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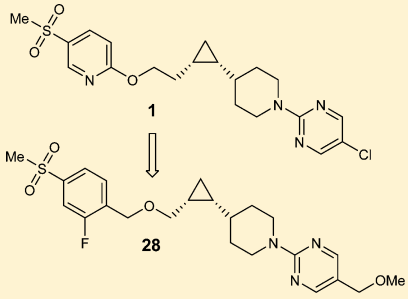
Design of Potent and Orally Active GPR119 Agonists for the Treatment of Type II Diabetes

Ping Liu,*[,†] Zhiyong Hu,[†] Byron G. DuBois,[†] Christopher R. Moyes,[†] David N. Hunter,[†] Cheng Zhu,[†] Nam Fung Kar,[†] Yuping Zhu,[†] Joie Garfunkle,[†] Ling Kang,[‡] Gary Chicchi,[§] Anka Ehrhardt,[§] Andrea Woods,[§] Toru Seo,[§] Morgan Woods,[§] Margaret van Heek,[§] Karen H. Dingley,[∥] Jianmei Pang,[∥] Gino M. Salituro,[∥] Joyce Powell,[∥] Jenna L. Terebetski,[⊥] Viktor Hornak,[#] Louis-Charles Campeau,[▽] Joe Lamberson,[▽] Fez Ujjainwalla,[†] Michael Miller,[†] Andrew Stamford,[†] Harold B. Wood,[†] Timothy Kowalski,[‡] Ravi P. Nargund,[†] and Scott D. Edmondson[†]

[†]Departments of Medicinal Chemistry, [‡]Diabetes Biology, [§]Pharmacology, [∥]Pharmacokinetics, Pharmacodynamics and Drug Metabolism, [⊥]Basic Pharmaceutical Sciences, [#]Chemical Modeling and Informatics, and [▽]Process Research, Merck Research Laboratories, Rahway, New Jersey 07065, United States

Supporting Information

ABSTRACT: We report herein the design and synthesis of a series of potent and selective GPR119 agonists. Our objective was to develop a GPR119 agonist with properties that were suitable for fixed-dose combination with a DPP4 inhibitor. Starting from a phenoxy analogue (**1**), medicinal chemistry efforts directed toward reducing half-life and increasing solubility led to the synthesis of a series of benzyloxy analogues. Compound **28** was chosen for further profiling because of its favorable physicochemical properties and excellent GPR119 potency across species. This compound exhibited a clean off-target profile in counterscreens and good *in vivo* efficacy in mouse oGTT.



KEYWORDS: *Type II diabetes, GPR119 agonists, chiral cis-cyclopropanes, benzyloxy analogues, oGTT*

Diabetes mellitus is a serious and chronic medical condition that is rapidly growing throughout the world. Generally, diagnosis is determined by measurement of fasting plasma glucose and recently an international recommendation has been made for the use of hemoglobin A_{1C} (HbA_{1C}) as a time-integrated marker of glucose levels.[1] Approximately, 90−95% of diabetics have type 2 diabetes (T2D), and the pathogenesis of this disease involves hepatic glucose overproduction, insulin resistance, and dysfunction of insulin producing β-cells.[2] T2D is initially managed by regular exercise and dietary modifications; then, as it progresses, the disease is managed by oral medications or injectables such as insulin and GLP-1 agonists. Standard medications focus on glycemic control, either through monotherapies or combination therapies.[3] In spite of the large number of available medications, there is still an unmet medical need for orally effective new treatments for diabetes that will offer better safety profiles and reduced adverse effects.

GPR119 is a G protein-coupled receptor whose expression in humans, mice, and rats is highly restricted to pancreatic islets and specific intestinal regions.[4−6] GPR119 agonists are proposed to regulate glucose homeostasis through stimulating glucose-dependent insulin release both directly by enhancing pancreatic-cell function and indirectly by the release of incretin hormones from the small intestine.[7−9] Theoretically, the selectivity of expression, coupled with an ability to potentiate insulin secretion only when glucose levels are elevated, makes GPR119 a very attractive target for the development of new medications for T2D. Indeed, the industry has advanced multiple GPR119 agonists, for example, GSK-1292263, PSN-821, and MBX-2982, into the Phase II clinical trials.[8] However, despite tremendous efforts by academia and industry, the theoretical benefits that GPR119 agonists can offer have thus far been a challenge to demonstrate clinically.[10,11]

We were interested in developing a fixed-dose combination (FDC) of a GPR119 agonist and a DPP4 inhibitor in the hope that such a combination would provide greater effects than either agent alone.[12] Previously we reported the design and synthesis of a series of GPR119 agonists with a *cis*-cyclopropane as the core structure.[13,14] Herein we report our continued efforts in this area.

Compound **1**, our previous preclinical candidate, had excellent potency, selectivity, and *in vivo* efficacy,[14] but this compound had a long half-life ($t_{1/2}$) in rat (Figure 1), and the clinically observed human half-life after single dose administration was significantly longer than desired,[15] which rendered **1** unsuitable for FDC with sitagliptin (qd). Furthermore, this

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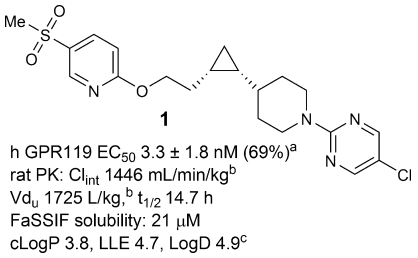


Figure 1. Previous preclinical candidate. [a]EC_{50} data: mean ± SD (% control at max dose). [b]Calculated from Cl 2.9 mL/min/kg, Vd 3.4 L/kg, and f_u 0.2%. [c]HPLC LogD at pH 7.

compound exhibited poor solubility in biorelevant media, including fasted-state simulated intestinal fluid (FaSSIF).[16−18] The low solubility resulted in a high calculated dose number, an increase in absorption risk and anticipated need for enhanced formulation complexity.[19−22] Since formulation complexity would increase FDC development challenges, it was desirable to identify compounds with improved physicochemical properties.[23] Therefore, the lead optimization objective was to reduce the projected human half-life and increase solubility, while simultaneously maintaining other favorable properties.

The plasma half-life is determined by two pharmacokinetic parameters, intrinsic clearance (Cl_{int}), and unbound volume of distribution (Vd_u).[24] Half-life can be shortened either by increasing Cl_{int} or by decreasing Vd_u of a compound. In most cases, increasing Cl_{int} also leads to an increased dose projection and potentially higher levels of metabolites, thus decreasing Vd_u is a preferable strategy to reduce half-life. Vd_u can be modified by adjusting the lipophilicity or introducing basic and acidic functional groups.[25] For compounds in the same class, reducing lipophilicity usually leads to decreased Vd_u. From phenoxy analogue **1** to benzyloxy analogue **2**, a significant drop in lipophilicity was predicted (cLogP 3.8 vs 2.2), and measured LogD dropped by 1.2. Indeed, lower unbound volume (81 vs 1725 L/kg) and shorter rat $t_{1/2}$ (1.8 vs 14.7 h) were observed in compound **2**, where GPR119 potency was almost maintained (human EC_{50} = 8.7 vs 3.3 nM). Similarly, from phenoxy analogue **3** to benzyloxy analogue **4**, unbound volume was decreased from 242 to 62 L/kg, and $t_{1/2}$ was reduced from 6.5 to 1.5 h (Figure 2). Although Cl_{int} changed in both cases, it was the magnitude of Vd_u reduction that caused the ratio of Vd_u to Cl_{int} to drop by 8-fold from **1** to **2** and 4-fold from **3** to **4**, which was approximately reflected in the reduction in $t_{1/2}$, respectively. In addition, from phenoxy analogues to benzyloxy analogues (**1**, **3** vs **2**, **4**), the decreased cLogP and LogD value correlated with an increase in solubility. For example, compound **4** demonstrated improved FaSSIF solubility over **3** (127 vs 61 μM). Finally, to our delight, compound **4** also displayed higher GPR119 potency (0.8 vs 1.7 nM).

In recent years the concept of lipophilic ligand efficiency (LLE), which combines both potency and lipophilicity, has been shown to be very useful in measuring the progress of the lead optimization process.[26] In this regard, the LLE was significantly increased from phenoxy analogues **1** and **3** to benzyloxy analogues **2** and **4**: LLE was 4.7 vs 5.9 for compounds **1** and **2**, and 3.8 vs 5.0 for compounds **3** and **4**.[27]

Encouraged by these initial results, further structure−activity relationship (SAR) efforts were directed toward finding a compound with an even more favorable physicochemical profile. Our optimization efforts kept the central cyclopropyl piperidine core intact and focused on surveying a variety of

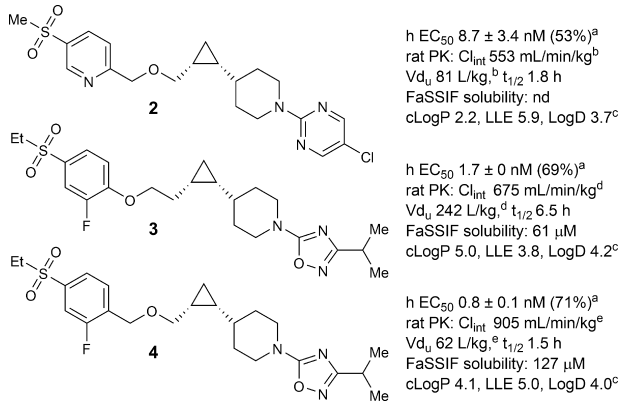
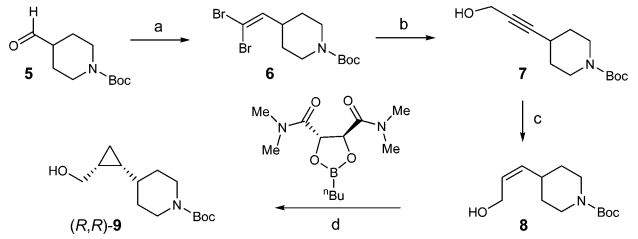


Figure 2. Comparison of benzyloxy and phenoxy analogues. [a]EC_{50} data: mean ± SD (% control at max dose). [b]From Cl 9.0 mL/min/kg, Vd 1.3 L/kg, and f_u 1.6%. [c]HPLC LogD at pH 7. [d]f_u of the corresponding methylsulfone analogue (2%) used; Cl 13.5 mL/min/kg, Vd 4.8 L/kg. [e]From Cl 13.5 mL/min/kg, Vd 4.8 L/kg, and f_u 5.8%.

functional groups at both ends, including the favorable piperidine right-hand side "capping" groups previously reported for GPR119 agonists.[12] As illustrated in Scheme 1, the synthesis

Scheme 1. Synthesis of Chiral Synthon (*R*,*R*)-9[a]



[a]Reagents and conditions: (a) CBr_4, PPh_3; (b) ^{n}BuLi, THF, then paraformaldehyde; (c) H_2, quinoline, Lindlar catalyst, EtOAc; (d) Charette cyclopropanation, Et_2Zn/CH_2I_2, dichloromethane, −20−0 °C.

of the central cyclopropyl piperidine piece, the chiral synthon **9**, started with the commercially available piperidine aldehyde **5**. Corey−Fuchs type reaction was used to convert aldehyde **5** to propargyl alcohol **7** by a two-step sequence via dibromo-olefin intermediate **6**.[28] Reduction of the alkyne in **7** with Lindlar's catalyst gave *cis*-alkene **8**, which was subject to Charette's enantioselective cyclopropanation reaction.[29] Thus, using the dioxaborolane ligand derived from (*S*,*S*)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide as a chiral auxiliary, the desired chiral synthon (*R*,*R*)-**9** was obtained as a white solid (>98% de and >98% ee) after recrystallization from heptane.[30]

With key intermediate **9** in hand, the benzyloxy analogues can be efficiently assembled (Scheme 2).[30] In the presence of a base such as NaH or NaHMDS, S_N2 type reaction between **9** and an appropriate benzyl halide gave benzyl ether **10**, which upon deprotection of the Boc group provided piperidine intermediate **11**. The synthesis was divergent at this point depending on the type of the piperidine capping groups. If the capping group is a pyrimidine, an S_NAr reaction was performed (**2**, **18**, **19**, **23**−**31**, **33**, and **34**). To introduce the 1-methylcyclopropyloxycarbonyl capping group in **22**, intermediate **11** was reacted with the preformed succinimide **12**.[31] In the case of the oxadiazole capping group (**4**, **20**, and **21**),

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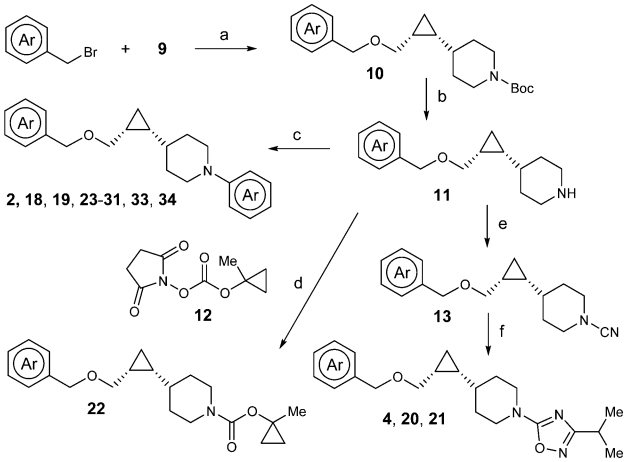
Scheme 2. Synthesis of Benzyloxy Analogues[a]

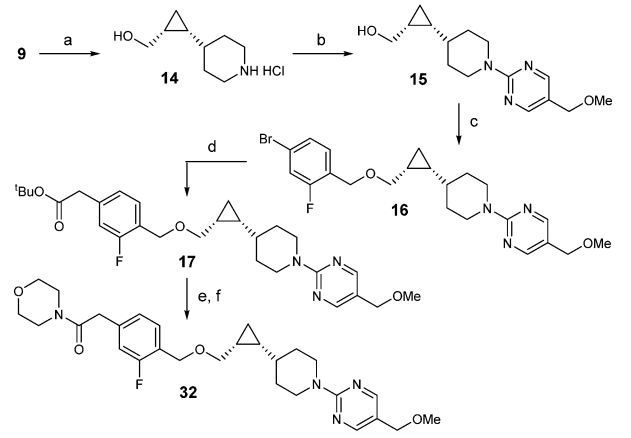


[a]Reagents and conditions: (a) Base, THF; (b) TFA, dichloromethane; (c) Het-X, Cs_2CO_3, DMF; (d) Et_3N, dichloromethane; (e) Br-CN, K_2CO_3, $CHCl_3$, reflux; (f) ^{i}Pr−C(=NH)NHOH, $ZnCl_2$, THF, reflux.

intermediate **11** was converted to cyano substituted piperidine **13** by treatment with cyanogen bromide; then the cyano group was converted to the isopropyl oxadiazole by zinc chloride mediated reaction with *N*-hydroxyisopropylimidamide, followed by acid mediated cyclization.[32]

The synthetic sequence for acetamide analogue **32** is shown in Scheme 3. After three straightforward manipulations, Boc

Scheme 3. Synthesis of Acetamide Analogue 32[a]



[a]Reagents and conditions: (a) 4 **N** HCl in dioxane; (b) 2-chloro-5-methoxymethylpyrimidine, Cs_2CO_3, DMSO, 60 °C, 76%; (c) NaH, 4-bromo-1-(bromomethyl)-2-fluorobenzene, DMF, 96%.; (d) $BrZnCH_2COO^tBu$, $Pd_2(dba)_3$, X-Phos, THF, 60 °C, 98%; (e) TFA, dichloromethane, 100%; (f) morpholine, HOBT, EDC, diisopropylethylamine, dichloromethane, 69%.

deprotection, pyrimidine installation, and benzyl ether formation, aryl bromide **16** was transformed to aryl acetate **17** through an efficient Negishi type coupling.[33] Finally, *tert*-butyl ester hydrolysis and amide formation completed the synthesis of **32**.

The *in vitro* agonist activity for human and mouse receptors was evaluated by two measures: the potency measure as expressed in EC_{50} values in a cAMP assay and the magnitude of agonist activity measure as expressed in % control at the maximum dose compared to an internal agonist control.[34] The data is summarized in Table 1. In general, these benzyloxy analogues possessed good to excellent potency and a full agonist response if the appropriate piperidine capping groups were chosen on the right, such as 5-substitued pyrimidine, isopropyl oxadiazole, and 1-methylcyclopropyloxycarbonyl, and favorable substituents were incorporated on the left, such as methylsulfone and tetrazole.[12−14] Several trends were observed. While hydroxyethylsulfone somewhat increased potency (**18** vs **2**), ethylsulfone somewhat decreased potency (**31** vs **28**). Replacing 2-pyridyl with 2-fluorophenyl group resulted in significant improvements in FaSSIF solubility (**27** vs **19**), which could not be predicted by the cLogP and measured LogD values. The 5-position of the pyrimidine capping group was compatible with many functional groups of which methoxy and methoxymethyl (MOM) were effective at improving solubility (**23**, **25**, and **28**). Finally, all the benzyloxy analogues in Table 1 exhibited relatively short $t_{1/2}$s in rat compared to the phenoxy analogues and had predicted human half-lives in the range of 2 to 38 h.[35]

Compound **28**, with FaSSIF solubility of 161 μM, cLogP of 2.4, and LLE of 6.3, was identified as a potent GPR119 agonist with suitable physicochemical properties for a fixed-dose-combination and therefore was further profiled. An off-target screen of this compound was performed against a panel of 168 receptors, ion channels, and enzymes, and no off-target activities were found with IC_{50}s < 10 μM. In a cardiac ion channel functional blockade activity panel,[36] **28** exhibited mild inhibition of hERG with a calculated IC_{50} of 13 μM.[37] There were no effects on I_{Ks} or I_{Na} up to the highest tested concentration of 30 μM. Compound **28** was also selective over CYP 3A4 (IC_{50} = 40 μM) and hPXR (EC_{50} > 30 μM, 39% Act).[38]

The promising *in vitro* profile of **28** was followed by characterization of this compound *in vivo*. In a mouse oGTT[39] and PK/PD dose−response study, compound **28** showed a dose-dependent lowering of blood glucose excursion, as represented by the excursion AUC from 0−120 min (Figure 3). Based upon this data, the MED_{max} (minimal efficacious dose for maximal efficacy) was 3 mpk. The blood concentrations of **28** at 90 min post-dosing increased approximately linearly at 0.3, 1, 3, and 10 mpk (18 ± 5, 86 ± 8, 302 ± 57, and 622 ± 160 nM, respectively).

The pharmacokinetic profile of **28** was evaluated in rat, dog, and monkey (Table 2). Overall, this compound possessed good PK properties in dogs ($t_{1/2}$ 17 h, *F* 60%), but lower oral bioavailability in rats and monkeys, likely due to more extensive metabolism in these species relative to dogs (Cl_{int} was 1104, 319, 60, and 42 mL/min/kg in rat, monkey, dog, and human liver microsomes, respectively).[41] Compared to lead compound **1**, **28** had a much lower Vd_u (1725 vs 54 L/kg) in rat, which contributed heavily to $t_{1/2}$ reduction (rat $t_{1/2}$ 14.7 vs 1.0 h). Based upon a plasma trough target of 549 nM (from the MED_{max} in mouse and a blood/plasma ratio of 0.55), the projected human half-life of **28** was ∼15 h and estimated human QD dose was ∼300 mg.[42]

The pharmaceutical properties of **28** were also assessed. The crystalline free base of this compound was obtained from recrystallization with water, and it was characterized as its solid state form. The solubility of this form was evaluated in IV and PO vehicles that were acceptable for safety studies. After equilibration in vehicles and biorelevant media, compound **28** demonstrated solubility of 129 mg/mL in PEG200, 325 mg/mL in PEG400, 56 μg/mL in FaSSIF, and 0.87 mg/mL in

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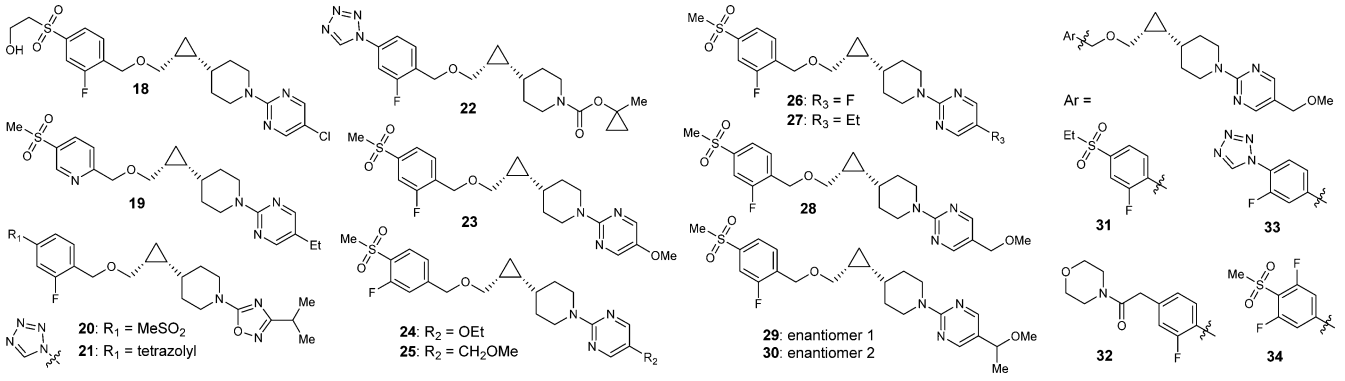
Table 1. SAR Efforts and Identification of Compound 28



cmpd	hGPR119[a] EC_{50} (nM)	mGPR119[a] EC_{50} (nM)	FaSSIF[b] (μM)	cLogP	HPLC LogD (pH 7)	rat $t_{1/2}$ (h)	pred. human $t_{1/2}$ (h)[d]
2	8.7 ± 3.4 (53%)	3.6 ± 0.1 (56%)	nd	2.2	3.7	1.8	nd
18	2.3 ± 0.3 (68%)	1.7 ± 0.4 (121%)	83	2.9	4.8	0.9	5–7
19	1.5 ± 0.1 (83%)	2.5 ± 2.1 (153%)	7	2.5	3.6	1.3	8–9
20	4.2 ± 1.0 (87%)	9.9 ± 5.5 (76%)	144	3.6	3.8	2.2	9–14
21	1.7 ± 0.1 (129%)	4.8 ± 0.1 (105%)	103	4.1	3.9	1.4	5–9
22	4.8 ± 1.8 (121%)	15 ± 0.3 (108%)	127	3.6	3.8	1.0	6–7
23	4.5 ± 2.9 (79%)	1.4 ± 1.2 (85%)	151	3.1	4.0	0.6	4–6
24	1.7 ± 1.1 (75%)	2.3 ± 0.6 (96%)	101	3.7	4.2	0.8	5–7
25	3.3 ± 1.9 (94%)	5.2 ± 2.1 (87%)	155	2.4	3.5	1.2[c]	8–9
26	2.4 ± 2.1 (85%)	4.5 ± 5.6 (131%)	92	2.8	4.2	1.5	12–13
27	2.5 ± 1.9 (98%)	5.5 ± 2.7 (115%)	140	3.6	4.3	1.0[c]	13
28	2.1 ± 1.3 (88%)	1.9 ± 0.8 (97%)	161	2.4	3.5	1.0	26
29	3.1 ± 1.2 (87%)	8.9 ± 9.5 (109%)	143	2.7	3.9	1.4	26
30	4.6 ± 5.0 (95%)	3.3 ± 1.6 (70%)	137	2.7	3.9	1.0[c]	21
31	7.1 ± 1.4 (58%)	12.5 ± 0.8 (87%)	129	2.9	3.8	2.1	21
32	3.2 ± 0.6 (104%)	3.7 ± 0.8 (99%)	172	3.0	3.4	0.4	2
33	1.1 ± 0.3 (84%)	3.8 ± 1.0 (75%)	133	2.9	3.7	3.0[c]	38
34	4.5 ± 1.9 (80%)	5.8 ± 3.3 (67%)	115	2.6	3.6	0.5	4

[a]Human and mouse GPR119 EC_{50} data expressed as mean ± SD ($n \geq 2$ independent experiments). The percentage in parentheses, % control at max dose: magnitude of cAMP stimulation expressed in % compared to an internal agonist control; the control was defined to have 100% cAMP stimulation. [b]Kinetic solubility in fasted-state simulated intestinal fluid (FaSSIF) at pH 6.5; in parentheses are cLogP values. [c]Effective $t_{1/2}$ calculated from MRT × 0.693 (for compounds exhibiting biphasic PK). [d]Predicted solely based on rat PK. Where there is only one number (compounds **27**–**34**), allometry was not used since rat Cl_{int} was much higher than human. Also, a predicted human half-life in the range of 8–48 h was considered acceptable for further profiling and could potentially support once daily dosing.

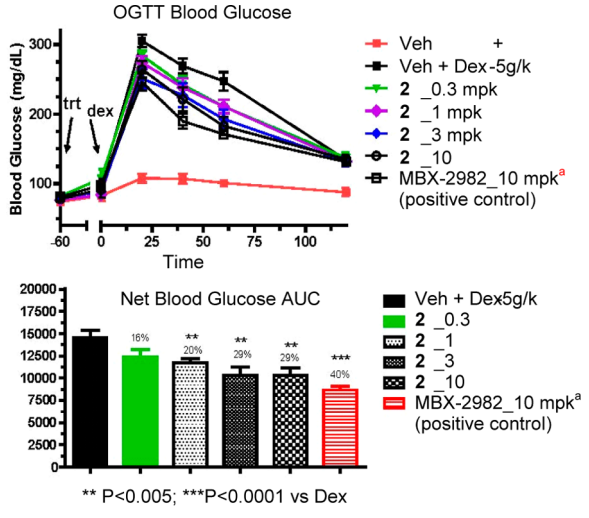


Figure 3. oGTT and PK/PD dose response of compound **28** in lean mice. [(a)]Positive control MBX-2982[40] was more efficacious than **28** probably because it had better mouse PK; the two compounds had comparable mouse potency.

Table 2. Plasma Pharmacokinetic Profile of Compound 28[a]

species	Plasma Cl (mL/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	F (%)
rat[b]	41	2.2	1.0	27
dog[c]	6.0	6.5	17	60
monkey[d]	16	2.0	2.3	5

[a]PPB for **28** (f_u): r 4.1%, d 5.5%, rh 3.2, h 4.9%. [b]Rat Wistar Han: Cl_{int} = 1000 mL/min/kg; Vd_u = 54 L/kg. [c]Dog Beagle. [d]Rhesus monkey.

simulated gastric fluid (SGF). Finally, compound **28** falls nicely within the druglike property space: MW 464, cLogP 2.4, HPLC LogD 3.5, LLE 6.3, and PFI 5.5.[43]

In summary, we have designed and synthesized a series of GPR119 agonists with properties that may be suitable for fixed-dose combination. A major focus of the optimization effort was to reduce the predicted $t_{1/2}$ in humans and improve solubility of the phenoxy lead. Half-life was reduced by modifying the unbound volume of distribution (Vd_u) through reducing lipophilicity, and solubility was improved by incorporating solubilizing groups such as MeO and MOM moieties. These efforts led to the identification of compound **28** that possessed excellent potency, selectivity, and improved physicochemical

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properties. Further optimization to improve overall PK profile and reduce projected human dose will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and characterization data of selected compounds, conditions for the biological assays, and protocol for pharmacokinetic and pharmacodynamic studies. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00207.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: 732-594-0321. Fax: 732-594-9556. E-mail: ping_liu2@merck.com.

Notes

The authors declare no competing financial interest.

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