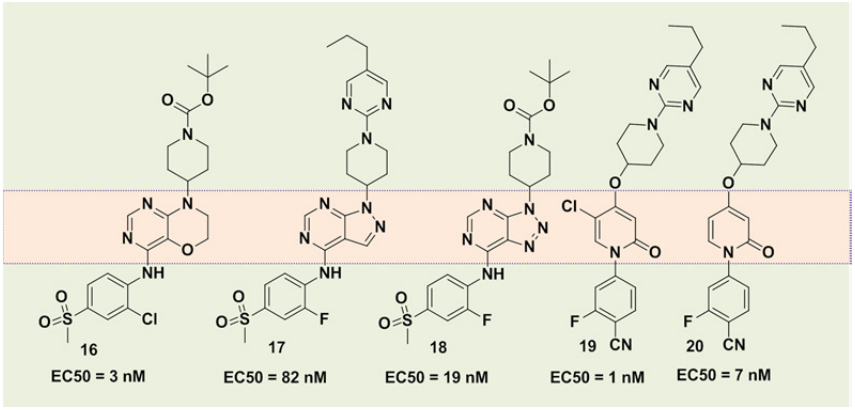

Figure 8. Compounds 16-20 from Bristol-Myers Squibb.

4.2.5. GlaxoSmithKline

Replacement of Arena's pyrazolopyrimidine ring system with a dihydropyrrolopyrimidine scaffold was shown to be successful by researchers at GlaxoSmithKline[45, 46]. The two initial filings, from July 2006, describe agonists that retain a 6,7-dihydro-5H-pyrrolo[2,3-

d]pyrimidine core unit (Figure 9). The third patent application contains compounds with a benzene, pyridine, pyrazine or pyridazine central core (e.g., **23**, **24**). The prototypical compound **21** (Figure 9) demonstrated an EC50 of 40 nM in a CHO6CRE reporter assay. In an oGTT, **21** reduced the glucose AUC by 28% (30 mg/kg) and 38% (10 mg/kg), respectively, in mice and rats. In addition, hyperinsulinemic clamp experiments in normal rats showed that compound **21** enhances whole body insulin sensitivity[8]. In these filings, compounds are described as having therapeutic value for diabetes and associated conditions, particularly T2DM, obesity, glucose intolerance, insulin resistance, metabolic syndrome X, hyperlipidemia, hypercholesterolemia and atherosclerosis.

In addition to the pyrrolopyrimidine scaffold, a series of GPR119 agonists based on monocyclic six-membered aryl and heteroaryl cores have also been reported by GlaxoSmithKline[47]. GSK1292263 (Phase 2, hGPR119 pEC50 = 6.9 nM, rat GPR119 pEC50 = 6.7 nM) augmented insulin secretion and decreased glucose AUC in rodent glucose tolerance tests; an increased incretin secretion (GLP-1 and GIP) was also observed[8]. The safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple oral doses of GSK-1292263 were evaluated in a completed randomized, placebo-controlled clinical trial in healthy volunteers (ClinicalTrials.gov Identifier NCT00783549). A total of 69 subjects received single escalating doses of GSK-1292263 (10-400 mg) prior to administration of a 250mg dose given once daily for 2 and 5 days, which was also evaluated in combination with sitagliptin (100 mg). Treatment with GSK-1292263 at all doses was described as well tolerated, with the most common drug-related effects being mild headache, dizziness, hyperhidrosis, flushing and post-oGTT hypoglycemia. Coadministration with sitagliptin increased plasma active GLP-1 concentrations and lowered total GLP-1, GIP and PYY levels; no effects on gastric emptying were observed with GSK1292263. The data support further evaluation of GSK-1292263 for the treatment of T2DM[48].

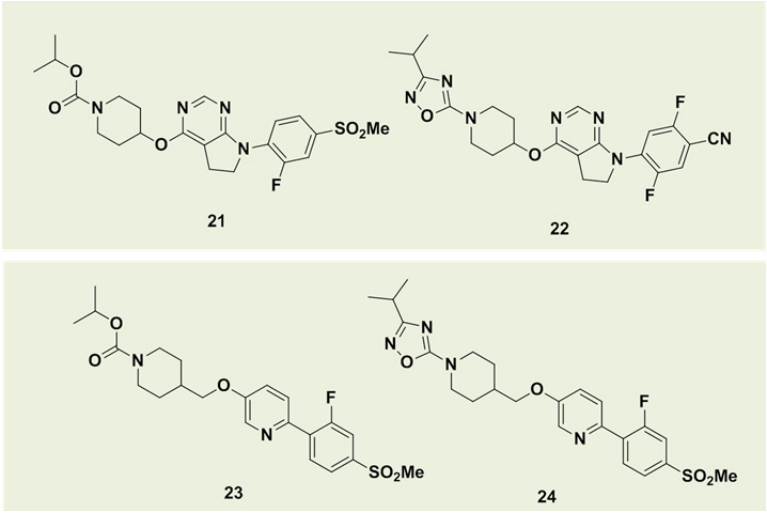

Figure 9. Compounds 21-24 from GlaxoSmithKline.

4.2.6. Merck

Merck has two published patent applications describing GPR119 agonists which retain a 4,4′-bipiperidine scaffold (Figure 10; **25** and **26**)[49, 50]. Compound **26** depicts one such example containing a 5-fluoro pyrimidine. Although the data for specific Merck analogs are not available, several compounds have been claimed to exhibit an EC50 < 10 nM in the cAMP homogeneous time-resolved fluorescence (HTRF) assay[8].

In 2006, Schering–Plough filed several patents describing spiro-azetidine and spiro-azetidinone derivatives, which are described as T-calcium channels blockers, GPR119 receptor agonists and Niemann-Pick C1-like protein-1 antagonists, with utility for the treatment of pain, diabetes and disorders of metabolism (Figure 10, **27**) [32, 51, 52]. Compound 28 was described as a modest GPR119 agonist (cAMP IC50 = 1922 nM); replacement of the amide functionality with a urea resulted in a potent T-type calcium channel blocker, 29 (IW hCav3.2 IC50 = 23nM).

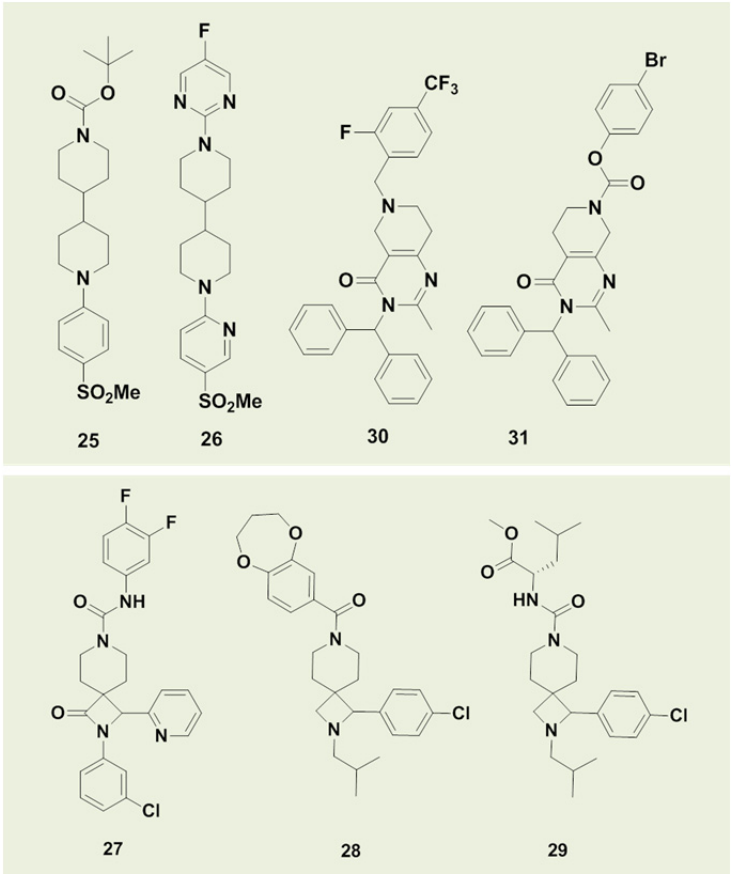

Figure 10. Compounds 25-29 from Merck.

More recent published patent filings from Schering describe selective GPR119 modulators comprised of a fused pyrimidinone core (compounds **30** and **31**)[53]. The patent application pertaining to 30 discloses a series of 6-substituted 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4(3H)-ones and the patent application associated with 31 describes a closely related chemical series of 7-substituted 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4(3H)-ones[54]. Both of these series of GPR119 modulators, which were reported to exhibit EC50 values ranging from about 50 nM to about 14,000 nM, are described as being useful for treating or preventing obesity, diabetes, metabolic disease, cardiovascular disease or a disorder related to the activity of GPR119 in a patient[32].

4.2.7. Metabolex

GPR119 agonists from Metabolex are based on a five-membered central heterocyclic core that is linked directly to the piperidine motif at its C4 position and to the aryl motif through an oxymethylene spacer[55-58] (Figure 11). Most examples in this application showed agonist activity at 10 μM in the fluorescence resonance energy transfer (FRET) assay corresponding to increased intracellular cAMP levels. Glucose stimulated insulin secretion experiments using isolated rat islets are described and compound **32** showed 1.78-fold stimulation of insulin secretion at 16 mM glucose. oGTTs in mice are described and both compounds **32** and **33** significantly reduce glucose AUC[8].

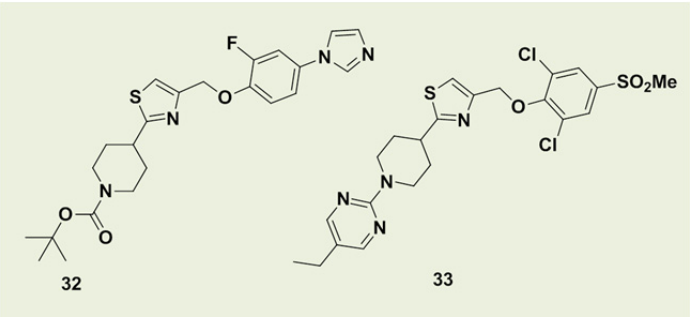

Figure 11. Compounds 32 and 33 from Metabolex.

Metabolex advanced their orally available GPR119 agonist MBX-2982 (Figure 4, **5**) into clinical trials of T2D (Phase 2, completed)[59, 60]; rights to this compound were recently acquired by Sanofi-aventis. In preclinical studies, MBX-2982 was shown to increase cAMP levels in CHO cells expressing human GPR119 (EC50 = 3.9 nM) and to stimulate GSIS from isolated islets. Metabolex has recently completed two additional Phase 1 studies of MBX-2982 in subjects with pre-diabetes. In both studies, subjects with either impaired fasting glucose or impaired glucose tolerance were enrolled. The first study investigated the effect of four consecutive once daily doses (100 or 300 mg) of MBX-2982 on the pharmacokinetics of the drug as well as its effect on glucose excursions following a mixed meal (Metabolex, Inc., Press Release, November 12, 2008 http://www.metabolex.com/news/nov122008.html). In addition, the effect of MBX-2982 on insulin secretion during a graded glucose infusion was examined. MBX-2982 was rapidly

absorbed and its exposure at both doses approximately doubled on day four compared to day one, consistent with a terminal half-life of ~18 hr and supporting once daily dosing. The glucose excursions (area under the curve) following a mixed meal were reduced relative to baseline by 26% and 37%, respectively, for the 100 and 300 mg cohorts. During the graded glucose infusions, the exposure to glucose was reduced relative to baseline by 11% and 18% for the 100 and 300 mg cohorts, respectively. This was attributable to increases in insulin secretion. These results were all statistically significant. The second study in a pre-diabetic population was a five-day placebo-controlled multiple ascending dose study with an alternate formulation of MBX-2982 at doses of 25, 100, 300 and 600 mg (Metabolex, Inc., Press Release, October 13, 2009; http://www.metabolex.com/news/oct132009.html). Once daily dosing provided markedly enhanced exposures and improved dose proportionality, giving sustained levels of MBX-2982 predicted to be maximally effective. The effect of each dose on the glucose excursions following a mixed meal and an oral glucose challenge was investigated. All four doses of MBX-2982 produced statistically significant decreases in the glucose excursion following a mixed meal ranging from 34% to 51%. Similar decreases were also observed following the glucose challenge. In both studies, MBX-2982 was safe and generally well tolerated with no serious adverse events, adverse event trends or dose-limiting toxicities. These results provide continued clinical validation of the potential therapeutic benefits of MBX-2982 in the treatment of type 2 diabetes. Phase 2 trials for MBX-2982 has been completed in evaluating its efficacy, safety, tolerability, and pharmacokinetics following daily administration for 4 weeks in patients with T2D.

4.2.8. Novartis/IRM

Genomics Institute of the Research Foundation (GNF) has disclosed an extensive set of GPR119 agonists containing a heterocyclic sulfonamide as a novel left-side structural motif[61-63]. Compounds of this patent application are defined in part by the terminal tetrahydroisoquinoline depicted in **34** (Figure 12)in February 2007. Compound **35** is representative of IRM's second chemical series of GPR119 modulators which was filed later in 2007[32, 64]. These compounds were reported to be similarly potent in stimulating cAMP in Flp-In-CHO-hGPR119 cells, and are purported to be useful for the treatment or prevention of disorders associated with this receptor.

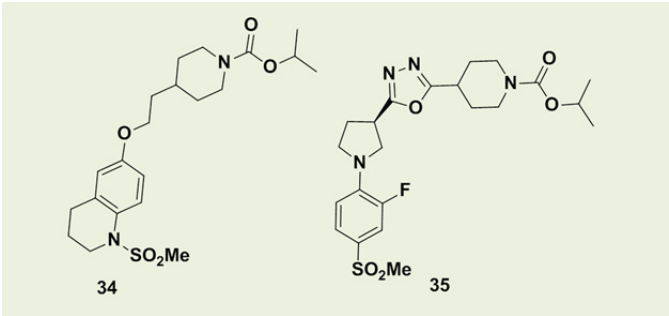

Figure 12. Compounds 34 and 35 from Novartis/IRM.

4.2.9. Prosidion Ltd.

The GPR119 agonist program at Prosidion evolved from their earlier lead PSN632408 (Figure 13, EC50 = 5.6 μM, E_{max} = 110%). Replacement of the left-side pyridine ring with the more commonly employed methanesulfonyl phenyl motif (Figure 13), while retaining the oxadiazole core, was shown to be tolerated (e.g., **37**: EC50 = 3.8 μM, E_{max} = 243%)[8, 65]. Refer to Arena analogs, introducing a fluoro substituent *meta* to the sulfone, moving the fluoro group adjacent to the sulfone moiety, as well as incorporating an (*R*)-methyl group to the methyleneoxy linker provided a more potent analog, PSN119-2 (EC50 = 0.4 μM, E_{max} = 358%), a potent GPR119 agonist that stimulated insulin secretion from HIT-T15 cells (EC50 = 18 nM) and GLP-1 release from GLUTag cells (EC50 = 8 nM)[65]. In rats, this compound improved oral glucose tolerance (10, 30 mg/kg, p.o.), delayed gastric emptying, and reduced food intake, thus supporting the premise that PSN119-2 as a GPR119 agonist could be effective oral antidiabetic agents that have the added potential to cause weight loss[8].

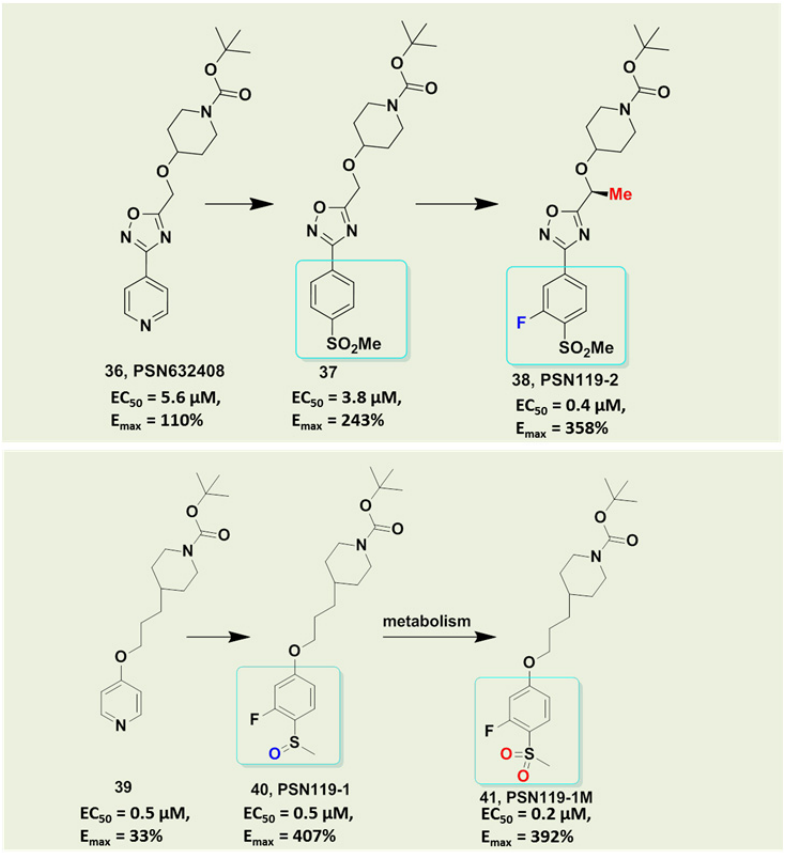

Figure 13. Compounds 36-41 from Prosidion Ltd.

Applications were filed in 2007 disclosed GPR119 agonists by Prosidion containing a central acyclic alkoxylene or alkylene spacer instead of the oxadiazole core. Compound **39** was the initial hit[66] (Figure 13), which demonstrated good potency (EC50 = 0.5 μM) but poor efficacy (E_{max} = 33%). replacing the pyridine ring with the 3-fluoro-4-methanesulfoxide phenyl moiety provided analogs with superior potency and efficacy (e.g., PSN119-1, EC50 = 0.5 μM, Emax = 407%). In several rodent models of obesity and type 2 diabetes, PSN119-1 reduced food intake and improved oral glucose tolerance, giving credence to the premise that GPR119 agonists have the makings of effective oral antidiabesic agents. When administered orally to rats, this compound achieved high plasma concentrations, as did its active sulfone metabolite PSN119-1M (EC50 = 0.2 μM, E_{max} = 392%)[67] (Figure 13).

More recently, the Prosidion group described GPR119 agonists in which the potentially labile tert-butylcarbamate functionality was replaced with bioisosteric heteroaryl groups, in particular with an oxadiazole similar to Arena's AR231453. Several azetidine-based GPR119 agonists (Figure 14) have also been disclosed by Prosidion [8, 68, 69]. These analogs featured an appropriately substituted biaryl moiety five-membered heterocycle connected to the azetidine through an oxygen atom (e.g., **42**, **43**). Preferred analogs within these inventions were claimed to exhibit an EC50 of less than 1 μM (HIT-T15 Camp and insulin secretion assays), to statistically reduce glucose excursion in rat oGTTs (≤ 10 mg/kg, p.o.), as well as to demonstrate a statistically significant hypophagic effect at a dose of ≤ 100 mg/kg.

Optimization of the above described chemical series resulted in identification of the clinical candidate PSN821[8], the structure of which has not been disclosed. In pre-clinical studies, PSN821 has demonstrated pronounced glucose lowering in rodent models of type 2 diabetes with no loss of efficacy on repeated administration, and substantial reductions of body weight in rodent models of obesity. In male diabetic ZDF rats, both acute and chronic oral administration of PSN821, significantly and dose-dependently reduced glucose excursions in an oral glucose tolerance test. In prediabetic male ZDF rats, weeks significantly lowered nonfasting blood glucose concentrations and HbA1c levels compared to vehicle. Furthermore, in weight-stable, dietary-induced obese (DIO) female Wistar rats, daily oral dosing of PSN821 for 4 weeks reduced body weight substantially and significantly by 8.8%, approaching the 10.6% weight loss induced by a high dose of the prescribed anti-obesity agent sibutramine[70].

In the double-blind, placebo-controlled, ascending single dose first-in-human study, PSN821 was generally well tolerated at doses up to 3000mg in healthy volunteers and 1000mg (the top dose tested) in patients with type 2 diabetes, with no clinically important adverse effects on laboratory tests, 12-lead ECGs or vital signs. Pharmacokinetics showed a profile consistent with once or twice daily dosing. In patients with type 2 diabetes, PSN821 showed substantial and statistically significant reductions in glucose responses to a standard nutrient challenge of approximately 30% at 250mg and 500mg. The data from this study was supportive of progression of PSN821 into a 14-day dosing ascending multiple dose study in healthy subjects and patients with type 2 diabetes and will be submitted for presentation at a scientific meeting together with the data from the multiple ascending dose study.

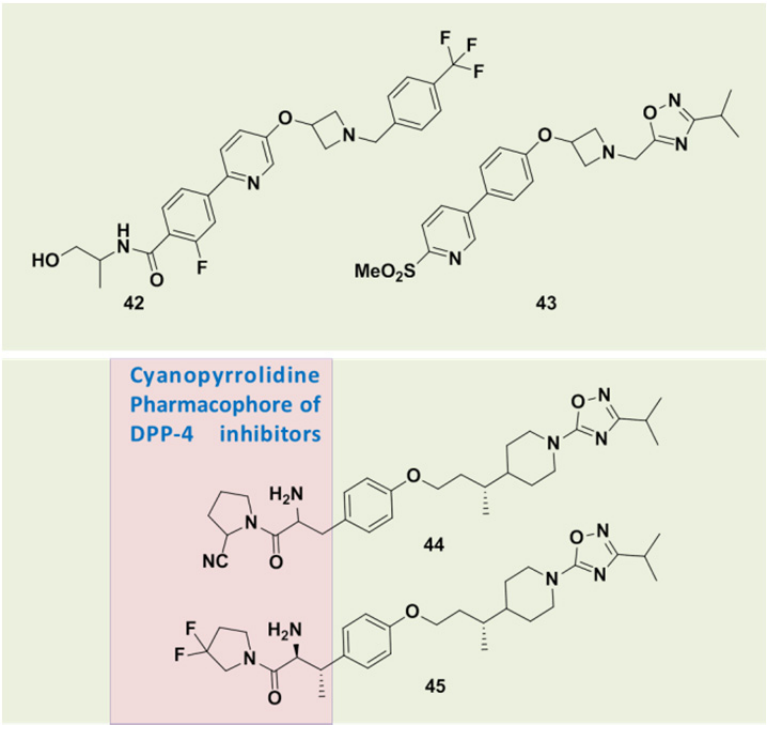

Figure 14. Compounds 42-45 from Prosidion Ltd.

The discovery team at Prosidion has explored a unique approach of combining DPP-4 inhibition and GPR119 agonism in a single molecule[71]. Introduction of the cyanopyrrolidine pharmacophore of known DPP-4 inhibitors on the aryl motif of their GPR119 agonists provided compounds, which displayed dual activity as agonists of GPR119 and inhibitors of DPP-IV (Figure 14, **44** and **45**). Limited biological data are available from this SAR effort. PSN-IV/119-1 (structure not disclosed) was recently reported to exhibit a GPR119 EC50 of 2.24mmol/L and DPP-4 IC50 of 0.2mmol/L[72]. Oral administration of PSN-IV/119-1 at a dose of 30mg/kg in diabetic ZDF rats led to a greater reduction in glucose AUC compared to the DPP-IV inhibitor sitagliptin (58% vs. 22%); at a lower dose of 10 mg/kg, the activity was comparable to sitagliptin (20 mg/kg).

4.3. The pharmacophore model for potent GPR119 agonists

Xiaoyun Zhu et al. have generated pharmacophore models using Discovery Studio V2.1 for a diverse set of molecules as GPR119 agonist with an aim to obtain the pharmacophore model that would provide a hypothetical picture of the chemical features responsible for activity[73]. The best hypothesis (Figure 15) consisting of five features, namely, two hydrogen bond acceptors and three hydrophobic features, has a correlation coefficient of 0.969, cost difference of 62.68, RMS of 0.653, and configuration cost of 15.24, suggesting that

a highly predictive pharmacophore model was successfully obtained. The Fit-Value and Estimate activity of GSK-1292263, which have completed phase II clinical trials as a GPR119 agonist (Figure 15), based on Hypo1 in Decoy set are 8.8 and 7.7 (nM), respectively. The validated pharmacophore generated can be used to evaluate how well any newly designed compound maps on the pharmacophore before undertaking any further study including synthesis, and also used as a three-dimensional query in database searches to identify compounds with diverse structures that can potentially agonist GPR119[73].

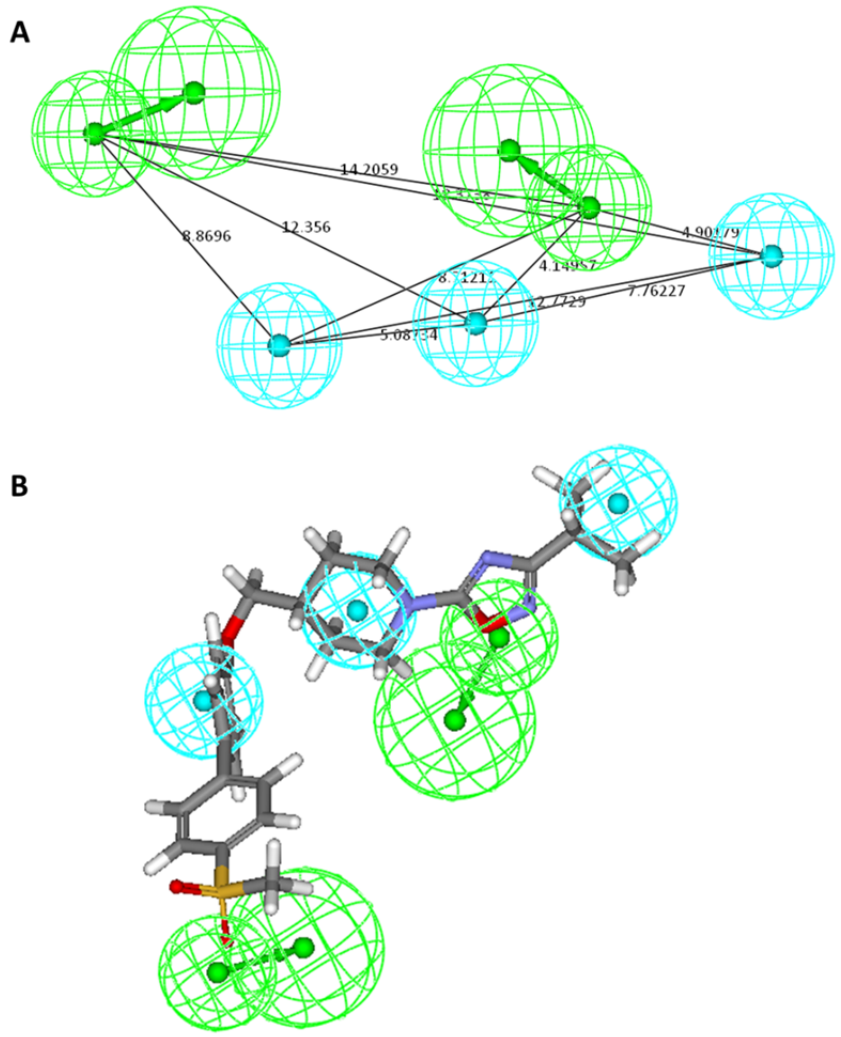

Figure 15. The first pharmacophore model for potent G protein-coupled receptor 119 agonist[73]. A: The best pharmacophore model Hypo1 where H and HBA are illustrated in cyan and green, respectively. B: Best pharmacophore model Hypo1 aligned to GSK1292263.

5. Future directions and concluding remarks

In summary, GPR119 agonists seem to provide a completely novel and previously unexplored approach to incretin therapy in patients with T2DM, increasing glucose-dependent insulin secretion through two complementary mechanisms: directly, through actions on the β cell, and indirectly, through enhancement of GLP-1 and GIP release from the GI tract. It is also worth pointing out the obvious potential advantages that could theoretically be obtained by the co-administration of a GPR119 agonist (with a mechanism as a GLP-1 secretagogue) and a DPP-4 inhibitor (with a mechanism to protect secreted GLP-1), and some preliminary and recent published data support this attractive concept. Such a strategy may not only provide improved glycemic control, but also induce weight loss, a feature observed with GLP-1 mimetics but not with DPP-4 inhibitors. Following the recent entry of the GPR119 agonists MBX-2982, GSK-1292263 and PSN821 into clinical development, the value of these compounds as a new class of therapeutics for type 2 diabetes and associated obesity is likely to be determined within the next few years.

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