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Bioorganic & Medicinal Chemistry Letters 16 (2006) 6120–6123
Bioorganic & Medicinal Chemistry Letters

Pyridine-3-propanoic acids: Discovery of dual PPARα/γ agonists as antidiabetic agents

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Received 9 May 2006; revised 23 August 2006; accepted 28 August 2006
Available online 14 September 2006

Abstract—A series of novel pyridine-3-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, compounds (***S***)-**14** and (***S***)-**19** were selected for further profiling.

Type 2 diabetes is a metabolic disorder that accounts for 120 million patients worldwide and the number is likely to grow to greater than 200 million by the year 2010.[1] This is a complex disease and invariably type 2 diabetic patients also display cardiovascular risk factors including hypertension and dyslipidemia.[2,3] Both Avandia (rosiglitazone) and Actos (pioglitazone) are PPARγ agonists and elicit their insulin sensitizing effect through activating the PPARγ nuclear receptor. The clinical use of PPARγ agonists in type 2 diabetes has been plagued by mechanism based side effects including weight gain, fluid retention, and edema. PPARα is the molecular target for the fibrate class of lipid-modulating drugs.[4] Designing compounds with PPARα activity in addition to PPARγ agonist activity may offer improved alternatives toward control of hyperglycemia and hypertriglyceridemia in type 2 diabetic patients.[5] Scientists at Kyorin disclosed novel antidiabetic KRP-297,[6] the first published example of a dual PPARα and PPARγ agonist.[7]

In 1991, a series of PPAR analogues were disclosed, which for the first time did not contain a thiazolidine-2,4-dione pharmacophore.[8] These were propanoic acid derivatives with a substituent placed in the α-position such that the whole group could mimic the thiazolidine-2,4-dione ring. Based on the above and a knowledge of PPAR ligands publicly disclosed, we wished to synthesize compounds represented by the general structure **1** (Fig. 1). These efforts 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.[9]

The synthetic route for the preparation of compounds **5**–**22** is shown in Scheme 1. Coupling of commercially

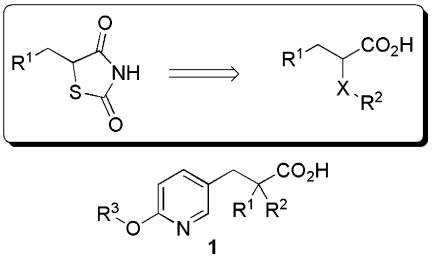

Figure 1. Thiazolidine-2,4-dione mimic and chosen lead scaffold **1**.

Keywords: PPAR; Diabetes; Carboxylic acid; SAR.
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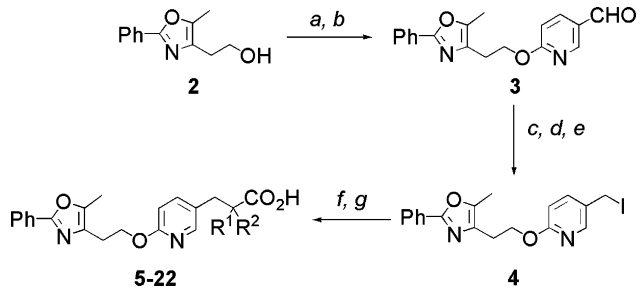
doi:10.1016/j.bmcl.2006.08.110

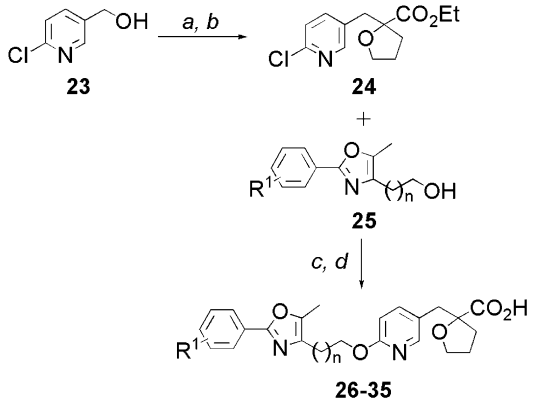


Scheme 1. Reagents and conditions: (a) 2,5-dibromopyridine, KO^{t}Bu, THF, reflux, 16 h, 83%; (b) ^{n}BuLi, Et_2O, THF, −78 °C then DMF, 0 °C, 1 h, 72%; (c) $NaBH_4$, MeOH, rt, 1 h, 100%; (d) $(COCl)_2$, DMF, CH_2Cl_2, rt, 3 h, 100%; (e) NaI, Me_2CO, rt, 4 h, 75%; (f) $R^1R^2CHCO_2Et$, NaHMDS, THF, −50 °C, 3 h; (g) LiOH, THF, MeOH, H_2O, rt, 16 h.

available 2,5-dibromopyridine and alcohol **2**, followed by conversion of the 5-bromo for an aldehyde moiety, afforded **3**. Aldehyde **3** was reduced to the alcohol, converted to the benzyl chloride and further transformed to iodide **4** via a Finkelstein reaction. Reaction of **4** with a variety of ester enolates allowed for an efficient variation of α-substituents. The final step was ester hydrolysis, giving final products **5**–**22**.

In an effort to look at the effects of substitution on the phenyloxazole moiety, a new synthetic route was required (Scheme 2). Commercially available alcohol **23** was converted to the benzyl bromide, which was then reacted with the enolate of ethyl tetrahydrofuran-2-carboxylate to afford **24**. Alcohols **25**, prepared in two steps, were then coupled to chloropyridine **24** via the method described by Buchwald.[10] Finally, hydrolysis of the esters gave products **26**–**35**.

The newly synthesized compounds were evaluated in the PPAR SPA binding assay to ascertain γ and α binding affinity.[11] 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 activation were measured.[12] Initially, we decided to investigate the effects of varying the α-substituents of **1**



Scheme 2. Reagents and conditions: (a) PBr_3, 160 °C, 3 h, 44%; (b) ester, NaHMDS, THF, −50 °C, 3 h, 78%; (c) $Pd(OAc)_2$, racemic-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl, Cs_2CO_3, PhMe, 115 °C, 16 h; (d) LiOH, THF, MeOH, H_2O, rt, 16 h.

(R^1 and R^2), Table 1. Compounds **5**–**10** highlight monoalkyl derivatives, which demonstrated that binding affinity and isoform selectivity are sensitive to the size of the substituent. Propyl and *iso*-butyl both proved optimal (compounds **7** and **9**). Compound **11** showed that acyclic dialkyl substitution offered no benefits over monoalkyl (cf. compound **5**). Compounds **12**–**15** highlight acyclic alkoxy derivatives, with compounds **12**–**14** proving especially interesting. Compounds **16**–**22** all contained cyclic α-substituents, with **16**–**18** being cycloalkyl and **19**–**22** being cycloalkoxy. Of particular note are compounds **17** and **19**, which displayed excellent potency in both the binding and transactivation assays. Differences between compounds **19** versus **20** and **21** versus **22** demonstrated that there was an optimal positioning of the heteroatom in these cycloalkoxy moieties.

The observed potency enhancement associated with the 2-tetrahydrofuran moiety (e.g., compound **19**) prompted us to hold this moiety constant and make changes to the substituents on the phenyloxazole group (Table 2). 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 **26**). Compounds **27**–**35** demonstrated that binding affinity and isoform selectivity were sensitive to the positioning of substituents on the phenyl ring. 4-substituents tended to afford compounds with a more balanced isoform profile, whereas 3-substituents tended to impart isoform selectivity favoring PPARγ (e.g., compound **27** versus **28**).

Finally, we shifted our attention to finding alternatives to the phenyloxazole group. Figure 2 depicts compound **36** as an example of this effort (Table 2). The synthesis of this class of compounds has been described previously and further information will be reported elsewhere.[9]

The synthetic route for the preparation of compound (***S***)-**19** is shown in Scheme 3. Reaction of **4** with the sodium enolate of oxazolidinone **37** (prepared from tetrahydrofuran-2-carbonyl chloride and (4*S*)-4-benzyl-1,3-oxazolidin-2-one) furnished a single diastereomer (as determined by HPLC, ^1H and ^{13}C NMR).[13] The final step was hydrolysis of the chiral auxiliary, affording compound (***S***)-**19** in >95% ee (as determined by chiral SFC). Compound (***S***)-**19** was subsequently determined to be the eutomer and thus predicted to have the *S* configuration based on literature precedent.[14]

The synthetic route for the preparation of compound (***S***)-**14** is shown in Scheme 4. Following work by Andersson,[14] racemic **14** was successfully reacted with (*R*)-phenylglycinol to afford a pair of diasteromeric amides. The two diastereomeric amides were easily separated by flash column chromatography. The first eluting product **38** (a single diastereomer as determined by HPLC, ^1H and ^{13}C NMR) was a white solid and the second eluting product (not shown) an oil. The final step was hydrolysis of the chiral auxiliary, affording compound (***S***)-**14** in >95% ee (as determined by chiral SFC). Compound (***S***)-**14** was subsequently determined

Table 1. In vitro activities of compounds **5**–**22**

Compound	R^1	R^2	*h*PPARγ SPA K_i[a] (μM)	*h*PPARα SPA K_i[a] (μM)	*h*PPARγ TA EC_{50} (μM) (% max activation)[b]	*h*PPARα TA EC_{50} (μM) (% max activation)[b]
Rosiglitazone			0.44	45% at 100 μM	0.158 (100%)	>10 (6%)[c]
5	Me	H	2.1	3.0	0.268 (113%)	0.287 (93%)
6	Et	H	1.1	1.3	0.065 (99%)	0.15 (106%)
7	^{n}Pr	H	0.24	0.88	0.454 (69%)	0.77 (92%)
8	^{i}Pr	H	8.8	4.1	1.28 (87%)	0.426 (93%)
9	^{i}Bu	H	0.36	0.43	1.65 (104%)	1.72 (98%)
10	^{t}Bu	H	12.0	9.4	NT	NT
11	Me	Me	5.1	6.8	0.984 (72%)	0.534 (112%)
12	OMe	H	0.063	0.18	0.013 (98%)	0.083 (95%)
13	OEt	H	0.15	0.043	0.006 (105%)	0.033 (96%)
14	OMe	Me	0.56	0.33	0.232 (116%)	0.144 (106%)
(***S***)-**14**	OMe	Me	0.27	0.57	0.110 (97%)	0.111 (99%)
15	OEt	Et	14.4	15.1	2.81 (64%)	4.67 (64%)
16	Cyclopropyl		7.98	44% at 100 μM	1.01 (80%)	6.15 (39%)
17	Cyclobutyl		0.394	0.633	0.125 (93%)	0.238 (94%)
18	Cyclohexyl		3.5	8.3	NT	NT
19	2-Tetrahydrofuran		0.038	0.078	0.012 (89%)	0.048 (106%)
(***S***)-**19**	2-Tetrahydrofuran		0.006	0.032	0.014 (93%)	0.165 (89%)
20	3-Tetrahydrofuran		17.0	33% at 100 μM	NT	NT
21	2-Tetrahydropyran		0.081	0.078	0.209 (103%)	0.228 (96%)
22	4-Tetrahydropyran		32% at 100 μM	2% at 11 μM	NT	NT

[a] Binding affinities were measured using radioligands (darglitazone for PPARγ and GW2331 for PPARα) following published procedures.[12]
[b] Agonist activities were measured in human PPAR-GAL4 chimeric HepG2 cells analogous to published procedures.[13] 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. NT, not tested

Table 2. In vitro activities of compounds **26**–**36**

Compound	R^1	*n*	*h*PPARγ SPA K_i (μM)	*h*PPARα SPA K_i (μM)	*h*PPARγ TA EC_{50} (μM) (% max activation)	*h*PPARα TA EC_{50} (μM) (% max activation)
26	H	2	0.81	1.84	NT	NT
27	4-Me	1	0.023	0.031	0.022 (96%)	0.023 (84%)
28	3-Me	1	0.016	0.277	0.005 (130%)	0.134 (86%)
29	4-Cl	1	0.052	0.014	0.042 (89%)	0.010 (87%)
30	3-Cl	1	0.011	0.099	0.001 (103%)	0.046 (117%)
31	4-CF3	1	0.094	0.021	0.006 (95%)	0.011 (143%)
32	3-CF3	1	0.015	0.100	NT	0.008 (81%)
33	4-OMe	1	0.017	0.065	0.005 (115%)	0.486 (96%)
34	3-OMe	1	0.007	0.215	0.002 (93%)	0.090 (104%)
35	4-CN	1	0.334	0.314	0.028 (96%)	0.031 (167%)
36			0.015	0.013	0.05 (95%)	0.133 (100%)

NT, not tested.

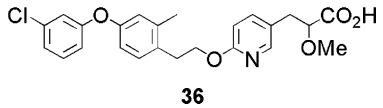


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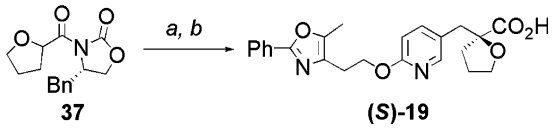
Figure 2. Biaryl ether **36**.

to be the eutomer, and again predicted to have the *S* configuration.[14]

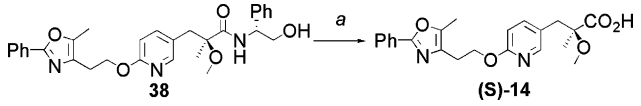
Both compounds were then selected for rat pharmacokinetic (PK) studies. Administration to male Sprague–Dawley (SD) rats resulted in satisfactory PK parameters for compound (***S***)-**19**—59% oral bioavailability, dose normalized oral AUC of 8.0 h μg/mL, iv clearance of 2.5 mL/min/kg, and oral half-life of 4.7 h. Compound (***S***)-**14** also displayed acceptable PK parameters—87% oral bioavailability, dose normalized oral AUC of 13.4 h μg/mL, iv clearance of 2.2 mL/min/kg, and oral half-life of 9.7 h.

In light of the above PK results, both compounds were evaluated in a *db*/*db* mouse model, using rosiglitazone as the comparator (Table 3).[15] Compound (***S***)-**19** was shown to effectively lower glucose by 99% at 1 mg/kg in an 8-day study. Compound (***S***)-**14** was shown to effectively lower glucose by 106% at 10 mg/kg. Rosiglitazone exhibited a lowering of 78% glucose at 30 mg/kg in this study.

Compounds (***S***)-**19** and (***S***)-**14** were also shown to effectively lower triglycerides (Table 3). Unfortunately, both



Scheme 3. Reagents and conditions: (a) **5**, NaHMDS, THF, −50 °C, 2 h, 85%; (b) LiOH, THF, MeOH, H_2O, 50 °C, 5 h, 17%.



Scheme 4. Reagents and conditions: (a) H_2SO_4, 1,4-dioxane, H_2O, 90 °C, 16 h, 96%.

Table 3. Effect of rosiglitazone (Rosi), (***S***)-**20**, and (***S***)-**15** 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	−46	−67	−5.3	+13.1
Rosi	30	−78	−138	−8.5	+17.3
(***S***)-**19**	0.03	−37	−67	−7.2	+11.7
(***S***)-**19**	1	−99	−147	−8.7	+15.7
(***S***)-**14**	1	−88	−177	−3.8	+13.2
(***S***)-**14**	10	−106	−205	−7.2	+16.8

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.

compounds also caused an increase in body weight and a reduction in hematocrit (suggesting the presence of hemodilution) to a similar extent as rosiglitazone.

In summary, we have identified a pyridine-3-propanoic acid class of potent dual PPARα/γ agonists. Systematic SAR studies generated a multitude of potent compounds with varied isoform selectivity. Compounds (***S***)-**14** and (***S***)-**19** displayed oral efficacy with greater apparent potency, at a given dose, than the benchmark rosiglitazone in the *db*/*db* mouse model of diabetes.

Acknowledgments

The authors gratefully acknowledge all our colleagues in the PPAR program for their technical support in the evaluation of the compounds presented in this manuscript. We also thank Bill Farrell and Christie Aurigemma for chiral SFC analysis.

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