Discovery and Preclinical Evaluation of BMS-711939, an Oxybenzylglycine Based PPAR α Selective Agonist

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S Supporting Information

ABSTRACT: BMS-711939 (**3**) is a potent and selective peroxisome proliferator-activated receptor (PPAR) α agonist, with an EC₅₀ of 4 nM for human PPAR α and >1000-fold selectivity vs human PPAR γ (EC₅₀ = 4.5 μ M) and PPAR δ (EC₅₀ > 100 μ M) in PPAR-GAL4 transactivation assays. Compound **3** also demonstrated excellent *in vivo* efficacy and safety profiles in preclinical studies and thus was chosen for further preclinical evaluation. The synthesis, structure–activity relationship (SAR) studies, and *in vivo* pharmacology of **3** in preclinical animal models as well as its ADME profile are described.

KEYWORDS: Peroxisome proliferator-activated receptor (PPAR) α selective agonist, high fat fed hamster model, human ApoA1 transgenic mice, pharmacokinetics

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors in the nuclear hormone receptor superfamily.^{1,2} Three subtypes of PPARs, namely, PPAR α , PPAR γ , and PPAR δ , have been identified in various species, including humans. PPAR α is highly expressed in the liver and regulates the expression of genes encoding lipid and lipoprotein metabolism.³ Upon binding of PPAR α ligand agonists, the resulting conformational change leads to the modulation of a number of PPAR α responsive genes, which in turn have pleiotropic effects on plasma lipoprotein levels, atherosclerosis and inflammation. There are currently several synthetic PPAR α ligands from the fibrate class of hypolipidemic drugs in clinical use.^{4,5} Although fibrates are ligands of PPARs, their binding affinity to PPAR α is relatively weak.^{6,7} This results in the relatively high doses (e.g., 200 mg of fenofibrate and 1.2 g of gemfibrozil) needed to achieve clinical efficacy, and unwanted side effects may occur at these high doses. Several potent PPAR α selective agonists have been progressed into various phases of clinical development, including GW590735⁸ and LY518674.⁹ However, the development of most of these potent and selective PPAR α agonist clinical candidates have been suspended. Recently, the PPAR α -selective α/γ dual agonist saroglitazar was approved in India for the treatment of diabetic dyslipidemia.¹⁰ A potent and efficacious PPAR α agonist with an excellent safety profile may provide an opportunity for the treatment of atherosclerosis and dyslipidemia as well as nonalcoholic steatohepatitis (NASH)¹¹ with minimized side effects. In addition, we considered that a more potent and selective PPAR α agonist with minimized disparity in interspecies PPAR

activities (particularly human vs rodent) will be useful for mechanism-based safety evaluation in preclinical animal models.

In continuation of our research in the field of PPARs to develop novel therapeutic agents to treat metabolic disorders,¹² we have reported the discovery of the selective PPAR α agonist **2**¹³ (Figure 1), which exhibited a high degree of selectivity

Figure 1. Fenofibric acid and BMS-687453.

toward PPAR α over PPAR γ (PPAR α EC₅₀ = 10 nM, EC₅₀ ratio: γ/α = 410), and demonstrated an excellent pharmacological and safety profile in preclinical studies. Inspection of the X-ray crystal structures of **2** bound to the PPAR α ligand binding domain (LBD; Figure 2) suggested that the carboxylic acid of **2** forms the well-recognized hydrogen-bonding network with neighboring residues: His440, Tyr464, Tyr314, and Ser280. The 1,3-oxybenzyl central core anchors the acid headgroup and the 4-chlorophenyl oxazole moiety into their appropriate binding pockets. Since the central phenyl core and the benzylic carbon

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Figure 2. X-ray crystal structure of **2** bound in PPAR α LBD with 2.7 Å resolution. Residues within 4.5 Å of benzylglycine are shown with thick sticks. Hydrogen bonds are shown as black dashed lines. The PDB deposition number is 3KDT.

are partially surrounded by hydrophobic residues such as Leu321, Ile317, and Phe318, we envisioned that small hydrophobic substituents on this region may be tolerated and that SAR investigations could be productively conducted within this portion of the molecule to further optimize the binding affinity/potency and/or reduce the human/rodent species difference in PPAR α activity. In this paper, we describe the SAR findings from this effort, which resulted in the discovery of **3** (BMS-711939). We also disclose the pharmacokinetic and *in vivo* efficacy profiling of **3**, which progressed into preclinical toxicology studies.

The syntheses of **3**–**6** are described in Scheme 1. Reductive amination of fluoro-substituted hydroxybenzaldehydes **21a**–**c** with glycine methyl ester hydrochloride **22** afforded the secondary amines **23a**–**c** in 85–95% yield. Reaction of **23a**–**c** with methyl chloroformate gave the corresponding methyl carbamates **24a**–**c** in 90–99% yield. Base-mediated alkylation of phenols **24a**–**c** with 4-(chloromethyl)-2-(4-chlorophenyl)-5-

methyloxazole **25a** at 80 °C provided the methyl esters **26a**–**c** in 86–99% yield. Basic hydrolysis of **26a**–**c** provided **3**–**5** in 90–93% yield. Compound **6** was synthesized in a similar fashion from intermediate **27**.¹⁴ Compounds **7**–**13** were synthesized from intermediate **24a** and oxazoles **25b**–**h**¹⁵ using the same synthetic sequence as described for **3**–**5**.

Compounds **14**–**20** were synthesized through a slightly different sequence as shown in Scheme 2. Alkylation of 2-fluoro-

Scheme 2. Synthesis of **14**–**20**^a

^aReagents and conditions: (a) K₂CO₃, MeCN, 80 °C; (b) **22**, Et₃N, MeOH, NaBH₄, 0 °C to rt; (c) ROCOCl, aq. NaHCO₃, THF; (d) LiOH, THF–H₂O, rt; (e) 1 N aq. HCl.

5-hydroxybenzaldehyde **21a** with 4-(chloromethyl)oxazole **25a** provided aldehyde **28** in 95% yield. Reductive amination of **28** with **22** afforded the secondary amine **29** in 90% yield. Reaction of **29** with different chloroformates and subsequent hydrolysis of the resulting esters provided compounds **14**–**20** in 80–93% yield.

Our initial effort to further optimize **2** focused on structural modifications of the central core and the benzylic position of the benzylglycine. The SAR results are shown in Table 1. Introducing a fluorine atom at the 2-position of central core resulted in a very potent and selective PPAR α /γ agonist **3** (EC₅₀ γ/α ratio = 1128), with PPAR α EC₅₀ = 4 nM and PPARγ EC₅₀ = 4.51 μM in the transactivation assays.¹³ This compound is ~2.5-fold more potent than **2** (EC₅₀ = 10 nM) at PPAR α and is slightly

Scheme 1. Synthesis of **3**–**6**^a

^aReagents and conditions: (a) Et₃N, MeOH, NaBH₄, 0 °C to rt; (b) methyl chloroformate, aq. NaHCO₃, THF; (c) **25a**, K₂CO₃, MeCN, 80 °C; (d) LiOH, THF–H₂O, rt; (e) 1 N aq. HCl.

Table 1. Transactivation EC₅₀ and Binding IC₅₀ of **2**–**6**^a

compd	R	αEC ₅₀ (nM)	γEC ₅₀ (nM)	γ/α EC ₅₀ ratio	αIC ₅₀ (nM)	γIC ₅₀ (nM)
2	H	10	4096	410	260	>48000
3	2-F	4.0	4511	1128	97	>98400
4	3-F	18	2819	157	1341	>15000
5	4-F	94	9168	98	1563	>15000
6		8.6	2857	332	671	>15000

^aCompounds were tested for agonist activity in hPPAR-GAL4 HEK transactivation assays. Transactivation efficacy was defined as percentage of maximum activity as compared with an appropriate standard set at 100% (100 μM fenofibric acid for PPAR α , 1.0 μM rosiglitazone for PPARγ). Full PPAR α intrinsic activity (>50% relative to 100 μM fenofibric acid) was observed for all tested compounds (*n* = 1–3).

less potent at PPAR γ than **2** (PPAR γ EC₅₀ = 4.1 μ M). These functional data correspond well to their PPAR α and PPAR γ binding affinities (Table 1).¹⁶ However, the opposite effects were observed when introducing a fluorine atom at the 3-position of central phenyl core; compound **4** (EC₅₀ γ/α ratio = 157) is less potent at PPAR α (EC₅₀ = 18 nM) and more potent at PPAR γ (EC₅₀ = 2.82 μ M) than **2**. Interestingly, the 4-fluoro-substituted analogue **5** is less active than **2** at both PPAR α and PPAR γ with a γ/α EC₅₀ ratio of 98. When an (*S*)-methyl group is placed at the α -position of the benzylglycine of **2**, the resulting **6** (EC₅₀ γ/α ratio = 332) has similar potency at PPAR α but is more potent at PPAR γ than **2**. These results indicate that a subtle substitution change on the central phenyl core or at the benzylic position can result in changes in both the PPAR α and PPAR γ agonist activities and thus the PPAR α/γ selectivity. The 2-fluorophenyl glycine analogue **3** has the most potent PPAR α agonist activity and is also the most selective PPAR α agonist among the three isomeric monofluorinated analogues.

With lead compound **3** in hand, we systematically investigated the SAR of the “left-hand” phenyl ring substituents and the “right-hand” carbamate substituents, as shown in Table 2. In

Table 2. In Vitro Activity of 2-Fluoro Substituted Benzylglycine **3 and **7–20**^a**

3, 7–20

compd	R ¹	R ²	α EC ₅₀ (nM)	γ EC ₅₀ (nM)	γ/α EC ₅₀ ratio
3	Cl	Me	4.0	4511	1128
7	Me	Me	2.8	2182	787
8	F	Me	14.5	10010	691
9	H	Me	59	8607	146
10	CF ₃	Me	3.6	2062	566
11	OCF ₃	Me	4.3	2384	556
12	C(CH ₃) ₃	Me	2.7	414	154
13	SO ₂ Me	Me	>2500	>25000	NA
14	Cl	Et	4.0	4273	1085
15	Cl	<i>n</i> -Pr	3.4	2013	594
16	Cl	F(CH ₂) ₃	10.6	4383	413
17	Cl	<i>n</i> -Bu	2.8	1235	435
18	Cl	<i>i</i> -Bu	2.3	1504	666
19	Cl	4-MePh	5.6	1255	224
20	Cl	4-MeOPh	6.8	1087	160

^aSee notes for Table 1.

general, all the 2-fluoro-phenyl central core based compounds show enhanced PPAR α agonist activity and PPAR α/γ selectivity versus their corresponding unsubstituted phenyl analogues.¹³ On the “left-hand” phenyl ring (of the oxazole), while the compound without a *para* substituent (**9**, PPAR α EC₅₀ = 59 nM, γ/α ratio = 146) is ~15-fold less potent and far less selective than **3**, the *para*-fluoro compound **8** is only about 3.5-fold less potent than **3** at PPAR α and maintains high selectivity (PPAR α EC₅₀ = 15 nM, γ/α ratio = 691). Compounds with a nonpolar substituent (**7**, **10–12**) at the *para* position generally have similar PPAR α potencies to **3**. However, the relatively bulky polar methylsulfonyl substituent (**13**) obliterates both PPAR α and γ activities. Interestingly, a bulky aliphatic substituent such as *t*-butyl (**12**) significantly improved PPAR γ potency while maintaining PPAR α activity, thus resulting in a significant reduction in PPAR α selectivity versus **3**. These results suggested that polarity and steric effects play important roles in determining PPAR α/γ functional activities and selectivity in this portion of the molecule. This SAR study of the “left-hand” phenyl ring substituents showed that the 4-Cl-phenyl moiety was optimal, providing potent PPAR α activity and the highest level of PPAR α selectivity.

The corresponding SAR study of the “right-hand” side carbamate showed that simple alkyl carbamates (**14–20**) generally provide excellent PPAR α potency and selectivity (EC₅₀ γ/α ratio > 400-fold), with the ethyl carbamate **14** having almost the same PPAR α potency and selectivity (PPAR α EC₅₀ = 4 nM, γ/α ratio = 1085) as **3**. Interestingly, replacing the terminal methyl group of the *n*-propyl carbamate **15** with a fluoromethyl (**16**) resulted in a >2-fold decrease in potency at both PPAR α and γ , but retained the high α/γ selectivity. The aryl carbamates (**19** and **20**) were also potent PPAR α agonists, but with slightly lower α/γ selectivity compared to the simple alkyl carbamates. The overall SAR in this carbamate region is similar to that previously observed with **2**, with the methyl carbamate being optimal.¹³

The PPAR α potency and selectivity of **3** were further confirmed by testing it in cotransfection assays in HepG2 cells using full length human PPAR α and PPAR γ receptors.¹³ In these assays, compound **3** showed excellent PPAR α potency (EC₅₀ = 5 nM) with >320-fold selectivity vs PPAR γ (EC₅₀ > 1.61 μ M). These results correlated well with the data observed from the primary GAL-4 HEK transactivation based screening assays as shown in Table 1. Compound **3** also is a full PPAR α agonist in the rodent assays and is >2.5-fold more potent than **2** in rodent PPAR α functional assays, with EC₅₀s of 178, 144, and 123 nM for hamster, mouse, and rat, respectively.¹⁷ Importantly, compound **3** showed negligible activity (EC₅₀ for transactivation >25 μ M and efficacies <15% of standard) against a panel of human

Table 3. Pharmacokinetic Profile of **3^a**

species	dose route	dose (mg/kg)	<i>t</i> _{max} (h)	<i>C</i> _{max} (μ M)	AUC ^b (μ M·h)	CL _{pl} (mL/min/kg)	V _{ss} (L/kg)	<i>t</i> _{1/2} (h)	F%
mouse	IV	5			13	13.8	0.6	1.8	
	PO	10	0.25	22.7	17				66
rat	IV	4			9.4	15.3 $\pm$ 0.7	2.2 $\pm$ 0.5	3.3	
	PO	8	0.3 $\pm$ 0.1	14.9	32				100
dog	IV	1			3.5	10.7 $\pm$ 2.4	2.1 $\pm$ 1.2	5.5	
	PO	2	0.8 $\pm$ 0.3	1.5	4.0				59
monkey	IV	1			7.5	5.9 $\pm$ 2.7	3.9 $\pm$ 1.5	26.3	
	PO	2	0.9 $\pm$ 0.1	1.4	8.5				65

^aFor each experimental study, *n* $\geq$ 3. ^bAUC_{0–8h} reported here, not AUC_{INF}.

nuclear hormone receptors, including PPAR δ , LXR, GR, and RXR.

Compound 3 did not show any significant activity in liability profiling assays (e.g., in 5 human CYP isozymes, PXR, and hepatocyte toxicity assays (HHA)).¹⁸ No *in vitro* liabilities were noted in (1) extensive screens for receptor/enzyme binding inhibition; (2) assays for bacterial mutagenicity or CHO cell clastogenicity; and (3) an exploratory Ames test at up to 5000 μ g per plate in TA98 and TA100 strains. Cardiovascular safety evaluations were carried out on 3: (1) no hERG and sodium channel activity was observed at concentrations up to 30 and 10 μ M, respectively; and (2) no drug-related changes in hemodynamic and electrocardiographic (ECG) effects were observed at up to 20 mg/kg of 3 in a single-dose monkey telemetry study.

Compound 3 also exhibited an excellent pharmacokinetic profile across all tested animal species. Table 3 shows the pharmacokinetic parameters of 3 in mouse, rat, dog, and monkey (cynomolgus). It exhibited low plasma clearance in the mouse, rat, and monkey, and moderate plasma clearance in the dog. The half-life of ranged from 1.8 h in mouse to 26.3 h in monkey. It also had excellent absolute oral bioavailability ranging from 59% (dog) to 100% (rat). Additionally, it has excellent crystalline aqueous solubility (367 μ g/mL at pH 7.2).

Compound 3 has been profiled in multiple animal models of dyslipidemia.¹⁹ In a 10-day dose response study in the human ApoA1 transgenic mouse,²⁰ it robustly and dose-dependently increased both ApoA1 and HDL cholesterol, as shown in Table 4. In this study, the reference compound fenofibrate (at a dose of

Table 4. Effect of 3 and Fenofibrate on Plasma Parameters in Human ApoA1 Transgenic Mice^a

treatment	serum hu-ApoA1 mg/dL $\pm$ SEM (% change)	triglycerides mg/ dL $\pm$ SEM (% change)	HDLc mg/dL $\pm$ SEM (% change)
vehicle	731 $\pm$ 73	69.4 $\pm$ 6.5	192 $\pm$ 8
fenofibrate, 100 mg/kg/day	5592 $\pm$ 403 (665%*)	46.9 $\pm$ 5.8 (−32.5%*)	362 $\pm$ 23 (88%*)
3, 3 mg/kg/day	1431 $\pm$ 179 (96%*)	59.6 $\pm$ 5.1 (−14.2%)	223 $\pm$ 16 (16%)
10 mg/kg/day	3656 $\pm$ 865 (400%*)	53.1 $\pm$ 3.7 (−23.5%)	334 $\pm$ 19 (74%*)
50 mg/kg/day	6193 $\pm$ 1147 (747%*)	29.1 $\pm$ 4.6 (−58.1%*)	402 $\pm$ 18 (109%*)

^a p < 0.05 compared to vehicle-treated group (n = 10). Data represent the mean $\pm$ SEM (n = 10).

100 mg/kg) raised serum HDL cholesterol by 88% and lowered triglycerides by 33% after 10 days of dosing. By comparison, compound 3 (at a dose of 50 mg/kg/day) raised HDL cholesterol by 109% and lowered triglycerides by 58%, respectively. These data clearly demonstrated that 3 robustly elevated HDLc and lowered triglycerides in the human ApoA1 transgenic mouse model.

In a 21-day head-to-head comparison study in a high fat fed hamster model,²¹ both 2 and 3 dose dependently lowered triglycerides and LDL levels. As shown in Table 5, after 3 weeks of dosing, compound 3 lowered fasting plasma LDLc by 61% at the 3 mg/kg/day dose and 87% at the 10 mg/kg/day dose, respectively; it also reduced plasma triglycerides by 50%, 74%, and 85% at the 1, 3, and 10 mg/kg/day doses, respectively. In comparison, compound 2 lowered fasting plasma LDLc by 46% at the 3 mg/kg/day dose and 60% at the 10 mg/kg/day dose, respectively; it reduced plasma triglycerides by 40%, 45%, and

Table 5. Effect of Compounds 2 and 3 on Lipid Parameters in High Fat-Fed Hamsters^a

entry	liver TG mg/ dL $\pm$ SEM (% change)	liver chol mg/dL $\pm$ SEM (% change)	plasma LDLc mg/dL $\pm$ SEM (% change)	plasma TG mg/dL $\pm$ SEM (% change)
high fat vehicle	24.1 $\pm$ 1.5	16.9 $\pm$ 1.2	91.7 $\pm$ 8.1	173.5 $\pm$ 17
3, 10 mg/kg	12.5 $\pm$ 1.2 (−48%*)	5.5 $\pm$ 0.5 (−67.5%*)	12.2 $\pm$ 4.6 (−87%*)	25.2 $\pm$ 2.6 (−85%*)
3 mg/kg	14.5 $\pm$ 0.8 (−39.8%*)	7.3 $\pm$ 0.7 (−56.8%*)	35.7 $\pm$ 4.5 (−61%*)	44.7 $\pm$ 4.3 (−74%*)
1 mg/kg	19.6 $\pm$ 0.9 (−18.7%*)	14.7 $\pm$ 1.9 (−13%)	69.3 $\pm$ 11 (−24%)	85.7 $\pm$ 18 (−50%*)
2, 10 mg/kg	18.5 $\pm$ 1.2 (−23%*)	10.0 $\pm$ 1.0 (−40.8%*)	36.3 $\pm$ 5.7 (−60%*)	39.7 $\pm$ 3.6 (−77%*)
3 mg/kg	19.9 $\pm$ 3.0 (−17%)	14.3 $\pm$ 2.4 (−15.4%)	49.9 $\pm$ 8.4 (−46%*)	95.2 $\pm$ 13 (−45%*)
1 mg/kg	22.6 $\pm$ 1.1 (−6%)	20.7 $\pm$ 2.1 (+22%)	89.3 $\pm$ 9.4	103.2 $\pm$ 11 (−40%*)

^a p < 0.05 versus vehicle control. Data represent the mean $\pm$ SEM (n = 8).

77% at the 1, 3, and 10 mg/kg/day doses, respectively. For liver triglycerides and cholesterol, compound 3 lowered liver cholesterol by 57% at the 3 mg/kg/day dose and 68% at the 10 mg/kg/day dose, respectively; it also reduced liver triglycerides by 19%, 40%, and 48% at the 1, 3, and 10 mg/kg/day doses, respectively. By comparison, compound 2 only impacted the hepatic lipids at the 10 mg/kg dose level (41% for liver cholesterol and 23% for liver triglycerides). Overall, compound 3 significantly lowered plasma triglycerides and LDLc in a chronic dyslipidemic hamster model and compares favorably to 2 in terms of both potency and overall efficacy in lipid lowering in this model.

In summary, the SAR investigation on the oxybenzylglycine-based lead 2 led to the discovery of a series of 2-fluoro-substituted benzylglycine analogues as potent and highly selective PPAR α agonists. BMS-711939 (3) was found to be a potent and highly selective PPAR α agonist (PPAR α EC₅₀ = 4 nM, EC₅₀ γ/α ratio = 1128) that is highly efficacious in elevating HDLc in human ApoA1 transgenic mice and lowering LDLc in dyslipidemic hamsters in chronic efficacy studies. It also robustly lowers triglycerides in both of these animal models. In comparison to 2, BMS-711939 is more potent at PPAR α and more selective against PPAR γ , and shows superior potency on lowering LDLc and TG in hamsters. On the basis of its potency and selectivity, its excellent *in vitro* liability profile, favorable pharmacokinetics and pharmacodynamic effects in animal models, compound 3 was selected for further evaluation in preclinical animal toxicity studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.6b00033.

Synthetic methods, characterization of key compounds, and biology assay protocols (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PPAR peroxisome proliferator activated receptor; LBD ligand binding domain; LDLc low-density lipoprotein-cholesterol; HDLc high-density lipoprotein-cholesterol; TG triglycerides; CYP cytochromes P450; hERG Human Ether-à-go-go-Related Gene; LXR liver X receptor; GR glucocorticoid receptor; PXR pregnane X receptor; RXR retinoid X receptor

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