Design and Synthesis of Dual Peroxisome Proliferator-Activated Receptors γ and δ Agonists as Novel Euglycemic Agents with a Reduced Weight Gain Profile

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Abstract: The design and synthesis of the dual peroxisome proliferator-activated receptor (PPAR) γ/δ agonist (*R*)-3-{4-[3-(4-chloro-2-phenoxy-phenoxy)-butoxy]-2-ethyl-phenyl}-propionic acid (**20**) for the treatment of type 2 diabetes and associated dyslipidemia is described. The compound possesses a potent dual hPPAR γ/δ agonist profile (IC_{50} = 19 nM/4 nM; EC_{50} = 102 nM/6 nM for hPPARγ and hPPARδ, respectively). In preclinical models, the compound improves insulin sensitivity and reverses diabetic hyperglycemia with less weight gain at a given level of glucose control relative to rosiglitazone.

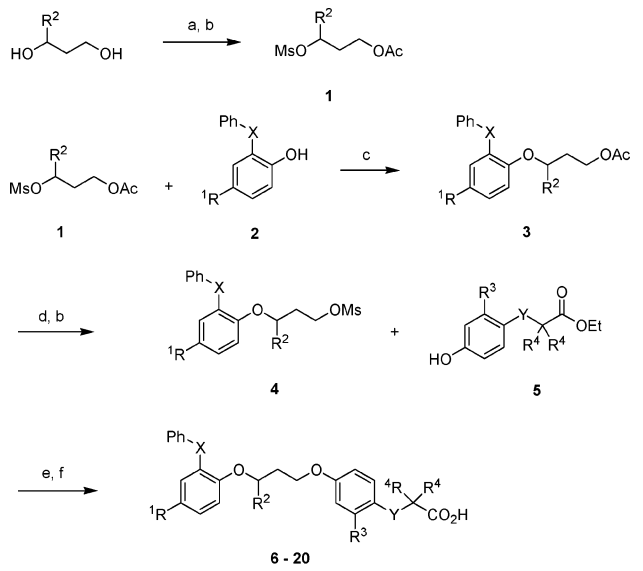
Type 2 diabetes is a debilitating metabolic disorder, affecting over 150 million people worldwide,[1] that culminates in a range of progressive secondary complications.[2] Therapy for type 2 diabetes primarily has been aimed at improving glycemic control via a combination of diet, exercise, and the use of oral agents[3] including sulfonylureas, metformin, acarbose, and thiazolidinediones (TZDs). TZDs, which are high affinity ligands for the peroxisome proliferator-activated receptor γ (PPARγ), impact a key underlying feature of type 2 diabetes, insulin resistance.[4,5]

The peroxisome proliferator-activated receptors (PPARs) are a highly conserved set of ligand-activated transcription factors in the nuclear hormone receptor superfamily.[6] Three distinct PPAR subtypes (PPARγ, PPARα, and PPARδ or PPARβ) have been identified in most mammalian species,[7] each forming a functional heterodimer complex with the 9-cis retinoid acid receptor (RXR). In addition to its role in modulating the antidiabetic activity of the TZDs, PPARγ is well-known for its role in adipogenesis at a cellular level.[8] A selective PPARγ agonist, rosiglitazone (5-{4-[2-(methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazoli-dine-2,4-dione), reduces fasting plasma glucose concentration and fasting insulin level in type 2 diabetic patients.[9] However, some notable side effects, weight gain and edema, were also observed in patients at efficacious doses.[9,10]

In contrast to the other PPAR isoforms, the physiological function of PPARδ is less well understood. It appears, however, to play a prominent role in lipid metabolism.[11] A selective PPARδ agonist, {2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid, has demonstrated the ability to dose-dependently increase serum high-density lipoprotein cholesterol while lowering the level of small dense low-density lipoprotein cholesterol, fasting triglycerides, and fasting insulin.[11] The cholesterol mediating effects observed in this study were explained, at least in part, through the PPARδ's ability to upregulate the expression of the ABC-A1[a] reverse cholesterol transporter, which promotes apolipoprotein A1-specific cholesterol transport of cholesterol to the liver. In addition, PPARδ also plays a critical role in the transcriptional repression of atherogenic inflammation in macrophages.[12]

The pivotal role that PPAR receptors play in the regulation of metabolism makes them inviting targets for the treatment of diabetes mellitus, atherosclerosis, and obesity.[12−15] It is our hypothesis that a PPARγ/δ dual agonist could differentiate from other currently marketed antidiabetic agents through its ability to effectively lower glucose and hemoglobin A1c levels while simultaneously improving the dyslipidemia common in diabetic patients (elevated triglycerides and low HDL cholesterol). It is expected to have significant impact on the progression of atherosclerosis not only stemming from lipid alterations but also as a result of its ability to stimulate reverse cholesterol transport. As a result of PPARδ's propensity to improve insulin sensitivity[11] and stimulate fatty acid oxidation,[16] our hypothesis was that a dual PPARγ/δ agonist could mitigate some of the weight gain associated with a selective PPARγ agonist. Previously two

Scheme 1[a]



6: R^1 = Et; R^2, R^3 = H; R^4 = Me; X = C=O; Y = O;
7: R^1 = Et; R^2, R^4 = Me; R^3 = H; X = C=O; Y = O; racemate
8: R^1 = Et; R^2, R^3 = Me; R^4 = H; X = C=O; Y = CH_2; racemate
9: R^1 = Et; R^2, R^3 = Me; R^4 = H; X = C=O; Y = CH_2; *R* enantiomer
10: R^1 = Et; R^2, R^3 = Me; R^4 = H; X = C=O; Y = CH_2; *S* enantiomer
11: R^1 = Et; R^2 = Et; R^3 = Me; R^4 = H; X = C=O; Y = CH_2; racemate
12: R^1 = Et; R^2 = ^{n}Pr; R^3 = Me; R^4 = H; X = C=O; Y = CH_2; racemate
13: R^1 = Et; R^2, R^3 = Me; R^4 = H; X = CH_2; Y = CH_2; racemate
14: R^1 = Et; R^2, R^3 = Me; R^4 = H; X = O; Y = CH_2; *R* enantiomer
15: R^1 = Cl; R^2, R^3 = Me; R^4 = H; X = O; Y = CH_2; *R* enantiomer
16: R^1 = OCF_3; R^2, R^3 = Me; R^4 = H; X = O; Y = CH_2; *R* enantiomer
17: R^1 = CF_3; R^2, R^3 = Me; R^4 = H; X = O; Y = CH_2; *R* enantiomer
18: R^1 = Cl; R^2 = Me; R^3 = CF_3; R^4 = H; X = O; Y = CH_2; *R* enantiomer
19: R^1 = Cl; R^2 = Me; R^3 = F; R^4 = H; X = O; Y = CH_2; *R* enantiomer
20: R^1 = Cl; R^2 = Me; R^3 = Et, R^4 = H; X = O; Y = CH_2; *R* enantiomer

[a] Reagents and conditions: (a) Ac_2O, CH_2Cl_2, −78 °C; (b) MsCl, Et_3N; (c) K_2CO_3, DMF, 50 °C; (d) K_2CO_3, MeOH, rt; (e) Cs_2CO_3, DMF, 55 °C; (f) 5N NaOH, EtOH, reflux.

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[a] Abbreviations: ABC-A1, ATP-binding cassette, subfamily A (ABC1), member 1; TZD, thiazolidinedione; PK, pharmacokinetic; HDL, high-density lipoprotein; ZDF rat, Zucker diabetic fatty rat.

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Table 1. Binding IC_{50}[a] and Receptor Transactivation EC_{50}[b] Data[c] on Human PPAR Receptor Subtypes[d]

		hPPARα[g]		hPPARγ[h]		PPARδ[g]	
compound	stereo[f]	IC_{50} (nM)	EC_{50} (nM)[e]	IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)	EC_{50} (nM)[d]
6		1398 ± 0	710 ± 278	38 ± 0	112 ± 11	6 ± 0	47 ± 12
7	*rac*	1323 ± 0	686 ± 211	6 ± 0	6 ± 0	5 ± 0	45 ± 8
8	*rac*	8251 ± 1592	1529 ± 123	12 ± 1	9 ± 1	7 ± 1	7 ± 1
9	*R*	4257 ± 235	877 ± 174	5 ± 1	4 ± 0	3 ± 1	5 ± 1
10	*S*	*i*	*j*	1130 ± 0	674 ± 0	183 ± 0	339 ± 0
11	*rac*	8919 ± 0	2929 ± 23	18 ± 0	46 ± 3	6 ± 1	25 ± 5
12	*rac*	*i*	*j*	417 ± 0	968 ± 128	9 ± 0	52 ± 12
13	*R*	10897 ± 0	2813 ± 163	59 ± 0	228 ± 17	8 ± 0	70 ± 22
14	*R*	3758 ± 0	1524 ± 346	6 ± 0	8 ± 0	4 ± 0	5 ± 0
15	*R*	5303 ± 466	2204 ± 183	15 ± 1	52 ± 8	4 ± 0	8 ± 3
16	*R*	897 ± 117	642 ± 154	6 ± 0	5 ± 1	5 ± 0	2 ± 1
17	*R*	1037 ± 61	488 ± 0	6 ± 1	4 ± 0	5 ± 0	1 ± 0
18	*R*	4386 ± 0	2067 ± 424	61 ± 0	355 ± 87	5 ± 0	73 ± 6
19	*R*	2681 ± 145	2224 ± 0	63 ± 6	402 ± 0	4 ± 0	34 ± 0
20	*R*	6932 ± 677	2800 ± 33	19 ± 2	102 ± 16	4 ± 1	6 ± 0
rosiglitazone	*rac*	*i*	*j*	67 ± 8	308 ± 21	*i*	*j*

[a] Concentration of test compound required to displace 50% of tritiated ligand. [b] Concentration of test compound that produced 50% of the maximal reporter activity. [c] $n = 3-6$. [d] Compounds **6**−**20** showed no binding or receptor transactivation on murine PPARα receptor. [e] Gal4-hPPARα and hPPARδ was used to eliminate interference by endogenous PPARγ receptors in CV-1 cells. [f] Stereochemistry of the chiral center. [g] Tritium-labeled PPARα/PPARδ agonist, 2-(4-{2-[3-(2,4-difluoro-phenyl)-1-heptyl-ureido]-ethyl}-phenoxy)-2-methyl-butyric acid, was used as radioligand for generating displacement curves and IC_{50} values. [h] Tritium-labeled PPARγ agonist, 2-methyl-2-(4-{3-[propyl-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-propyl}-phenoxy)-propionic acid, was used as radioligand for generating displacement curves and IC_{50} values. [i] No binding. [j] Efficacy relative to control was less than 20% at 10 μM.

research groups also reported their dual PPARγ/δ agonist studies.[17] We herein report our design, synthesis, and preclinical evaluation of a novel class of dual PPARγ/δ agonists.

A general synthetic scheme is outlined in Scheme 1. Mono-mesylates **1** were prepared from commercially available diols by first selective acylation of the primary alcohols followed by mesylation of the secondary alcohols. Nucleophilic substitution of mono-mesylates **1** with phenols **2** afforded ethers **3**. Removal of the acetyl groups of **3** followed by methylsulfonylation gave **4**. Treatment of **4** with various phenols **5**[18] and subsequent hydrolyses afford carboxylic acids **6**−**20**.

Diabetic male db/db mice, purchased from Harlan Sprague Dawley, were placed on study at ∼7 weeks of age. Plasma glucose was assessed for all animals (tail vein) at the beginning of the study under fed conditions. Animal were assigned to groups ($n = 5$) based on plasma glucose levels. All animals were dosed by oral gavage with either vehicle (CMC/Tween 80) or vehicle and compound (30 mg·kg^{-1}) once daily for 7 days. One hour after the seventh dose, plasma glucose was re-assessed for all animals.

Diabetic male and nondiabetic female ZDF rats, purchased from Charles River Labs, were divided into groups (control, rosiglitazone, and compound at indicated doses). Vehicle (1% w/v CMC, 0.25% Tween 80) was used in all in vivo studies. Male ZDF rats (∼8 weeks of age, $n = 5$ per group) were dosed once daily by oral gavage in the morning for 7 days. Male ZDF rat plasma glucose levels were determined 1 h after dosing. Body weight and food consumption were assessed in all groups over the course of the study. Female ZDF rats (∼8 weeks of age, $n = 6$ per group) were dosed by oral gavage for 14 days and then subjected to an oral glucose tolerance test (2.5 g of glucose/kg of body weight) following an overnight fast. Plasma was collected at times 0, 15, 30, 60, and 120 min post oral glucose administration. Plasma glucose and insulin levels were assessed at all the indicated time points. Body weight and food consumption were assessed in all groups over the course of the study.

Through our early SAR effort, compound **6** was identified as a dual agonist ($EC_{50}\gamma = 112$ nM, $EC_{50}\delta = 47$ nM, Table 1) with moderate selectivity over the PPARα isoform ($EC_{50}\alpha = 710$ nM) (see assays description in Supporting Information). Introduction of an R^2 group significantly improved in vitro receptor potency. Methyl branching ($R^2 =$ Me) in **7** significantly improved PPARγ in vitro profile ($EC_{50}\gamma = 6$ nM, $EC_{50}\delta = 45$ nM). However, this modification had little effect on PPARα activity ($EC_{50}\alpha = 686$ nM). The PPARα selectivity is further improved by using a dihydrocinnamic acid headpiece. Compound **8** was identified as a potent dual PPARγ/δ agonist with excellent selectivity. The enantiomers of this racemate were separated by preparative HPLC using a chiral column. The absolute configurations of the enantiomer were assigned by comparing the chiral HPLC retention times with the material synthesized from (*S*)-butane-1,3-diol. *R*-Stereoisomer **9** was ca. 100 times more potent than the *S* isomer **10** on all PPAR subtypes. Increasing the size of the R^2 group, for example, **11** ($R^2 =$ Et) and **12** ($R^2 = {}^n$Pr), resulted in sharp losses (5−10-fold loss) of PPARγ/δ activities. In liver microsome assays, **9** showed 70%, 60% and 69% metabolism in mouse, rat, and human liver microsomes, respectively. Studies from human and rat liver slices identified multiple metabolic pathways for **9**, namely, reduction of the benzoyl carbonyl group, oxidation of the tailpiece Et group, and oxidation of the dihydrocinnamate headpiece to cinnamate.[19] In a search for metabolically stable replacements of the benzoyl carbonyl group, a dramatic loss of PPARγ activity in **13** was noticed when the carbonyl group was replaced by a CH_2 group. However, PPAR γ/δ activities were maintained when the carbonyl group was replaced by an oxygen atom in **14**. Various R^1 groups were evaluated to address the metabolic liability of the ethyl group. Results indicated that a lipophilic group at this position, for example, **15** ($R^1 =$ Cl), **16** ($R^1 = OCF_3$), and **17** ($R^1 = CF_3$), is desirable for PPARγ/δ dual activity. Compound **15** maintained good selectivity, while lipophilic groups such as OCF_3 (**16**) and CF_3 (**17**) increased PPARα activity. Various R^3 groups were pursued to improve the stability of the dihydrocinnamate headpiece. Electron withdrawing groups, for example, CF_3 (**18**) and F (**19**), attenuate both PPAR γ and δ activities. Compound **20**, with an electron-donating group $R^3 =$ Et, offered a potent PPAR γ/δ dual agonist profile with good selectivity over PPARα. In theory, this ethyl group could sterically block the β-oxidative degradation of the cinnamate headpiece. In liver microsome assays, **20** showed improvement in metabolic stability with 27%, 20%, and 25% metabolism in mouse, rat, and human liver microsomes,

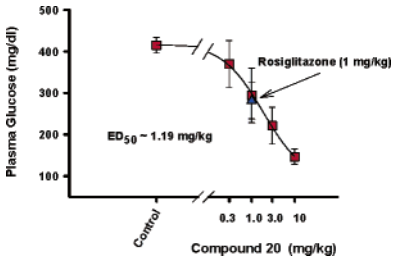

Figure 1. Dose-response for effects of compound **20** on plasma glucose in ZDF rats ($n = 5$ per group) after 7 days of oral gavage dosing.

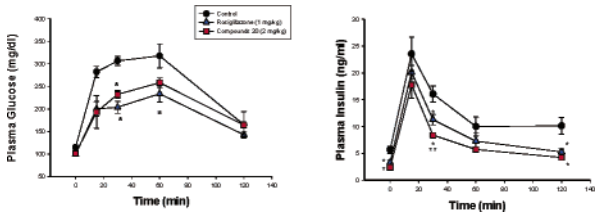

Figure 2. Glucose and insulin responses to a glucose challenge (2.5 g·kg^{-1} BW) in female ZDF rats ($n = 6$ per group) dosed by oral gavage for 14 days with **20** or rosiglitazone (∗ indicates significantly different than control; ∗∗ indicates significantly different than rosiglitazone).

respectively. In db/db mice, at single dose of 30 mg·kg^{-1}, **20** showed significantly better glucose lowering of 64% compared with 28% for **9**.

Compound **20** was tested over a range of oral dose levels in 51 day old male ZDF rats. As shown in Figure 1, **20** dose-dependently lowered plasma glucose levels in ZDF rats. The ED_{50} for half-maximal glucose normalization was estimated by curve fitting to be 1.19 mg·kg^{-1}·d^{-1}. Included as a positive control, rosiglitazone, exhibited 50% glucose normalization at 1.0 mg·kg^{-1}·d^{-1}. At the ED_{50} dose, **20** lowers plasma triglycerides 27% compared with control animals (data not shown). Similarly, plasma free fatty acids were reduced by 9% compared with the control group (data not shown).

A two week female ZDF study was conducted with **20** to determine whether the previously noted effects on glucose homeostasis were attributable to an improvement in insulin sensitivity and to more thoroughly evaluate the weight gain profile. At 2 mg·kg^{-1}·d^{-1} dose, **20** significantly lowered the glucose response to an oral glucose challenge (Figure 2). This response is equivalent to the effects exhibited by a 1 mg·kg^{-1}·d^{-1} dose of rosiglitazone. Furthermore, both fasting insulin levels and the insulin response to the glucose challenge were significantly reduced in the rats treated with both **20** and rosiglitazone. Thus both compounds enhanced whole body insulin sensitivity equally at the corresponding doses.

The weight gain profiles for this study are depicted in Figure 3. At 2 mg·kg^{-1}, **20** increased body weight 14.4 g above control levels whereas an equally efficacious dose of rosiglitazone (1 mg·kg^{-1}) induced a 26.0 g increase in body weight above control. Whereas both **20** and rosiglitazone significantly increased weight gain relative to control, the weight gain induced by **20** was significantly different than that induced by rosiglitazone in this study ($P < 0.05$). Furthermore rosiglitazone-treated rats possessed significantly more fat mass (148.4 ± 4.3 g) than either **20**-treated (136.8 ± 2.6 g) or control animals (129.9 ± 2.9 g) as assessed by quantitative magnetic resonance spectroscopy.

In summary, **20** was identified as a dual PPAR γ/δ agonist with high-affinity binding to hPPARγ and hPPARδ and potent agonist activity in cell-based transactivation assays. In male ZDF rats, it exhibited potent glucose lowering activity with an ED_{50} of 1.19 mg·kg^{-1}. At the same dose, the compound lowered

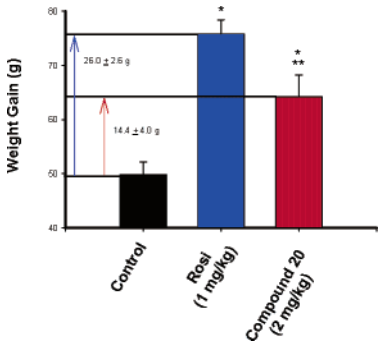

Figure 3. Weight gain profiles for female ZDF rats ($n = 6$ per group) dosed by oral gavage for 14 days with **20** or rosiglitazone.

plasma triglycerides by 27% and plasma free fatty acids by 9% compared with the control group. In female ZDF rats, **20** significantly improved both the glucose and the insulin response to a glucose challenge. Animals dosed with 2 mg·kg^{-1} of **20** showed significantly less weight gain ($P < 0.05$) and fat mass relative to animals treated with 1 mg·kg^{-1} of rosiglitazone where glycemic efficacy was equivalent. These studies suggest that a PPARγ/δ dual agonist approach can attenuate the weight gain side effect commonly associated with marketed TZDs. Our recent SAR suggests that a PPARγ/δ agonist with a properly controlled γ/δ ratio can be effective on glucose control with less weight gain relative to rosiglitazone in our preclinical models. The result will be reported in due course.

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Supporting Information Available: Experimental details on in vitro binding and co-transfection studies, animal models, and the synthetic procedures and characterization data for intermediates and final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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