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Discovery of a second generation agonist of the orphan G-protein coupled receptor GPR119 with an improved profile

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ABSTRACT

The design and synthesis of a second generation GPR119-agonist clinical candidate for the treatment of diabetes is described. Compound **16** (APD597, JNJ-38431055) was selected for preclinical development based on a good balance between agonist potency, intrinsic activity and in particular on its good solubility and reduced drug–drug interaction potential. In addition, extensive in vivo studies showed a more favorable metabolic profile that may avoid the generation of long lasting metabolites with the potential to accumulate in clinical studies.

GPR119 is a recently discovered rhodopsin-like, class A GPCR that is highly expressed in pancreatic β-cells[1] and incretin releasing cells in the gastrointestinal tract.[2] Small molecule GPR119 agonists (e.g., **1**, AR231453)[3] have been shown to promote postprandial insulin and incretin secretion in a glucose dependent fashion via their ability to increase cAMP levels in the appropriate cell types. As a result, there is significant interest in whether this target could provide a new therapeutic approach for the treatment of type 2 diabetes.[4]

We have previously reported the discovery of two compounds derived from **1** that were both considered for progression into human clinical studies. Both **2a** and **3** (Fig. 1) were shown to be potent and selective GPR119 agonists that showed excellent in vivo activity in various rodent models.[5,6] From these two candidates, **3** (APD668) was selected for further development based on its superior intrinsic activity in an oral glucose tolerance (oGTT) test in cynomolgus monkey, despite it being a potent inhibitor of CYP2C9 (IC_{50} = 0.1 μM).[5] In clinical studies APD668 was well tolerated and showed good, albeit somewhat less than dose proportional (based on $AUC_{0-\infty}$), exposure in a single ascending dose study in the dose range 20–600 mg. In a multiple ascending dose study, steady state was achieved within 4–5 days of dosing (25–400 mg, QD) with a half life appropriate for once daily dosing (mean $T_{1/2}$ = 27–41 h).[7] However even in this dose range in human, a hydroxylated metabolite **4** 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). Although **4** showed only 80–90% of the exposure of **3** after 24 h, as a result of its significantly longer half-life (41–50 h) compared to **3** 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. As a result we began the search for second generation compounds that might avoid this and some of the other potential issues associated with APD668. To tackle the CYP2C9 inhibition we elected to focus primarily on our alternative scaffold, as exemplified by **2**, which generally had significantly lower CYP2C9 inhibition than the pyrazolopyrimidine series (e.g., CYP2C9 IC_{50} for **2a** = 5.3 μM) without bringing other obvious liabilities into play. In addition, although **2a** was quite stable in microsomal preparations it was susceptible to the same hydroxylation of the isopropyl carbamate group but at least 3 other metabolites were observed both in vitro and in vivo in preclinical species. We were therefore encouraged that switching to this scaffold may also be the best approach to try to

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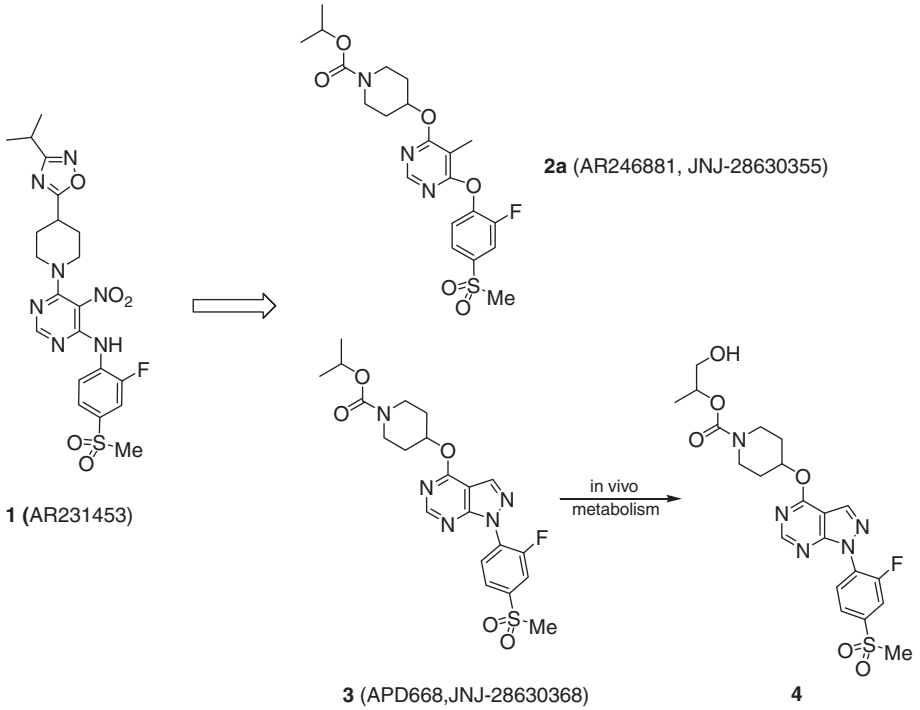

Figure 1. Early clinical candidates for GPR119 derived from the tool compound AR231453 and the structure of the major hydroxylated metabolite of APD668.

increase the range of possible sites of metabolism, without greatly increasing clearance. As a further precautionary measure we also sought to decrease the lipophilicity and improve the aqueous solubility of the compounds. We herein describe the discovery of second generation trisubstituted pyrimidine agonists with improved solubility, pharmacokinetic and metabolism characteristics and excellent in vivo activity.

In our first approach to improve the key properties for the series we focused on the incorporation of pyridyl nitrogen groups into the aromatic ring of **2a** in combination with both ether and aniline linkers, and looked at the effect both on receptor agonist potency (EC_{50} using either the human, i.e., hGPR119 or rat, i.e., rGPR119 sequence) and intrinsic activity (IA)[8] as well as solubility.[9] All of the compounds shown in Table 1 were prepared by the route shown in Scheme 1. Nucleophilic substitution with the isopropyl carbamate of 4-hydroxy piperidine in the presence of potassium *tert*-butoxide furnished the intermediate **7** in high yield. Thereafter, a second nucleophilic substitution with the requisite phenol or aniline (which were generally palladium catalyzed in the case of the latter) provided the test compounds.[10] Solubility was first measured in 40% Hydroxypropyl-β-cyclodextrin (HPβCD) in water and later, as this parameter improved, in 20% HPβCD. In each case, these formulations represented the vehicle of choice for oGTT studies in rodents at the time.

In the first example of the series, the 2-fluorophenylsulfone group from **2a** was replaced by a simple 2-methyl pyridinyl moiety (**9a**) we observed a >10-fold increase in solubility in 40% HPβCD. However, there was a concomitant 2-fold decrease in in vitro agonist potency and a highly significant reduction in intrinsic activity. This specific compound has also been described by other groups[11] and interestingly, in the one case where the intrinsic activity was reported, the data reported herein are in very close agreement.[12] Previous experience with compounds of this type had suggested that switching the linker group from ether to aniline would also enhance solubility. Indeed, when this modification was made in the 5-methyl pyrimidine series (**2b**) we again observed a significant improvement in solubility compared to **2a**. Once again however, there was a reduction in potency, but in this case intrinsic activity was not reduced. The combination of these two modifications, or the addition of small substituents on the pyridine ring (**9b–g**) did not improve activity or solubility with the exception of **9e** which showed improvements in both parameters but was a very poorly efficacious partial agonist relative to AR231453. The reintroduction of the methyl sulfone moiety which has been previously identified as making a favorable hydrogen bond acceptor interaction with GPR119,[3] enabled an increase in intrinsic activity in most cases while maintaining good solubility in 20% HPβCD. Compound **9j** appeared to have the best balance of properties between agonist potency (albeit significantly reduced relative to **2a**) intrinsic activity and solubility. However, **9j** still showed significant inhibition of CYP2C9 (IC_{50} = 2.5 μM) and was still essentially insoluble in water except at low pH.

We next turned our attention to the substituent in the 5-position of the pyrimidine core (Table 2). Again compounds of this type could be readily prepared using a route similar to the one shown in Scheme 1, but using the appropriate 5-substituted pyrimidine in place of the 5-methyl pyrimidine.[10] Having introduced groups that provided promising physical properties in **9j**, we elected to use this scaffold to examine the SAR around the 5-substituent. As can be seen in Table 2, this position was rather sensitive to substituent size and polar groups in particular were poorly tolerated. Whereas it was clear that some kind of substituent was required to provide adequate agonist activity (**11** was apparently significantly less potent than almost all the 5-substituted analogues, although the increased intrinsic activity is a confounding factor in making such a comparison), increasing the size of the group beyond 2 carbons had a highly detrimental effect on intrinsic activity (**13**). An ether function could be introduced (**16**) but again, increasing the size of the group beyond 2 atoms led to a significant reduction in intrinsic activity. Switching from an ether to a more polar hydroxyl group resulted in a significant loss of both agonist potency and intrinsic activity (**19**). Interestingly, the 5-nitro substituent that had been key to the identification of the original tool compound AR231453,[3] was not tolerated in the presence of the pyridine in