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Synthesis and structure–activity relationships of 2-aryl-4-oxazolylmethoxy benzylglycines and 2-aryl-4-thiazolylmethoxy benzylglycines as novel, potent PPARα selective activators- PPARα and PPARγ selectivity modulation

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ABSTRACT

The synthesis and follow-up SAR studies of our development candidate **1** by incorporating 2-aryl-4-oxazolylmethoxy and 2-aryl-4-thiazolylmethoxy moieties into the oxybenzylglycine framework of the PPARα/γ dual agonist muraglitazar is described. SAR studies indicate that different substituents on the aryloxazole/thiazole moieties as well as the choice of carbamate substituent on the glycine moiety can significantly modulate the selectivity of PPARα versus PPARγ. Potent, highly selective PPARα activators **2a** and **2l**, as well as PPARα activators with significant PPARγ activity, such as **2s**, were identified. The in vivo pharmacology of these compounds in preclinical animal models as well as their ADME profiles are discussed.

The PPARs belong to a nuclear hormone receptor superfamily which act as transcription factors in the regulation of genes involved in glucose and lipid homeostasis.[1] Three PPAR subtypes have been identified: PPARα, PPARγ and PPARδ (β). PPARα is highly expressed in liver, but is also present in heart, kidney, and muscle, and regulates the transcription of numerous genes encoding proteins involved in lipid and lipoprotein metabolism.[2] Elevated circulating levels of triglycerides (TG) and low circulating levels of high-density lipoprotein cholesterol (HDL-c) represent independent risk factors for coronary artery disease (CAD).[3] Activation of PPARα, or both PPARα and γ should address these risk factors.[4] Recent studies have shown that activation of PPARα results in beneficial effects on prevention of atherosclerosis and liver inflammation.[4,5] Currently marketed PPARα agonists are the fibrate class of drugs (including fenofibrate[6] and gemfibrozil[7]), which moderately elevate HDL levels and lower triglyceride and low-density lipoprotein cholesterol (LDL-c) levels. Despite the widespread use of fibrates for the treatment of dyslipidemia in patients, their efficacy is likely limited by their relatively weak PPARα functional activity (αEC_{50} >15 μM).[8] In addition, the efficacious human clinical doses of the fibrates need to be relatively high (200 mg/day for fenofibrate and 1200 mg/day for gemfibrozil) in order to achieve even moderate lipid lowering effects. Therefore, the discovery of more potent and selective PPARα agonists should result in anti-dyslipidemic agents with enhanced efficacy in the treatment of CV disease/atherosclerosis.

PPARγ is highly expressed in adipose tissue and macrophages. PPARγ agonists, as exemplified by the thiazolidinedione class of drugs (e.g., rosiglitazone and pioglitazone), have been primarily used for the treatment of diabetes. Recent data has indicated that PPARγ agonism may also result in anti-dyslipidemic and anti-atherosclerotic effects in animals and humans.[9] However, due to the undesirable side-effects (e.g., edema and weight gain) occasionally observed in the clinic with highly selective and potent PPARγ agonists, it may be desirable to incorporate PPARγ functional activity

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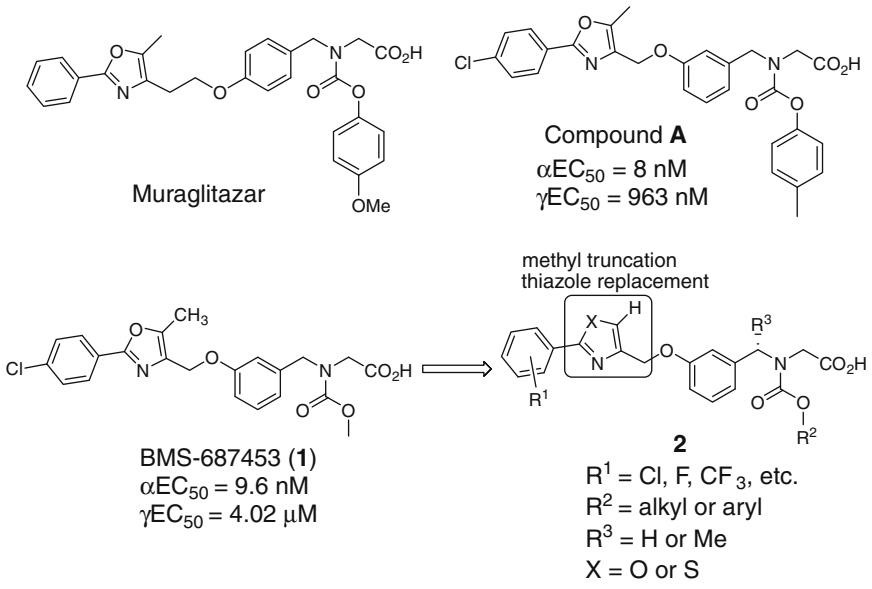


Figure 1. Structure of Muraglitazar, compound **A**, and BMS-687453 (**1**). SAR of 2-aryl-4-oxazolylmethoxy benzylglycines and 2-aryl-4-thiazolylmethoxy benzylglycines (**2**).

only as a minor (but still measurable) component of selective PPARα agonists. Therefore, we set out to explore the SAR of the oxybenzylglycine[10a,b] framework of our PPARα/γ dual agonist muraglitazar[10c,d] with the goal of identifying PPARα agonists which have a range of (relatively low) PPARγ functional activity. Based on these SAR studies, we identified the PPARα selective agonist compound **A** as a starting point for the program (Fig. 1). Through lead optimization of **A**, we discovered our initial development candidate, BMS-687453, a highly potent and selective PPARα agonist (**1**, αEC_{50} = 9.6 nM; $\gamma EC_{50}/\alpha EC_{50}$ = 420).[11] In the current letter we disclose the follow-up SAR studies to BMS-687453, as we continue to be interested in profiling other structurally related PPARα agonists, particularly those compounds with a significantly greater PPARγ component (but not sufficient to elicit the PPARγ-mediated side-effects).

As a starting point, the X-ray structure of compound **A** bound to the PPARα ligand-binding domain (LBD) was determined.[12] The ligand binds in a complementary manner to the Y-shaped ligand-binding pocket while the carbonyl group of the acid forms hydrogen bonds with SER280, TYR314, HIS440, and TYR464 (Fig. 2). These critical interactions stabilize the AF-2 region of the PPARα LBD and define the receptor's agonist conformation. The methyl group in the 5-position (blue arrow (a)) of the oxazole moiety does not visibly interact with the receptor.

Based on this structural analysis we decided to explore the SAR of the des-methyl oxazole and thiazole analogs of **1** (Fig. 1).[13] This letter will discuss the structure–activity relationship of this modification (2-aryl oxazole and 2-aryl-thiazole) as well as the structural modifications that were carried out concurrently in the glycine-carbamate portion of the skeleton of **1**. A wide range of selectivity of PPARα versus PPARγ has been achieved through these modifications. From these SAR studies, we have identified **2a** and **2l** as highly selective PPARα activators with minimal PPARγ activity. In addition, **2s** was identified as a moderately selective PPARα activator with significant PPARγ efficacy. The pharmacology of these compounds in a high fat-fed hamster model as well as their ADME profiles will be discussed.

We began with the synthesis of the key intermediate secondary amine **6** to enable the rapid exploration of the SAR of the carbamate moiety of compound **2** (Scheme 1). Phenol **3** was alkylated with a variety of 2-aryl-4-chloromethyl oxazoles and 2-aryl-4-chloromethyl thiazoles (**4**) under standard conditions (K_2CO_3/acetonitrile/reflux) to afford compounds **5** in 75–95% yield. After the deprotection of the Boc group (4 M HCl in dioxane/MeOH), the secondary amine **6** was obtained quantitatively as its HCl salt. Carbamate formation (**6** reacts with a variety of aryl or alkyl chloroformates), followed by subsequent ester deprotection (aqueous LiOH in THF) afforded analogs of general structure **2** in excellent yield.

2-Aryl-4-chloromethyl oxazoles and 2-aryl-4-chloromethyl thiazoles (**4**) were synthesized by a slight modification of a literature procedure[14] (Scheme 2). Commercially available substituted benzamides or thiobenzamides (**7**) react smoothly with 1,3-dichloroacetone (**8**) upon heating in a sealed tube in the presence of 1,2-dichloroethane to afford **4** in 40–80% isolated yield.

We first synthesized **2a**, the direct des-methyloxazole analog of **1**, for a head-to-head comparison (Table 1). Compound **2a** remains a full agonist at PPARα, although it is ~sixfold less potent (αEC_{50} = 64 nM, maximal efficacy = 78%) versus its parent **1** (αEC_{50} = 9.6 nM, maximal efficacy = 79%). Significantly, the maximal efficacy of **2a** at PPARγ was decreased (46% vs 82% for **1**). Thus,

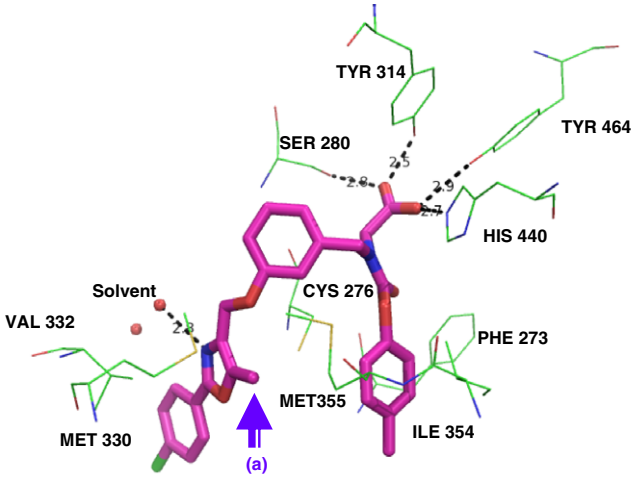
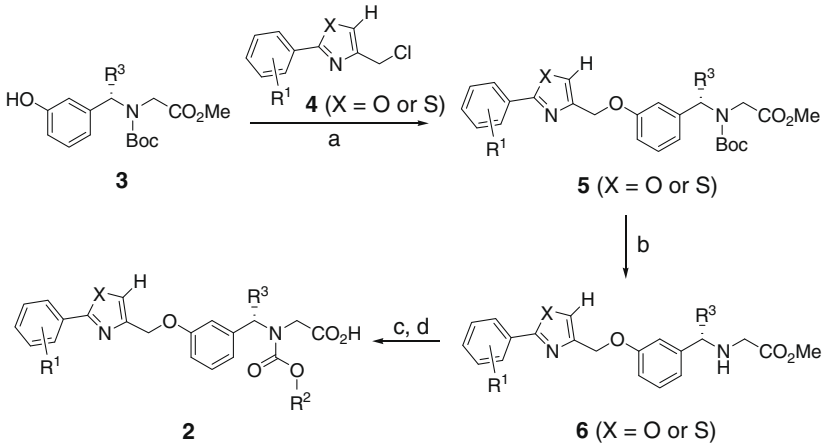
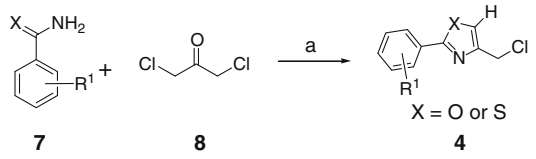


Figure 2. X-ray crystal structure of PPARα in complex with compound **A** at 2.07 Å resolution. The ligand is shown with purple carbons and thicker lines while the protein is shown with green carbons. The protein residues displayed are those within 3.5 Å from the ligand. The blue arrow (a) identifies the methyl group of interest of the oxazole ring.



Scheme 1. The synthesis of compound **2**. Reagents and conditions: (a) K_2CO_3/acetonitrile, reflux, 12 h; (b) 4 M HCl in dioxane/MeOH, rt, 5 h; (c) R_2O-C(O)-Cl, K_2CO_3 (aqueous)-THF, rt, 2 h; (d) LiOH (aqueous)-THF, rt, 12 h.



Scheme 2. The synthesis of **4**. Reagents and conditions: (a) 1,2-dichloroethane, 130 °C, 5 h.

by eliminating the methyl group in the oxazole of **1**, retention of full PPARα agonist activity with only partial PPARγ agonist activity has been achieved. We postulated that further structural modifications based on des-methyl analogs such as **2a** would enable us to achieve our goal of identifying PPARα agonists which have a range of PPARγ functional activity. Interestingly, in a hamster PK study, **2a** showed improved oral exposure at 10 mpk dose versus **1** (C_{max} 19.4 μM, AUC 55.1 μM h versus **1**: C_{max} 3.6 μM, AUC 7.6 μM h).

The SAR of different substituents on the aryl group in the oxazole/thiazole moieties in conjunction with modification of the benzylic R^3 group (methyl vs H) has been examined extensively and the data for a set of select substituents are shown in Table 1. In the oxazole series, where R^3 = H (**2a**–**2h**), **2c** (R^1 = 4′-Me) shows the highest PPARα potency and the greatest selectivity versus PPARγ (α/γ EC_{50} ratio = 522). Smaller groups such F and H in the 4′-position attenuate PPARα functional activity (**2d**: αEC_{50} = 234 nM; **2e**: αEC_{50} = 1225 nM). Substituents at the 3′- and 2′- positions of the aryl group also attenuate PPARα functional activity, as seen in **2f**, **2g**, and **2h**. When R^3 = Me, **2i** shows comparable PPARα functional activity and selectivity versus **2a**, while **2j** is twofold less potent than **2c**. The analogs in the thiazole series (**2k** – **2p**) show similar SAR trends as observed in the oxazole series.

A PDK4 acute gene induction assay in normal chow-fed hamsters was used to prioritize compounds for chronic studies in hamsters.[17] Only PPARα or PPARα/γ dual agonists robustly induce PDK4 and HD (hydratase) mRNA levels in the liver. At a 10 mpk dose, both **2a** and **2l** show increased induction of both PDK4 and HD versus 100 mpk of fenofibrate (Table 2).

Table 2
Hamster acute gene induction

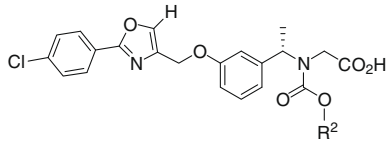
Entry[a]	Hamster acute PDK4[b] (% induction)	Hamster acute HD[b] (% induction)
1	230	277
2a	505	192
2l	308	126
Fenofibrate	100	100

[a] All compounds were dosed at 10 mpk, except fenofibrate (dosed at 100 mpk).
[b] Results of PDK4 mRNA and HD mRNA level in liver measured at 6 h post dose relative to fenofibrate. Fenofibrate (100 mpk) was used as the reference and its activity is expressed as 100% for both PDK4 and HD.

Table 1
Highly selective PPARα activators: In vitro activities of selected analogs **2** (see Scheme 1 for structure, R^2 = Me) at human PPARα and γ

Entry	X	R^1	R^3	αEC_{50} (nM) (maximal efficacy)[15]	γEC_{50} (nM) (maximal efficacy)[15]	Ratio
2a	O	4′-Cl	H	64 (78%)	9193 (46%)	143
1	—	—	—	9.6 (79%)	4017 (82%)	418
2b	O	4′-CF_3	H	68 (74%)	4815 (34%)	71
2c	O	4′-Me	H	29.9 (85%)	15,580 (94%)	522
2d	O	4′-F	H	235 (88%)	>25,000 (ND)	>106
2e	O	4′-H	H	1225 (105%)	>25,000 (ND)	>20
2f	O	3′-Me	H	451 (92%)	>25,000 (ND)	>55
2g	O	2′-F-4′-F	H	1086 (78%)	>25,000 (ND)	>23
2h	O	3′-Cl-4′-F	H	395 (97%)	6386 (54%)	16
2i[16]	O	4′-Cl	Me	73 (65%)	>8300 (189%)	114
2j[16]	O	4′-Me	Me	87 (87%)	20,690 (130%)	156
2k	S	4′-Cl	H	90 (90%)	4692 (35%)	52
2l	S	4′-CF_3	H	46.6 (73%)	3443 (73%)	74
2m	S	4′-Me	H	41.8 (71%)	9288 (84%)	222
2n	S	4′-H	H	304 (70%)	>25,000 (ND)	>82
2o	S	3′-Cl	H	1453 (117%)	4018 (54%)	2.8
2p	S	2′-Cl	H	>2500	5036 (55%)	2

Table 3
PPARα activators with significant PPARγ activity: In vitro activities of a set of selected analogs **2** (R^2 = aryl) at human PPARα and γ



Entry	R^2	αEC$_{50}$ (nM) (maximal efficacy)[15]	γEC$_{50}$ (nM) (maximal efficacy)[15]	Ratio[a]
2q	Ph-	145 (53%)	1692 (43%)	12
2r	3-Me-Ph-	22 (62%)	571 (83%)	26
2s	3-MeO-Ph-	13 (69%)	772 (95%)	59
2t	4-MeO-Ph-	66 (69%)	970 (62%)	15
2u	2-F-5-Me-Ph-	471 (56%)	710 (58%)	1.5
2v	3-MeO-4-F-Ph-	51 (64%)	1444 (74%)	28

[a] Ratio = γEC$_{50}$/αEC$_{50}$.

PPARγ agonists are also known to be anti-dyslipidemic/anti-atherosclerotic agents,[9] but with the limitation that potent PPARγ activation can result in undesirable side-effects such as edema. Therefore, in addition to highly PPARα selective agonists, we were also interested in profiling PPARα agonists which had a significant component of PPARγ functional activity (e.g., compounds with a γEC$_{50}$/αEC$_{50}$ ratio of ~30–60, with maximal functional activity of PPARγ at 1 μM >50%). From the SAR studies summarized in Table 1, we have learned: (1) oxazole analogs generally show increased potency at PPARγ versus thiazole analogs; (2) PPARα selectivity versus PPARγ is decreased when R_3 is methyl rather than hydrogen. Therefore, we focused on the SAR of analogs which vary the carbamate R^2 using 2-(4′-chlorophenyl)oxazolylmethoxy as the 'left hand side' and R^3 is methyl (data shown in Table 3).[16]

As can be seen from the results shown in Table 3, the unsubstituted phenyl carbamate (**2q**) has moderate PPARα functional activity (αEC$_{50}$ = 145 nM) and selectivity (γEC$_{50}$/αEC$_{50}$ = 12) as well as partial PPARγ agonism activity (maximal efficacy is only 43%). Compound **2q** thus shows decreased potency at PPARα and increased potency at PPARγ versus the methyl carbamate analog **2a**. Substituents such as methyl or methoxy group at the 3-position of the phenyl group (**2r** and **2s**) result in potency increases both at PPARα (7- to 10-fold) and PPARγ (2- to 3-fold). Substituents at other positions on the phenyl group such as 2′- and 4′- (eg., **2t**), and disubstituted analogs (eg., **2u** and **2v**) give a less favorable in vitro profile. Notably, **2s** is a 59-fold PPARα selective PPARα/γ activator based on EC$_{50}$ ratios, although its effective selectivity is probably somewhat higher in view of its partial activity at PPARγ (55% maximal efficacy at 1 μM concentration).

Recently, Wang et al. reported that the high fat-fed hamster is a unique animal model to evaluate the effects of PPARα selective agoinsts on dyspidemia.[18] We therefore treated high fat-fed hamsters with compounds **2a**, **2l**, and **2s** at a dose of 10 mg/kg via oral gavage once daily (qd) for **21** days, and the pharmacological effects (HDL-c and TG) as well as drug concentrations were measured in the end of the studies (Table 4). Studies showed that **2a**, **2l**, and **2s** were highly efficacious in reducing HDL-cholesterol (39−52% lowering)[19] and triglycerides (49−84% lowering), with comparable or better effects than **1**. In addition, both **2a** and **2l** lowered LDL-c significantly at 10 mpk (−84% and −68%, respectively).

Table 4
Hamster PPARα EC$_{50}$, in vivo studies[a] and exposure

Entry	Hamster αEC$_{50}$ (nM) (maximal efficacy)[14]	HDL-c lowering	TG lowering	Liver concn[c] (μM)	Plasma concn[d] (μM)
2a	979 (84%)	−44%*[b]	−84%*	83.8	72.9
2l	811 (65%)	−52%*	−72%*	86.8	10.9
2s	66 (71%)	−39%*	−49%	ND	ND
1	488 (83%)	−20	−77*	55.2	2.81

[a] Hamsters were on high fat diet for 2 weeks before treatment (n = 8). Vehicle: 5% cremophor, 10% NMP, 5% EtOH, 80% water. All compounds were dosed at 10 mg/kg po.
[b*] Indicates statistical significance (p value <0.05, Dunnett).
[c] Liver drug level at 1 h post-dose (fed).
[d] Fasted plasma drug level at 18 h post dose.

Table 5
Pharmacokinetic profile of **2a**, **2l** and **1** in male Sprague-Dawley rats (n = 2)

Compound	**2a**	**2l**	**1**
V_{ss} (L/kg)	0.2	0.3	0.7
CL (mL/min kg)	0.7	0.5	4.3
$T_{1/2}$ (h)	4.6	7.9	3.2
MRT (h)	10.7	6.0	2.8
F (%)	75	75	91

Vehicle: 10% NMP, 20% PEG-400, 70% potassium phosphate buffer. Doses: IV: 5 mg/kg; PO: 10 mg/kg.

Both **2a** and **2l** have excellent ADME profiles as well as good oral bioavailability in several animal species. The ADME data for compounds **2a**, **2l**, and **1** in SD rats are shown in Table 5. In cynomolgus monkeys, **2a** has a reasonable plasma half-life ($t_{1/2}$ = 9 h) and low systemic clearance (CL = 1 mLmin^{-1}kg^{-1}), while **2l** has a $t_{1/2}$ of 8 h and clearance of 3 mLmin^{-1}kg^{-1}.

Compound **2a** is the des-methyl analog of **1**. The lack of a substituent at the 5-position of the oxazole ring of **2a** theoretically could increase the risk of formation of reactive metabolites, for example, an epoxide. This concern was addressed by subjecting analogs from this series to a glutathione (GSH) adduct assay.[20] Compounds **2a** and **2l** were incubated in human liver microsomes in the presence of GSH for 30 min, and LC–MS techniques were then used to quantify GSH adduct formation. The data showed no GSH incorporation into either **2a** or **21**, thus suggesting that reactive metabolite formation at the 4- or 5-position of either the oxazole/thiazole does not represent an issue.

We have explored the SAR of PPARα agonists based on the novel 2-aryl-4-oxazolyl methoxybenzylglycine and 2-aryl-4-thiazolylmethoxy benzyl glycine frameworks. We have discovered that: (1) analogs from both series show improved oral exposure compared with the corresponding 5-methyl oxazole compounds; (2) substituents in the phenyl ring on the oxazole/thiazole moiety as well as the carbamate of the glycine can significantly modulate the selectivity of PPARα versus PPARγ; (3) PPARγ maximal efficacy for these two series of analogs is generally reduced versus the corresponding 5-methyl oxazole analogs. Highly selective PPARα modulators such as **2a** and **2l** have been identified which showed excellent lipid lowering effects at 10 mg/kg in chronic studies in high fat-fed hamsters. In addition, through an SAR study of a series of aryl carbamate analogs in conjunction with the 2-aryl-4-oxazole and 2-aryl-4-thiazole moieties, we have identified PPARα agonists with a significant PPARγ component, such as **2s**, which have also shown good anti-dyslipidemic effects in vivo.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.03.019.

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16. Compounds **2i** and **2j** have the (*S*)-configuration, as indicated in Scheme 1. We have found that their corresponding (*R*)-enantiomers are less active.
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