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Bioorganic & Medicinal Chemistry Letters 15 (2005) 5035–5038
Bioorganic & Medicinal Chemistry Letters

Synthesis and biological activities of novel aryl indole-2-carboxylic acid analogs as PPARγ partial agonists

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Received 25 April 2005; revised 29 July 2005; accepted 1 August 2005
Available online 8 September 2005

Abstract—A series of novel aryl indole-2-carboxylic acids has been identified as potent selective PPARγ modulators. Their chemical synthesis and in vitro activities are discussed. Compound **5** was selected for in vivo testing in the *db*/*db* mouse model of type 2 diabetes and resulted in reduction of hyperglycemia at comparable plasma exposure when compared to rosiglitazone.

The peroxisome proliferator-activated receptor γ (PPARγ) is a member of the nuclear hormone receptor superfamily of ligand-dependent transcription factors and has been shown to be intimately involved in the regulation of adipogenesis, insulin action, and glucose homeostasis.[1,2] PPARγ is also the target protein for two drugs currently marketed for the treatment of type 2 diabetes, rosiglitazone and pioglitazone.[3,4] These PPARγ full agonists modestly ameliorate hyperglycemia. However, undesirable side effects are also associated with these agents.[5,6] The most significant side effects, including peripheral edema and weight gain, are serious enough to limit their clinical use in some diabetic patients. Recent work in the drug discovery community has focused on identifying selective PPARγ modulators (SPPARγMs). Such ligands are typical partial agonists in cell-based PPARγ transcriptional assays. The clinical application of the SPPARγMs promises to surpass that of the currently available PPARγ full agonists if their desirable efficacy profile can be maintained, while their negative side effects are minimized.[7–9]

Research in our laboratories was initiated based on a class of indole-2-carboxylates, which was identified as a screening lead in the infancy of this project. Compound **1a** is a novel SPPARγM and was highly selective for PPARγ versus the other PPAR isoforms, namely PPARα and PPARδ.[10] However, compound **1a** lacks useful in vivo activity in our *db*/*db* mouse efficacy model, presumably due to its poor pharmacokinetic (PK) properties. A medicinal chemistry effort was initiated based on the interesting biological profile of compound **1a**. The initial goal was to retain the indole-2-carboxylate core while introducing chemical diversity in a fashion that would result in unique compounds with improved PK profiles. To this end, two major structural changes have been introduced to compound **1a** to create the new scaffolding represented by compound **1b** (Fig. 1). First, the benzyl linkage of compound **1a** was eliminated in an effort to remove a potentially metabolically labile moiety. Second, the thioether linkage was replaced with an oxygen linkage not only to eliminate another potential metabolic liability but also to distinguish this class from the indole compounds patented recently by Bayer.[11] These efforts have led to the identification of a new class of potent SPPARγMs with improved in vivo efficacy. Herein, we report the synthesis, structure–activity relationships (SAR), and in vivo activity of this new class of compounds.

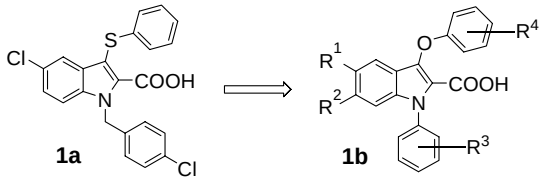

Figure 1. Screening lead and chosen scaffold.

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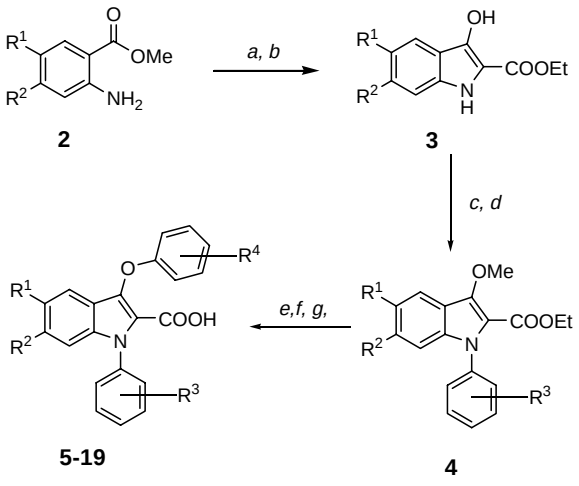
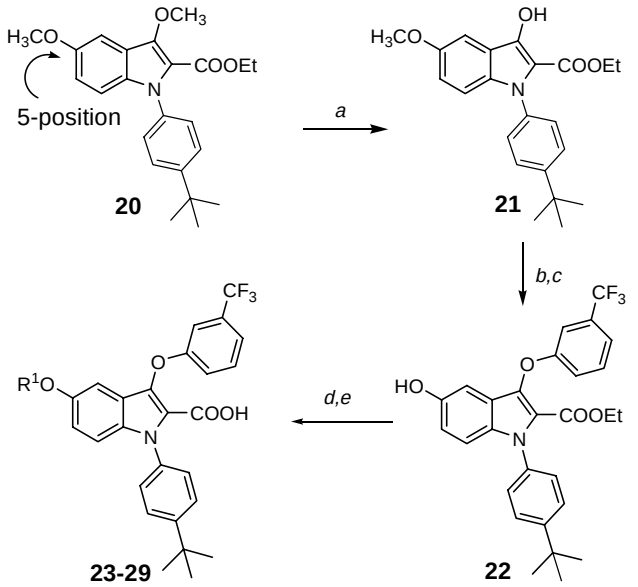
doi:10.1016/j.bmcl.2005.08.002



Scheme 1. Reagents and conditions: (a) Na_2CO_3, $BrCH_2CO_2Me$, 16 h, 80 °C, 90%; (b) NaOEt, Et_2O, 2 h, reflux, 90%; (c) excess CH_2N_2, CH_3OH, rt, 95%; (d) Ar-$B(OH)_2$, $Cu(OAc)_2$, Et_3N, 4 Å molecular sieves, CH_2Cl_2, 16 h, rt, 50–70%; (e) BBr_3, CH_2Cl_2, 1 h, 0 °C, 95%; (f) Ar-$B(OH)_2$, $Cu(OAc)_2$, Et_3N, 4 Å sieves, CH_2Cl_2, 16 h, rt, 50–70%; (g) NaOH, CH_3OH, 16 h, 60 °C, 90%.



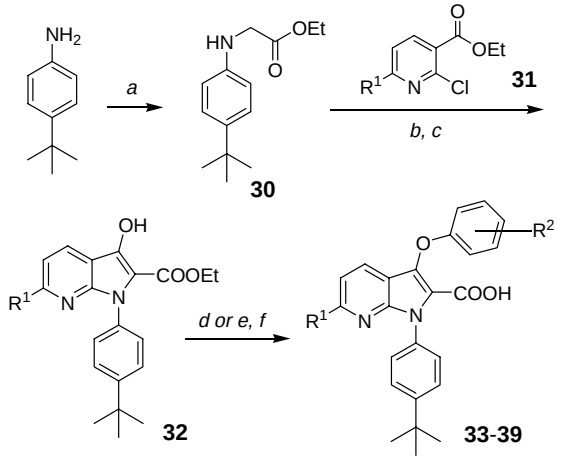
Scheme 2. Reagents and conditions: (a) 1.0 BBr_3, CH_2Cl_2, 1 h, −78 °C, 80%; (b) 3-(trifluoro-methyl)phenylboronic acid, $Cu(OAc)_2$, Et_3N, 4 Å molecular sieves, CH_2Cl_2, 16 h, rt, 65%; (c) BBr_3, CH_2Cl_2, 1 h, 0 °C, 80%; (d) R^1-Cl, Cs_2CO_3, DMF, 1 h, 80 °C, 75–85% or Ar-$B(OH)_2$, $Cu(OAc)_2$, Et_3N, 4 Å molecular sieves, CH_2Cl_2, 16 h, rt, 50–60%; (e) NaOH, CH_3OH, 16 h, 60 °C, 90%.

The synthetic route for the preparation of compounds **5–19** is shown in Scheme 1. Commercially available anthranilates were converted to the 3-hydroxy-indole core **3** in two steps.[12] Sequential N-arylation and O-arylation of compound **3** by two consecutive copper-catalyzed coupling reactions using various arylboronic acids were used as key steps for the introduction of aryl groups on the top and bottom of the molecule. Since there was no differentiation of reactivity between the hydroxy and NH groups, a protection strategy was developed to allow selective manipulation at each site. The 3-hydroxyl group was protected as the methyl ether by treatment with diazomethane (note: use of trimethylsilyldiazomethane gave no conversion). Subsequent N-arylation was readily accomplished by a copper-catalyzed coupling reaction with arylboronic acids to give compound **4**. To our knowledge, this is the first application of this copper-mediated coupling reaction to the arylation on an indole nitrogen.[13] The 3-hydroxy group in **4** was then deprotected and a second copper-mediated coupling reaction was performed on the hydroxyl group. The final step was the simple hydrolysis of the ethyl ester, which gave final products **5–19**.

To investigate the effects of chemical diversity at the 5 position of the indole scaffold, compound **20** (obtained as an intermediate from Scheme 1) was used for further derivatization. It was found that the 3-methyl ether in **20** could be selectively demethylated at −78 °C in the presence of the 5-methyl ether, which could then be removed at 0 °C. The 5-hydroxyl group was either arylated or alkylated using boronic acid coupling or halide displacement chemistry, respectively. This route led to 5-position variants that include compounds **23–29** (see Scheme 2).

A series of azaindoles was prepared to create further chemical diversity by incorporating a heteroatom, namely nitrogen, into the indole core. The synthesis of this new aza-construct is shown in Scheme 3. Alkylation of 4-*t*-butylaniline with ethyl bromoacetate, followed by cyclocondensation with the appropriate chloropyridines (**31**), afforded the hydroxyazaindole core (**32**). The latter was converted to compounds **33–39** using either the previously discussed copper coupling or halide displacement chemistry.

The newly synthesized compounds were evaluated in the PPAR SPA binding assay to ascertain γ and α binding profiles. The active analogs were also tested for functional activity in a PPAR-GAL4 transactivation (TA) assay,



Scheme 3. Reagents and conditions: (a) $BrCH_2CO_2Et$, Et_3N, DMF 16 h, 50 °C, 100%; (b) neat, 130 °C, 6 h, 50%; (c) NaOEt (21 wt% in EtOH), Et_2O, 2 h, reflux, 40%; (d) Ar-$B(OH)_2$, $Cu(OAc)_2$, 5.0 Et_3N, 4 Å molecular sieves, CH_2Cl_2, 16 h, rt, 30–50%; (e) R^2-Cl, Cs_2CO_3, DMF, 1 h, 80 °C, 75–85%; (f) NaOH, CH_3OH, 16 h, 60 °C, 90%.

where EC_{50} values, as well as percent maximal activation, were measured. One of the early compounds that emerged from our SAR studies was compound **5**, which gave very potent γ binding and transactivation activity (Table 1) and showed modest in vivo glucose lowering activity (vide infra). Compound **5** quickly established itself as a comparator for future SAR studies. Notably, *para* substitution different than tBu at R^3 (e.g., **9** and **10**) resulted in diminished binding and functional activities. The combination of a lipophilic trifluoromethoxy group at R^2 and a chlorine at R^4 (e.g., **14**) led to a similar erosion of activity when compared to compound **5**. Chloro substitution at R^1 or R^2 retained the same binding potency as compound **5**, but a 5-fold loss in functional activity was observed. The pyridyl analogs at R^1 (e.g., **28** and **29**) were the most potent compounds prepared in this series with respect to intrinsic in vitro activity. Unfortunately, **28** and **29** suffered from poor PK and low bioavailability (dose normalized AUC = 0.0 and 0.3 μM h, t1/2 = 0.8 and 1.8 h, F = 2.4% and 9.8% for **28** and **29**, respectively) and thus were not extensively studied. The detailed SAR is given in Table 1.

Observations of the potency enhancing features of a pyridyl moiety in the previous set of compounds prompted the introduction of nitrogen directly into the core. A series of azaindoles was prepared and the SAR of analogs **33**–**39** is shown in Table 2. It was found that chlorine substitution at R^1 led to potency comparable to that of compound **5**. Also, as with the previous group of compounds, the pyridyl analogs (**34** and **39**) again showed the best in vitro potency. However, in the *db*/*db* mouse model, compounds **33**, **35**, and **39** at 30 mpk showed no efficacy and subsequent exposure measurements revealed that drug levels were below the limits of detection.

Since compound **5** appeared to possess the most interesting biological profile, as well as desirable pharmacokinetic properties (dose normalized AUC = 9.19 μM h,

Table 1. In vitro activities of compounds **5**–**19** and **23**–**29**

Compound	R^1	R^2	R^3	R^4	*h*PPAR γ/α SPA binding IC_{50} (μM)[a]	*h*PPAR γ TA EC_{50} (μM)[b] (%max at 3 μM)
Rosiglitazone					0.210	0.022 (168%)
1a					0.026/>15	0.055 (31%)
5	H	H	*p*-tBu	*m*-CF_3	0.012/10.575	0.013 (31%)
6	H	H	*p*-tBu	*p*-OCF_3	0.049/3.577	(13%)*
7	H	H	*p*-tBu	*m*-OEt	0.049/>50	0.233 (30%)
8	H	H	*p*-tBu	*m*-OH	0.078/>50	0.161 (22%)
9	H	H	*p*-OMe	*m*-CF_3	0.115/>50	0.334 (25%)
10	H	H	*p*-CF_3	*m*-CF_3	0.107/3.197	NT
11	H	H	*m*-iPr	*m*-CF_3	0.060/>15	NT
12	H	H	*m*-iPr	*p*-CF_3	0.120/>15	NT
13	H	H	*m*-iPr	*m*-OH	0.102/>50	NT
14	H	OCF_3	*p*-tBu	*p*-Cl	0.298/>15	0.411 (22%)
15	H	Cl	*p*-tBu	*m*-CF_3	0.027/>15	0.106 (27%)
16	H	Cl	*p*-tBu	*m*-iPr	0.019/>15	NT
17	Cl	H	*p*-tBu	*m*-CF_3	0.017/>15	0.136 (37%)
18	Cl	H	*p*-tBu	3,5 di-CF_3	0.083/>15	(53%)*
19	Cl	H	*p*-tBu	3-CF_3, 4-Cl	0.013/4.482	(45%)*
23	CH_3	H	*p*-tBu	*m*-CF_3	0.039/>15	(41%)*
24	H	H	*p*-tBu	*m*-CF_3	0.318/>50	NT
25	Et	H	*p*-tBu	*m*-CF_3	0.018/6.271	0.034 (21%)
26	*i*Bu	H	*p*-tBu	*m*-CF_3	0.018/4.154	0.091 (34%)
27	pyr-2-yl	H	*p*-tBu	*m*-CF_3	0.011/9.024	0.126 (32%)
28	4-CF_3-pyr-2-yl	H	*p*-tBu	*m*-CF_3	0.005/11.475	0.006 (42%)
29	4-Cl-pyr-2-yl	H	*p*-tBu	*m*-CF_3	0.002/>15	0.002 (20%)

Note: No δ activity <50 μM and thus not shown here.

[a] Binding affinities were measured using radioligands following published procedures.[14]

[b] Agonist activities were measured in a PPAR-GAL4 construct following published procedures.[14] The EC_{50} refers to the concentration which yields a 50% response relative to the standard; partial agonism percentages are given in parentheses.

* No EC_{50} was obtained; no plateau reached in titration; maximal activity only reported. NT = not tested.

Table 2. In vitro activity of compounds **33**–**39**

Compound	R^1	R^2	*h*PPAR γ/α IC_{50} (μM)	*h*PPAR γ TA EC_{50} (μM) (%max at 3 μM)
33	H	*m*-CF_3	0.075/>50	0.464 (30%)
34	H	4-CF_3-pyr-2-yl	0.251/>50	0.034 (56%)
35	Cl	*m*-CF_3	0.021/>15	0.176 (23%)
36	OCH_3	*m*-CF_3	0.100/>15	0.299 (31%)
37	Cl	*m*-OCH_3	0.104/>15	0.755 (19%)
38	Cl	*m*-SO_2CH_3	0.202/>50	(29%)*
39	Cl	4-CF_3-pyr-2-yl	0.058/>50	0.095 (7%)

* No EC_{50} was obtained; no plateau reached in titration; maximal activity only reported. NT = not tested.

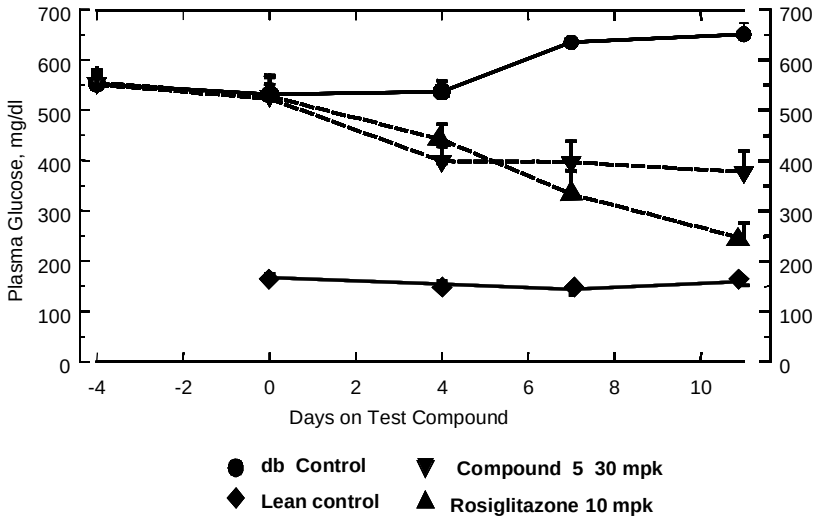


Figure 2. Effects of test compounds on plasma glucose levels in *db*/*db* mice. Male *db*/*db* mice (11–13 weeks old) and lean mice were dosed daily for 11 days by gavage with vehicle or the indicated doses of test compounds. Plasma glucose levels were measured before each dosing at days 4, 7, and 11. Each data point represents the mean value (±SD) of seven individual mice.

t1/2 = 0.5 h), our efforts were directed back to further profile compound **5** in our in vivo model.

Compound **5** was evaluated in the *db*/*db* mouse model, using rosiglitazone as the comparator. Compound **5** was shown to effectively lower glucose by 54% at 30 mpk in the 11-day study with 5% body weight increase vs the vehicle group. Rosiglitazone exhibited a lowering of 70% glucose at 10 mpk with 8% body weight increase. Pharmacokinetic measurements after the termination of the study showed that compound **5** gave a plasma exposure of 275 μM h. The exposure of rosiglitazone was not measured in this assay, but it typically gave an exposure of 300 μM h, derived from averaging values from six previous assays. Thus, compound **5** demonstrated about 80% of the glucose-lowering efficacy of rosiglitazone at comparable plasma exposure (see Fig. 2).

In summary, chemical modifications of the indole-2-carboxylate core led to novel and intrinsically potent SPPARγMs. The synthetic highlight was the extension of copper-catalyzed boronic acid coupling to include the indole nitrogen. This arylation strategy enabled rapid analoging and introduction of chemical diversity to evaluate this class better. The SAR was expanded to include insertion of a heterocycle into the core resulting in an azaindole core; however, these compounds were submitted for in vivo evaluation and showed no measurable plasma exposure. Compound **5** was evaluated in the *db*/*db* mouse model and resulted in comparable lowering of glucose at a similar plasma concentration as rosiglitazone.

Acknowledgments

The authors greatly acknowledge all our colleagues in the PPAR program for their technical support in the evaluation of the compounds presented in this manuscript.

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