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Pyridine-2-propanoic acids: Discovery of dual PPARα/γ agonists as antidiabetic agents

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Abstract—A series of novel pyridine-2-propanoic acids was synthesized. A structure–activity relationship study of these compounds led to the identification of potent dual PPARα/γ agonists with varied isoform selectivity. Based on the results of efficacy studies in diabetic (*db*/*db*) mice, and the desired pharmacokinetic parameters, compound (*S*)-**13** was selected for further profiling.

Type 2 diabetes is a chronic disease characterized by insulin resistance in the liver and peripheral tissues accompanied by a defect in pancreatic β-cells.[1,2] Between 1997 and 1999, a new class of drugs called 'glitazones'[3] was approved by the FDA for the treatment of type 2 diabetes. Glitazones correct hyperglycemia by enhancing tissue sensitivity to insulin. Because of this mechanism of action, glitazone treatment is not associated with dangerous hypoglycemic incidents that have been observed with conventional sulfonylurea agents and insulin therapy. In the mid-1990s the molecular target of the glitazones was reported to be the peroxisome proliferator-activated receptor-γ (PPARγ).[4–7] The PPARs are a group of nuclear receptors that act as transcriptional factors which play a major role in the regulation of lipid metabolism and storage.[8–10] PPARα is the molecular target for the fibrate class of lipid-modulating drugs.[11] Designing compounds with PPARα activity in addition to PPARγ agonist activity may offer improved alternatives toward control of hyperglycemia and hypertriglyceridemia in type 2 diabetics.[12] Scientists at Kyorin disclosed novel antidiabetic KRP-297, the first published example of a dual PPARα and PPARγ agonist.[13]

In the preceding paper, we disclosed the results of our efforts that led to the identification of compounds of type **1** as potent dual PPARα/γ agonists.[14] Based on their efficacy in the established rodent models of type 2 diabetes, and desirable PK profile, we initiated synthesis of various isomeric pyridine-2-propanoic acids **2** (Fig. 1). These additional efforts have led to the identification of a new class of potent dual PPARα/γ agonists with excellent in vivo efficacy. Herein, we report the synthesis, structure–activity relationships (SAR), and in vivo activity of this new class of compounds.[15]

The synthetic route for the preparation of compound **8** is shown in Scheme 1. Commercially available 5-hydroxy-2-methylpyridine **3** was converted to alcohol **5**, via pyridine *N*-oxide **4**, according to a procedure reported by Soga and co-workers.[16] Benzyl alcohol **5** was oxidized to the aldehyde, subjected to Wittig

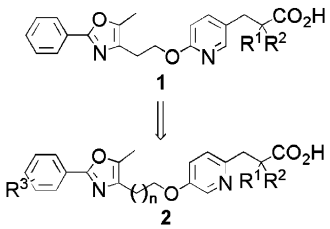

Figure 1. Previously described lead and isomeric scaffold.

Keywords: PPAR; Diabetes; Parallel synthesis; SAR; Pharmacokinetic studies; In vivo efficacy.
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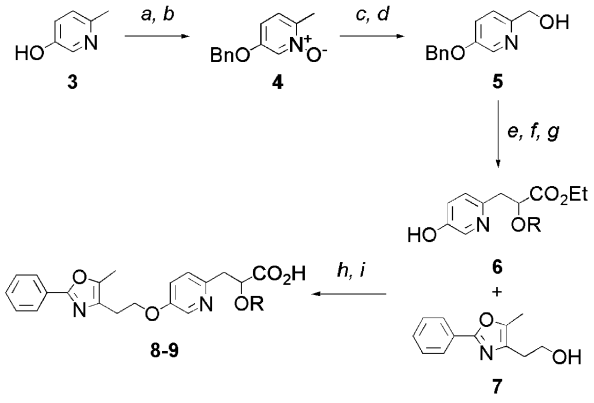


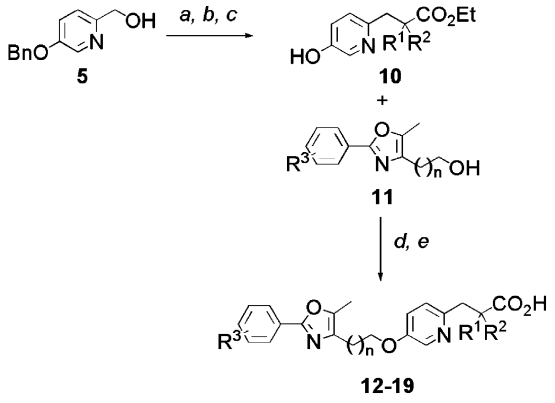
Scheme 1. Reagents and conditions: (a) BnBr, NaOH, H_2O, Me_2CO, reflux, 16 h, 96%; (b) *m*-CPBA, $CHCl_3$, rt, 1 h, 97%; (c) Ac_2O, 100 °C, 1 h; (d) K_2CO_3, MeOH, rt, 16 h, 82% (2 steps); (e) DMP, CH_2Cl_2, pyridine, rt, 16 h, 50%; (f) $EtO_2CCH(OEt)PPh_3^+Cl^-$, TMG, $CHCl_3$, rt, 16 h, 100%; (g) 10% Pd/C, H_2, EtOH, 50 psi, rt, 16 h, 93%; (h) PPh_3, THF, DEAD, rt, 16 h, 76%; (i) LiOH, THF, MeOH, H_2O, rt, 16 h, 92%. DMP, Dess–Martin periodinane.

olefination, followed by hydrogenation to afford phenol **6**.[17] Mitsonobu reaction of phenol **6** with alcohol **7**, followed by ester hydrolysis, gave final products **8**–**9**.

The synthetic route for the preparation of **12**–**19** is shown in Scheme 2. Conversion of alcohol **5** into the benzyl chloride, reaction with a variety of ester enolates, followed by debenzylation afforded phenols **10**. Mitsonobu reaction of phenols **10** with alcohols **11**, followed by ester hydrolysis, gave final products **12**–**19**.

Further chemical diversity was incorporated by investigating alternative heteroaromatic replacements for the pyridyl core. Figure 2 depicts pyrazine **19** and pyrimidine **20** as examples of this effort. The synthesis of these ligands has been described previously.[15]

The newly synthesized compounds were evaluated in the PPAR SPA binding assay to ascertain γ and α binding profiles.[18] The active analogs were also tested for functional activity in a PPAR-GAL4 transactivation (TA) assay, where EC_{50} values, as well as percent maximal



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, rt, 2 h; (b) $R^1R^2CHCO_2Et$, NaHMDS, THF, −50 °C, 3 h, 70–86% (2 steps); (c) 10% Pd/C, H_2, EtOH, 45 °C, 16 h; (d) PPh_3, THF, DEAD, rt, 16 h, 54–76% (2 steps); (e) LiOH, THF, MeOH, H_2O, rt, 16 h.

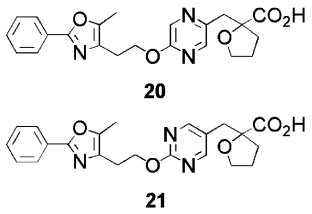


Figure 2. Pyrazine **20** and pyrimidine **21**.

activation, were measured (Table 1).[19] Initially, we decided to investigate the effects of varying the α-substituents of **2** (R^1 and R^2). Compounds **8**–**9** and **12**–**14** highlighted that both binding affinity and isoform selectivity were sensitive to the size of the α-substituent(s). We then shifted our attention to variation of substituents on the phenyloxazole group, whilst holding constant the 2-tetrahydrofuran moiety. Extension of the linker between the pyridyl core and the phenyloxazole moiety affected PPARγ more than PPARα, resulting in a more balanced dual agonist (compound **15**).

Compounds **16**–**19** demonstrated that binding affinity and isoform selectivity were sensitive to the positioning of substituents on the phenyl ring. 4-Cl afforded a compound with a more balanced isoform profile, whereas 3-OMe tended to impart isoform selectivity favoring PPARγ (e.g., compound **17** vs **18**). Finally, we briefly explored alternatives to the pyridyl core. Compounds **20** and **21** demonstrated that addition of another nitrogen into the central core also affects binding to both isoforms, with pyrazine **20** displaying selectivity for PPARγ.

Since compound **13** appeared to possess the most interesting biological profile and physical properties (e.g., biased toward PPARγ and satisfactory in vitro ADME data), we separated the enantiomers by chiral supercritical fluid chromatography (SFC). The eutomer, predicted to have the *S* configuration based on literature compounds,[20] demonstrated potent dual PPARγ and PPARα binding as well as functional agonism. Compound (*S*)-**13** was then selected for rat pharmacokinetic (PK) studies. Administration to male Sprague–Dawley (SD) rats resulted in satisfactory PK parameters—58% oral bioavailability, dose normalized oral AUC of 1.2 h μg/mL, iv clearance of 16.7 mL/min/kg, and oral half-life of 1.6 h.

Compound (*S*)-**13** was evaluated in the *db*/*db* mouse model, using rosiglitazone as the comparator.[21] Compound (*S*)-**13** was shown to effectively lower glucose by 94% at 30 mg/kg in the 8-day study. Rosiglitazone exhibited a lowering of 74% glucose at 30 mg/kg (Fig. 3). Interestingly, (*S*)-**13** appeared to be a more potent glucose lowering agent than rosiglitazone based on oral dose. This could be a reflection of its improved affinity for PPARγ, superior PK parameters, and/or suggestive of PPARα mediated insulin sensitization.[22]

Compound (*S*)-**13** was also shown to effectively lower triglycerides by 119% at 30 mg/kg (vs 106% for rosiglit-

Table 1. In vitro activities of compounds **8** and **11–20**

Compound	R^1	R^2	R^3	*n*	hPPARγ SPA K_i (μM)[a]	hPPARα SPA K_i (μM)[a]	hPPARγ TA EC_{50} (μM) (% max activation)[b]	hPPARα TA EC_{50} (μM) (% max activation)[b]
Rosiglitazone					0.44	45% at 100 μM	0.158 (100%)	>10 (6%)
8	OMe	H	H	1	0.348	3.7	0.280 (98%)	3.14 (95%)
9	OEt	H	H	1	0.073	2.0	0.129 (96%)	1.23 (100%)
12	OMe	Me	H	1	1.6	4.8	0.335 (104%)	0.882 (114%)
13	2-Tetrahydrofuran		H	1	0.21	1.6	0.041 (88%)	0.226 (90%)
14	2-Tetrahydropyran		H	1	1.1	1.8	>10 (4%)[c]	>10 (5%)[c]
15	OEt	H	H	2	1.1	0.84	0.887 (87%)	0.886 (76%)
16	2-Tetrahydrofuran		4-OMe	1	0.093	0.84	0.105 (90%)	0.437 (95%)
17	2-Tetrahydrofuran		4-Cl	1	0.3	0.15	0.130 (81%)	0.048 (122%)
18	2-Tetrahydrofuran		3-OMe	1	0.02	1.2	0.005 (93%)	1.57 (98%)
19	2-Tetrahydrofuran		3-Me	1	0.043	1.1	0.012 (93%)	0.867 (93%)
20					0.16	3.49	0.156 (102%)	1.89 (77%)
21					2.3	7.3	2.50 (56%)	>10 (58%)[c]
(*R*)-**13**	2-Tetrahydrofuran		H	1	21.0	41.0	>10 (3%)[c]	>10 (6%)[c]
(*S*)-**13**	2-Tetrahydrofuran		H	1	0.043	0.34	0.026 (98%)	0.10 (97%)

[a] Binding affinities were measured using radioligands (darglitazone for PPARγ and GW2331 for PPARα) following published procedures.[19]
[b] Agonist activities were measured in human PPAR-GAL4 chimeric HepG2 cells analogous to published procedures.[20] The EC_{50} refers to the concentration at which 50% of a given compounds' intrinsic maximal response has been reached. % max activation refers to the level of maximal activation achieved by a given compound when compared with the standard reference full agonists (darglitazone for PPARγ and GW2331 for PPARα).
[c] No EC_{50} was obtained; no plateau reached in titration; maximal activity only reported.

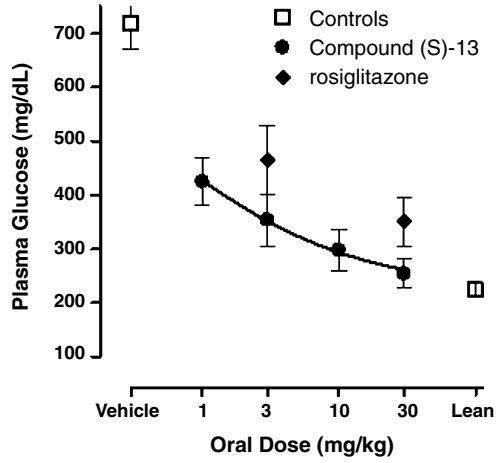


Figure 3. Effect of (*S*)-**13** on plasma glucose levels in *db*/*db* mice. Male *db*/*db* mice (7 weeks old) and lean mice were dosed daily for 8 days by oral gavage with vehicle or the indicated doses of test compound. Plasma glucose levels were measured before dosing on day −1 and 2 h post dose on day 8. Each data point represents the mean value (±SD) of six individual mice.

azone at 30 mg/kg). Unfortunately, (*S*)-**13** also caused an increase in body weight and a reduction in hematocrit (suggesting the presence of hemodilution) to a similar extent as rosiglitazone (Table 2).

In summary, we have identified a pyridine-2-propanoic acid class of potent dual PPARα/γ agonists. Systematic SAR studies generated a multitude of potent compounds with varied isoform selectivity. Compound (*S*)-**13** displayed oral efficacy greater than the benchmark rosiglitazone in a *db*/*db* mouse model of diabetes.

Table 2. Effect of Rosiglitazone (Rosi) and (*S*)-**13** on plasma glucose, triglycerides (TG), hematocrit (Hct), and body weight (BW)

Compound	Dose (mg/kg)	Glucose change (%)[a]	TG change (%)[a]	Hct change (%)[a]	BW change (%)[a]
Rosi	3	−51	−83	−1.2	+9.5
Rosi	30	−74	−106	−5.2	+17.4
(*S*)-**13**	3	−74	−105	−4.3	+15.5
(*S*)-**13**	30	−94	−119	−4.4	+20.5

Male *db*/*db* mice (7 weeks old) and lean mice were dosed daily for 8 days by oral gavage with vehicle or the indicated doses of test compound. Plasma glucose, triglycerides, hematocrit, and body weight were measured before dosing on day −1 and 2 h post dose on day 8.
[a] $p < 0.05$ versus vehicle control.

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