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Design and synthesis of a novel class of dual PPARγ/δ agonists

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Abstract—The design and synthesis of dual PPAR γ/δ agonist (*R*)-3-{2-ethyl-4-[3-(4-ethyl-2-pyridin-2-yl-phenoxy)-butoxy]-phenyl}propionic acid is described. This compound dose-dependently lowered plasma glucose in hyperglycemic male Zucker diabetic fatty (ZDF) rats and produced less weight gain relative to rosiglitazone at an equivalent level of glucose control.

Type 2 diabetes is a metabolic disorder characterized by hyperglycemia and/or insulin resistance. It is often associated with obesity, hypertension, and dyslipidemia. Current therapies for reducing plasma glucose include the use of sulfonylureas, metformin, acarbose, and thiazolidinones (TZDs). Statins and fibrates[1] are used to treat dyslipidemia. The antidiabetic effects of TZDs[2] and the hyperlipidemic effects of the fibrate drugs[3] are due to the activation of the peroxisome proliferator-activated receptors (PPARs) γ and α, respectively.

The PPARs constitute a highly conserved set of ligand-activated transcription factors in the nuclear hormone receptor subfamily. Three distinct PPAR subtypes (PPARγ, PPARα, and PPARδ) have been identified in most mammalian species, each forming a functional heterodimer complex with the 9-*cis* retinoic acid receptor (RXR). A potent selective PPARδ agonist, {2-methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl-methylsulfanyl]-phenoxy}-acetic acid (GW501516), has been reported to increase serum high-density lipoprotein cholesterol while lowering the level of low-density lipoprotein cholesterol, fasting triglicerides, and fasting insulin in a dose-dependent manner.[4] The cholesterol mediating effects were attributed to the ability of PPARδ to up-regulate the expression of the ABC-A1 reverse cholesterol transporter, which promotes apolipoprotein A1-specific cholesterol transport of cholesterol to the liver.[5] Recently, we reported the design and synthesis of a novel class of PPARγ/δ dual agonists, analogs of compound **1** (Fig. 1), which had potent PPARγ/δ activity and good selectivity versus PPARα.[6] We showed that a PPARγ/δ dual agonist with a properly controlled γ/δ ratio lowered glucose and caused less weight gain than a marketed PPARγ-selective agent, rosiglitazone, at an equivalent level of glucose control.This reduced side effect profile was attributed to the propensity of PPARδ to improve insulin sensitivity[5] and stimulate fatty acid oxidation.[7] Subsequent SAR efforts were undertaken to explore alternative ways to address the multiple metabolic pathways of **1**, namely reduction of the benzoyl group and oxidations of the ethyl group and the dihydrocinnamate. Herein, we report the design, synthesis and preclinical biological evaluation of 3-{4-[3-(2-aryl-phenoxy)butoxy]-phenyl}propionic acids as novel PPAR γ/δ dual agonists.

The chemistry used to prepare these analogs is illustrated in Scheme 1. Treatment of (*S*)-butane-1,3-diol (**2**)

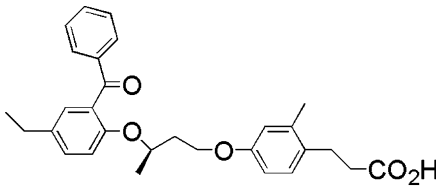

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Figure 1. Compound **1**.

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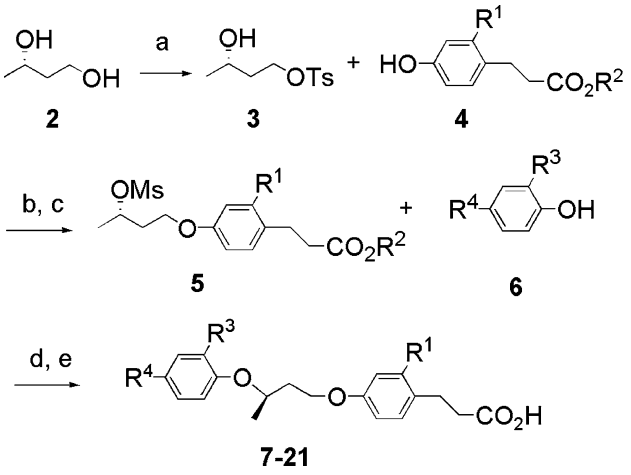


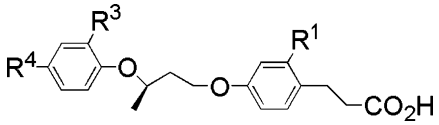
Scheme 1. Reagents and conditions: (a) *p*-TosCl, NEt_3, $(Bu_3Sn)_2O$, CH_2Cl_2, 72%; (b) Cs_2CO_3, DMF, 55 °C, 64% (R_1 = Me), 82% (R_1 = Et); (c) MsCl, NEt_3, CH_2Cl_2, 0 °C, 98%; (d) Cs_2CO_3, DMF, 55 °C; (e) R^2OH, NaOH aq, **7** (55%), **8** (63%), **9** (53%), **10** (65%), **11** (63%), **12** (59%), **13** (26%), **14** (71%), **15** (71%), **16** (53%), **17** (35%), **18** (54%), **19** (46%), **20** (39%), **21** (59%) both steps.

with *p*-TosCl, NEt_3, and $(Bu_3Sn)_2O$ provided **3**. Nucleophilic substitution of **3** with phenols **4** followed by mesylation provided intermediates **5**. Treatment of mesylates **5** with phenols **6** and subsequent hydrolyses afforded carboxylic acids **7**–**21**.[8]

First, we focused our efforts on the replacement of the benzoyl group to address the reduction of the carbonyl group we observed with human and rat liver slices. Removal of the carbonyl group and direct attachment of the two phenyl rings in the tailpiece gave **7** with the desired in vitro PPARα/δ selectivity but with significantly decreased PPARγ potency (Table 1).

Replacement of the benzoyl substituent R^3 with thiophene (**8**, **9**), furan (**10**), thiazole (**14**, **15**) or oxazole (**16** and **17**) rings was detrimental to PPAR γ and δ affinities. Interestingly, 2-pyridyl (**11**) and 3-pyridyl (**12**) replacements led to compounds with good selectivity over PPARα and potent PPAR γ/δ affinity and functional activity. Replacement of the ethyl substituent R^4 of **11** with Cl (**18**) attenuated the PPARγ and PPARδ transactivation EC_{50}'s, but with CF_3 (**19**) the desired in vitro profile was maintained. To protect the dihydrocinnamate headpiece from β-oxidation, we replaced the methyl group R^1 with a sterically more demanding ethyl group (**20** and **21**).[6] Compounds **20** and **21**, with potent PPARγ/δ dual agonist activity, were tested in db/db mice for 7 days at 30 mg/kg oral gavage dosing. Compound **20** showed 89 ± 4% glucose normalization, comparable to **21** that exhibited 81 ± 19% glucose normalization. The concentration in blood of compound **20** after 1 h of the last dose was 3.2 ± 1.3 μg/mL, comparable to **21** that exhibited a concentration of 4.2 ± 1.7 μg/mL.

Table 1. Binding IC_{50}[a] and transactivation EC_{50}[b,c] data[d] on human PPAR receptor subtypes



Compound	R^3	R^1	R^4	hPPARα IC_{50} (nM)	hPPARα EC_{50} (nM)	hPPARγ IC_{50} (nM)	hPPARγ EC_{50} (nM)	hPPARδ IC_{50} (nM)	hPPARδ EC_{50} (nM)
1	Benzoyl	Me	Et	4257	877	5	4	3	1
7	Phenyl	Me	Et	nb	2880	215	836	5	6
8	3-Thiophenyl	Me	Et	5950	na	568	1670	8	42
9	2-Thiophenyl	Me	Et	9110	2690	1090	1990	9	41
10	2-Furanyl	Me	Et	4500	2800	940	2300	14	399
11	2-Pyridyl	Me	Et	8290	2870	46	182	3	9
12	3-Pyridyl	Me	Et	nb	2900	60	140	5	15
13	4-Pyridyl	Me	Et	nb	na	520	576	5	5
14	4-Thiazolyl	Me	Et	4100	2680	346	837	3	22
15	2-Thiazolyl	Me	Et	nb	na	1530	2270	12	25
16	4-Oxazolyl	Me	Et	4990	2810	979	1980	13	274
17	2-Oxazolyl	Me	Et	10,400	2890	483	696	5	50
18	2-Pyridyl	Me	Cl	nb	2980	88	304	2	24
19	2-Pyridyl	Me	CF_3	5880	2340	20	67	4	6
20	2-Pyridyl	Et	Et	7350	2850	35	167	3	7
21	2-Pyridyl	Et	CF_3	6090	2630	16	111	3	6
Rosiglitazone				nb	na	67	308	nb	na

[a] Concentration of test compound required to displace 50% of tritiated ligand, PPARα/PPARδ agonist 2-(4-{2-[3-(2,4-difluoro-phenyl)-1-heptyl-ureido]-ethyl}-phenoxy)-2-methyl-butyric acid, and PPARγ agonist, 2-methyl-2-(4-{3-[propyl-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-propyl}-phenoxy)-propionic acid, nb = no binding.

[b] Concentration of test compound which produced 50% of the maximal reported activity, na = efficacy relative to control was less than 20% at 10 μM.

[c] Gal4-hPPARα and Gal4-hPPARδ were used to eliminate interference by endogenous PPARγ receptors in CV-1 cells.

[d] Minimum significant ratio (MSR),[9] hPPRα IC_{50} MSR = 1.53, hPPARα EC_{50} MSR = 2.48, hPPRγ IC_{50} MSR = 2.6, hPPARγ EC_{50} MSR = 1.79, hPPRδ IC_{50} MSR = 1.26, hPPARδ EC_{50} MSR = 2.89.

Compound **20**[10] was selected for further studies and exhibited an improved pharmacokinetic profile versus compound **1**. In Sprague–Dawley rats **20** was 71% bioavailable with a half life of 3.0 h and AUC of 75.5 ± 5.7 μg h/mL when dosed orally at 12 mg/kg as a suspension in sodium carboxymethyl cellulose (NaCMC)/sodium lauryl sulfate (SLS)/povidone. The clearance of **20** was 1.9 ± 0.1 mL/min/kg when dosed intravenous at 1 mg/kg in 6% solutol/EtOH (1:1 w/v) in saline. In contrast, **1** was 27% bioavailable with a half life of 1.4 h and AUC of 3.7 ± 0.1 μg h/mL when dosed orally at 10 mg/kg. The clearance of **1** was 11 ± 2 mL/min/kg when dosed intravenous at 1 mg/kg. These favorable features made **20** a good candidate for further evaluation using in vivo models.[11]

Compound **20** was tested over a range of oral dose levels in male ZDF rats. As shown in Figure 2, **20** dose-dependently lowered plasma glucose levels in ZDF rats.

At the oral dose of 1 mg/kg **20** exhibited 87 ± 10% glucose normalization, comparable to rosiglitazone with 89 ± 14% glucose normalization at the same dose of 1 mg/kg.[12] Compound **20** increased body weight

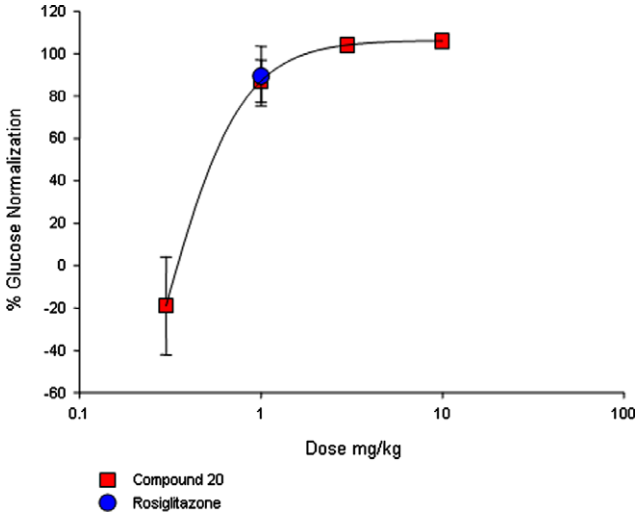


Figure 2. Dose–response for effects of compound **20** on glucose normalization in ZDF rats after 7 days of oral gavage dosing.

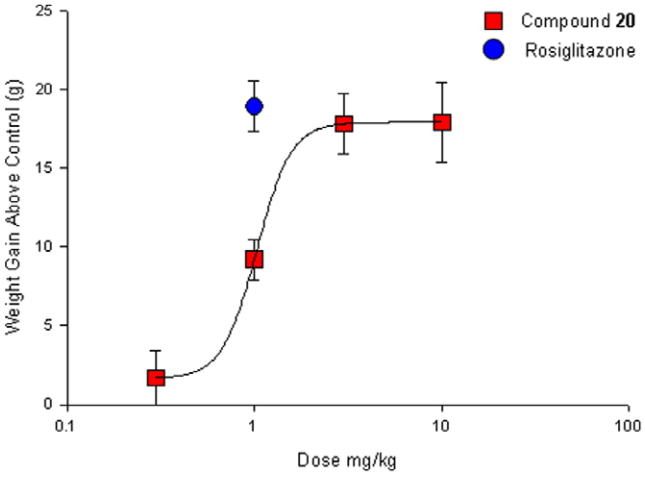


Figure 3. Dose–response for effects of compound **20** on body weight in ZDF rats after 7 days of oral gavage dosing.

9 ± 1 g above control, significantly less than the 19 ± 2 g increase noted with rosiglitazone ($P < 0.05$) (Fig. 3). At the 1 mg/kg oral dose, **20** lowered plasma triglycerides by 53% and plasma free fatty acids by 23% compared to control animals.

A 2-week female ZDF rat study was conducted with **20** to determine if the effects observed in glucose normalization were related to an improvement in insulin sensitivity. Compound **20** dosed orally at 2 mg/kg/d lowered the glucose response to an oral glucose challenge. Furthermore, both fasting insulin levels and the insulin response to the glucose challenge were significantly reduced with **20**. These effects were comparable to those observed with rosiglitazone at 1 mg/kg/d (Fig. 4).

In summary, we identified compound **20** as a PPARγ/δ dual agonist, with high affinity to hPPARγ and hPPARδ, and potent agonistic activity in cell-based transactivation assay. In male ZDF rats, compound **20** exhibited potent glucose lowering activity with less increase in body weight above control levels than rosiglitazone at the same dose of 1 mg/kg. In female ZDF rats, compound **20** significantly lowered both glucose and insulin responses to a glucose challenge. These studies corroborate our initial hypothesis that a PPARγ/δ dual

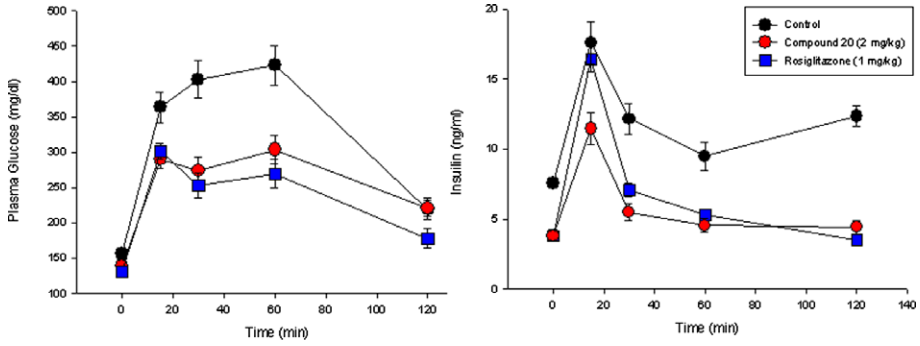


Figure 4. Glucose and insulin responses to a glucose challenge (2.5 g/kg/BW) in female ZDF rats dosed by oral gavage for 14 days with compound **20** or rosiglitazone.

agonist with a properly controlled γ/δ ratio can attenuate the weight gain side effect associated with marketed TZDs. Interestingly, a recent report indicated that GW501516, a potent and selective PPARδ agonist, did not influence the weight in db/db mice.[13] The evaluation of the in vivo side effect profile with respect to PPAR γ and δ potency ratio will be reported in due course.

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10. Compound **20**: HRMS calculated for $C_{28}H_{33}NO_4$ 447.5717, found 447.2409; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.58 (1H, d, J = 4.3 Hz), 7.79 (2H, m), 7.39 (1H, d, J = 1.8 Hz), 7.34 (1H, m), 7.22 (1H, dd, J_1 = 8.3 Hz, J_2 = 2.8 Hz), 7.07 (2H, m), 6.67 (1H, d, J = 2.4 Hz), 6.61 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.3 Hz), 4.68 (1H, m), 3.98 (2H, t, J = 6.6 Hz), 2.89 (2H, t, J = 8.2 Hz), 2.65 (4H, m), 2.49 (2H, J = 8.2 Hz), 2.03 (2H, m), 1.19–1.32 (9H, m).
11. *Male and female ZDF rat in vivo models:* ZDF male rats were divided into groups: control, different dose groups (0.3, 1, 3, and 10 mg/kg/d) with compound **20**, and one dose group (1 mg/kg/d) with rosiglitazone. Vehicle 1% wt/v CMC, 0.25% Tween 80 was used in all in vivo studies. ZDF rats (8 weeks of age) were dosed once daily by oral gavage in the morning for 7 or 14 days. The ZDF rats were weighted before dosing and plasma glucose levels were determined one hour after dosing.
12. Historical data for rosiglitazone tested in a dose–response ZDF male rat study for 7 days show that a 1 mg/kg/d dose is the dose that consistently produced a >80% glucose normalization to approximate the ED_{80}.
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