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Synthesis and pharmacological evaluation of novel benzoylazole-based PPAR α/γ activators

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ABSTRACT

In our search for new PPARα/γ agonists, we designed and synthesized a series of benzoylazole-based carboxylic acids. Compound **9** showed potent PPARγ partial agonistic activity with modest PPARα agonistic activity. The sodium salt of **9** (**9Na**) demonstrated potent efficacy in lowering both blood glucose and lipids in an animal model without causing significant body weight gain, a well-known side effect associated with PPARγ full agonists.

Peroxisome proliferator-activated receptors (PPARs) belong to a large family of ligand-activated nuclear transcription factors involved in glucose and lipid metabolism.[1] Three subtypes, PPARα, γ× and δ of this receptor family have been identified and found to be important targets for treating metabolic disease such as type 2 diabetes, dyslipidemia, atherosclerosis. Clinically used PPARα agonists include the fibrate class of drugs, such as fenofibrate and clofibrate, which elevate HDL cholesterol levels and reduce triglyceride levels. Clinically used PPARγ agonists, on the other hand, include the thiazolidinedione class of drugs, such as rosiglitazone[2] and pioglitazone,[3] which reduce blood glucose levels, but undesirably increase body weight and cause fluid retention.[4]

In recent years, the concept of PPARα/γ dual agonists has gained enormous attention.[5] Such dual agonists with both glucose and lipid lowering effects have been identified as potential therapeutic agents for diabetic hyperglycemia and dyslipidemia. However, the same disadvantages as those seen with PPARγ agonists, that is, body weight gain and fluid retention, have caused many development programs of PPARα/γ dual agonists to be discontinued. Therefore, novel PPARα/γ dual agonists with minimal side effects are needed.

Our group has recently reported the design, synthesis and biological activity of a novel benzoylpyrrole-based series of PPARα/γ dual activators derived from SMP-534, a TGF-β signaling pathway inhibitor as a starting compound.[6] A detailed study of these activators led to the identification of lead compound **1** (Fig. 1), which has balanced dual-activity for both receptor subtypes. As a part of exploring the scope of the structure–activity relationships, we decided to develop a PPARγ-weighted PPARα/γ activator and investigate the effects of expanding the pyrrole ring of **1** into an azole ring on the PPARα/γ dual agonistic activity. In this Letter, we focus on the design, synthesis, and structure–activity relationships of various benzoylazole analogs as PPARα/γ dual activators.

Synthesis of azole derivatives **5a**, **5d**, and **6a–d** is depicted in Scheme 1.[7] Treatment of imidazole **2a** with 4-toluoyl chloride in the presence of triethylamine and pyridine afforded the 2-(4-toluoyl)imidazole **3a** in 69% yield.[8] The other 2-(4-toluoyl)azoles **3b–d** (4,5-dimethylimidazole **3b**, 4,5,6,7-tetrahydrobenzimidazole **3c**, and benzimidazole **3d**) could be prepared from **2b–d** in 76–83% yield by the same procedure. Allylation of **3a–d** with allyl bromide in the presence of K_2CO_3 and 18-crown-6 gave allyl azoles **4a–d** quantitatively. **4a** and **4d** were coupled with ethyl 3-iodophenoxy acetate by means of Heck reaction, followed by standard hydrolysis to afford carboxylic acids **5a** and **5d**, respectively. Additionally, **4a–d** were coupled with *tert*-butyl 2-(3-iodophenoxy)-2-methylpropanoate by means of Heck reaction, followed by deprotection

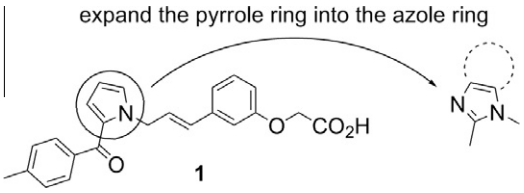

Figure 1. Design of benzoylazole-based carboxylic acids.

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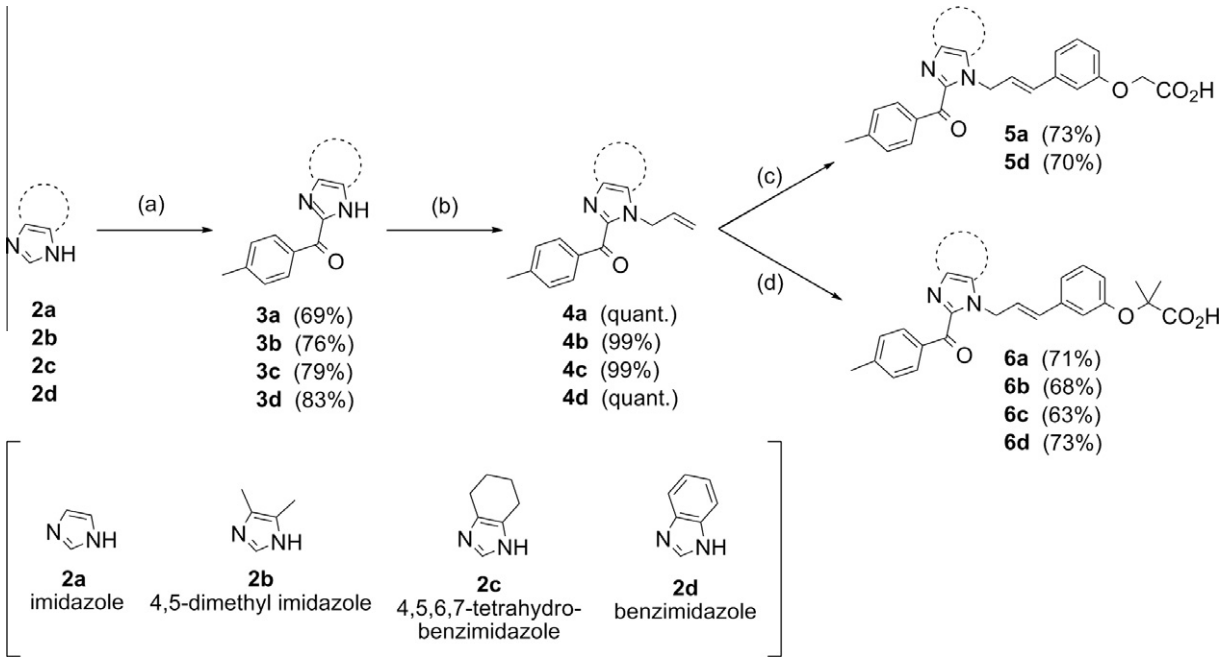
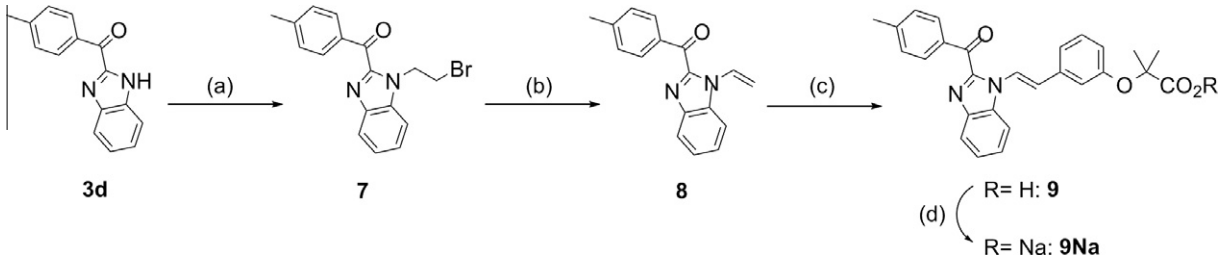
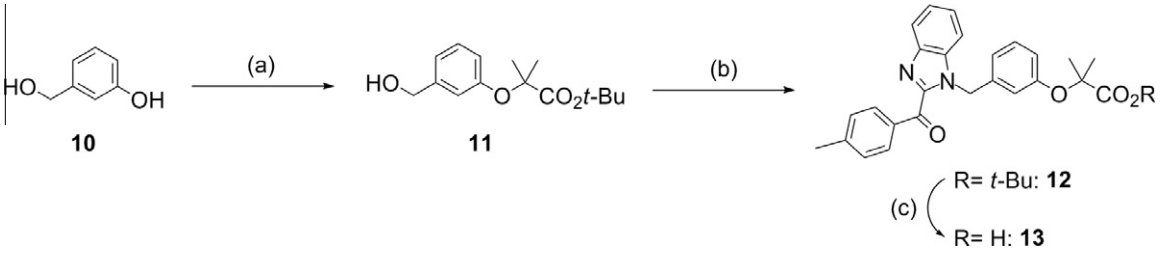


Scheme 1. Reagents and conditions: (a) (1) 4-toluoyl chloride, Et_3N, pyridine, 40 °C; (2) NaOH aq; (b) K_2CO_3, 18-crown-6, allyl bromide, THF, 40 °C; (c) (1) ethyl 3-iodophenoxy acetate, $Pd(OAc)_2$, Et_3NBnCl, Cy_2NMe, DMF, 70 °C; (2) NaOH aq, THF, MeOH, rt; (d) (1) *tert*-butyl 2-(3-iodophenoxy)-2-methylpropanoate, $Pd(OAc)_2$, Et_3NBnCl, Cy_2NMe, DMF, 70 °C; (2) TFA, $CHCl_3$, 40 °C.



Scheme 2. Reagents and conditions: (a) 1.2-dibromoethane, Cs_2CO_3, acetone, 50 °C, 85%; (b) DBU, DMSO, 50 °C, 94%; (c) (1) *tert*-butyl 2-(3-iodophenoxy)-2-methylpropanoate, $Pd(OAc)_2$, Et_3NBnCl, Cy_2NMe, DMF, 70 °C; (2) TFA, $CHCl_3$, 40 °C, 64%; (d) NaOH aq, MeOH, rt, 73%.



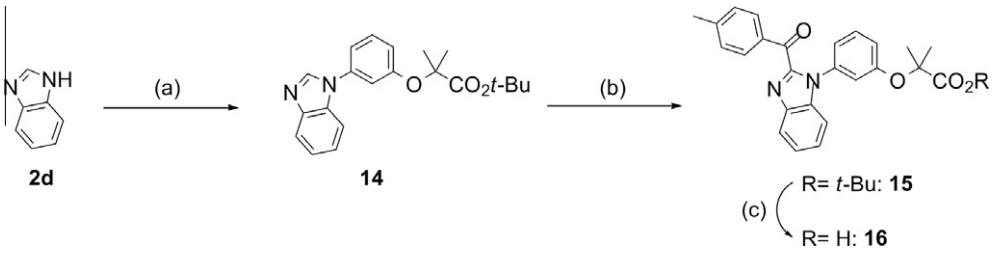
Scheme 3. Reagents and conditions: (a) *tert*-butyl 2-bromo-2-methylpropanoate, K_2CO_3, methylketone, 80 °C, 84%; (b) **3d**, DIAD, PPh_3, THF, rt; (c) TFA, $CHCl_3$, 72 °C, 58% (two steps from **11**).

of *tert*-butyl group with trifluoroacetic acid to afford the carboxylic acids **6a–d**.

Synthesis of benzimidazole derivative **9** or **9Na** is described in Scheme 2. Alkylation of **3d** with 5 equiv of 1,2-dibromoethane in the presence of copper iodide and Cs_2CO_3 gave *N*-(2-bromoethyl) analog **7** in 85% yield. Treatment of **7** with DBU in DMSO afforded the *N*-vinyl analog **8**. Heck reaction of **8** with *tert*-butyl 2-(3-iodophenoxy)-2-methylpropanoate, followed by deprotection of the *tert*-butyl group with trifluoroacetic acid afforded the carboxylic acid **9**. Compound **9** was converted to its sodium salt **9Na** to have better physical properties for in vivo study.

Synthesis of benzimidazole derivative **13** is shown in Scheme 3. Alkylation of 3-(hydroxymethyl)phenol **10** with *tert*-butyl 2-bromo-2-methylpropanoate selectively afforded phenol-modified ester **11** in 84% yield. Mitsunobu reaction[9] of **11** with **3d** afforded the *tert*-butyl ester **12**, which was subsequently deprotected with trifluoroacetic acid to give carboxylic acid **13**.

Synthesis of benzimidazole derivative **16** is described in Scheme 4. Benzimidazole **2d** was coupled with *tert*-butyl 2-(3-iodophenoxy)-2-methylpropanoate in the presence of Cs_2CO_3, 1,10-phenanthroline, and dibenzylideneacetone by means of Cu-mediated coupling reaction to provide **14** in 71% yield.[10]



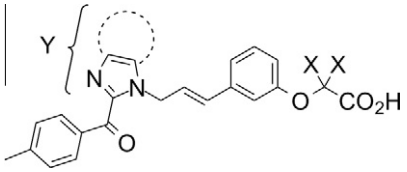
Scheme 4. Reagents and conditions: (a) *tert*-butyl 2-(3-iodophenoxy)-2-methylpropanoate, CuI, Cs_2CO_3, 1,10-phenanthroline, dibenzylideneacetone, DMF, 120 °C, 71%; (b) 4-toluoyl chloride, Et_3N, pyridine, 50 °C; (c) TFA $CHCl_3$, 40 °C, 58% (two steps from **14**).

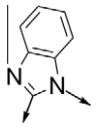
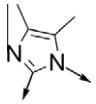
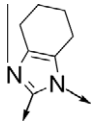
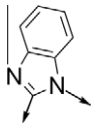
Reaction of **14** with 4-toluoyl chloride under basic conditions generated *tert*-butyl ester **15**, which was subsequently deprotected to furnish carboxylic acid **16**.

All the compounds prepared were screened in human PPARα and γ transactivation assays,[11] and the selected compound **9** was tested in mouse PPARα assay. As shown in Table 1, imidazole analog **5a** was inactive for both receptor subtypes (EC_{50} >10 μM), while benzimidazole analog **5d** showed moderate PPARγ activity. Dimethyl substitution at the α-position of the carboxylic group resulted in a marked increase in PPARα and PPARγ activity (**6a** vs **5a** and **6d** vs **5d**). Substituted imidazole analogs 4,5-dimethylimidazole **6b** and 5,6,7,8-tetrahydrobenzimidazole **6c** also displayed moderate PPARα/γ activity. Interestingly, increasing the volume of the substituent of the imidazole ring tended to boost potency at the γ-isoform. In this series, benzimidazole analog **6d** displayed the best result in terms of EC_{50} value for PPARγ. Next, Efficacy of compounds to activate PPARγ was examined. Compounds **5d** and **6a–d**, which activated PPARγ with a maximal efficacy 15–51% as compared to that of pioglitazone (defined as 100%), were considered as PPARγ partial agonists.

To develop benzimidazole-based PPARγ agonists with better activity, we examined the effects of shortening the linker between the left-hand phenyl ring and the benzimidazole ring, since the chemical structures of almost all known potent PPARγ partial agonists or modulators appear to be rigid and compact (Fig. 2).[12] The results are given in Table 2. As expected, compound **9** containing

Table 1
PPAR transactivation activity of benzoylazole-based derivatives **5a**, **5d** and **6a–d**



Compd	X	Y	EC_{50}[a] (μM)	
			hPPARγ[b] (%max)	hPPARα[c] (%max)
Pioglitazone			0.39 (100%)	n.t.
Fenofibric acid			n.t.[d]	12 (100%)
5a	H		>10	>10
5d	H		4.6 (15%)	>10
6a	Me		12 (36%)	0 62 (56%)
6b	Me		4.8 (36%)	3 6 (60%)
6c	Me		3.0 (33%)	3 6(60%)
6d	Me		1.7 (51%)	3.6 (42%)

[a] EC_{50} is the compound concentration at which 50% of the maximum efficacy of PPAR activation has been reached.
[b] The maximum efficacy of PPARγ activation of pioglitazone was defined as 100%.
[c] The maximum efficacy of PPARα activation of fenofibric acid was defined as 100%.
[d] n.t. = not tested.

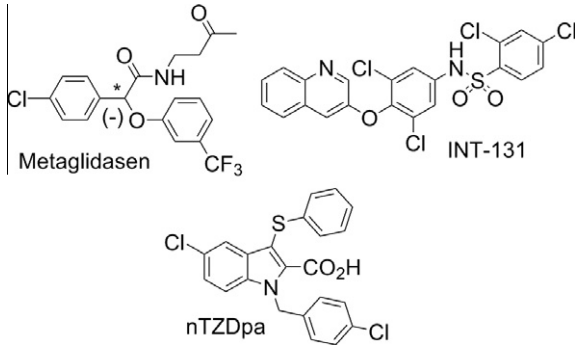
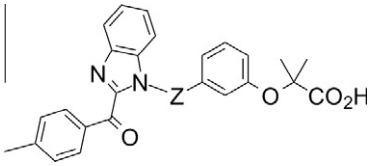
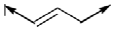


Figure 2. Chemical structures of selected PPARγ partial agonists or modulators.

Table 2
PPAR transactivation activity of **9**, **13** and **16**



Compd	Z	EC_{50}[a] (μM)		
		hPPARγ (%max)[b]	hPPARα (%max)[c]	mPPARα (%max)[c]
9		0.13 (39%)	2.4 (44%)	1.7 (77%)
13		6.0 (10%)	n.t.[d]	n.t.
16	None	3.3 (33%)	n.t.	n.t.
6d		1.7 (51%)	3.6 (42%)	n.t.

[a] EC_{50} is the compound concentration at which 50% of the maximum efficacy of PPAR activation has been reached.
[b] The maximum efficacy of PPARγ activation of pioglitazone was defined as 100%.
[c] The maximum efficacy of PPARα activation of pioglitazone was defined as 100%.
[d] n.t. = not tested.

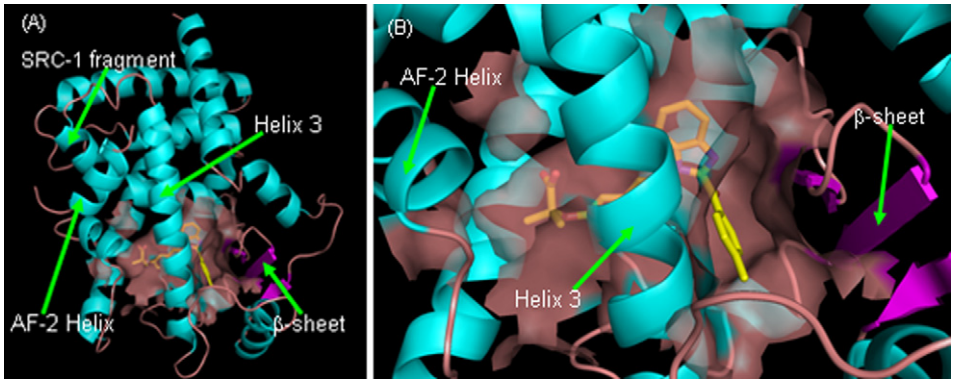


Figure 3. Crystal structure of the human PPARγ ligand binding domain complexed with compound **9**. Ribbons drawing showing the ternary complex of human PPARγ receptor ligand binding domain with compound **9** and the LXXLL helix domain of SRC-1. Compound **9** is shown in yellow. The accessible molecular surface area of the protein–ligand is shown as a semitransparent skin. (A) Overall view. (B) Zoomed view.

Table 3
Evaluation of **9Na** in *db*/*db* mice[a]

Treatment	Pioglitazone[b]	**9Na**[b]
Glucose correction[c] (%)	46	60
Triglyceride correction[c] (%)	69	86
HDL-C correction[c] (%)	10	38
Body weight gain (%)	17	11

[a] Male *db*/*db* mice were dosed daily for 14 days by gavage with vehicle or the test compounds.
[b] Pioglitazone and **9Na** were administrated orally with 30 mg/kg/day.
[c] Glucose, triglyceride and HDL-C concentrations were calculated at percent correction of vehicle control. Mean value ($n = 6$).

an (*E*)-vinylene linker (two carbon atoms) showed 13-fold enhanced PPARγ activity compared to the parent compound **6d**, which contains an allyl linker (three carbon atoms). In contrast, compounds **13** containing a methylene linker (one carbon atom) and **16** containing no linker (zero carbon atoms) displayed weaker PPARγ activity than **6d**. Compound **9**, on the other hand, exhibited high selectivity for human PPARγ over human PPARα and mouse PPARα (18-fold and 13-fold, respectively). Furthermore, compound **9** retained partial PPARγ agonistic activity defined as 39% of maximal activation by pioglitazone in transactivation assay.

To gain insight into the binding mode of compound **9** as a PPARγ partial agonist, we co-crystallized the ternary complex of the human PPARγ receptor ligand binding domain with **9** and a receptor co-activator SRC-1 fragment (Fig. 3).[13a] The shape of this complex in the AF-2 helix region was reminiscent of previously published PPARγ-ligand complex as a full-agonist type conformation.[13] However, unlike PPARγ full-agonists, compound **9** was found to have a hydrophobic interaction with lipophilic amino acid residues in Helix 3 and β-sheet. Since interaction of a ligand with helix 3 and β-sheet has recently been reported to be necessary for PPARγ partial agonistic activity,[14] we assume that PPARγ partial agonistic activity of **9** is mainly attributed to a characteristic hydrophobic interaction with helix 3 and β-sheet. Further structural analysis to clarify this matter is in progress.

The sodium salt of **9** (**9Na**) was next evaluated in an in vivo assay. In a rat pharmacokinetic study, C_{max} and bioavailability of **9Na** given orally at the dose of 10 mg/kg were 4.34 μg/mL and 110%, respectively. When **9Na** was intravenously administered to rats at 1 mg/kg, CL, V_d, and $t_{1/2}$ were 3.48 mL/min/kg, 0.747 L/kg and 87.1 min, respectively. This pharmacokinetic profile was suitable to perform further studies in an animal model of diabetes.

The in vivo anti-diabetic and lipid-lowering effects of **9Na** were evaluated in a 14-day study in *db*/*db* mice.[15] The data collected from this study are shown in Table 3. Compound **9Na** was orally administrated to *db*/*db* mice at 30 mg/kg/day and showed excellent efficacy characterized by significant reduction in plasma glucose levels (−60%) and triglyceride levels (−86%) and elevation of HDL cholesterol levels (+38%). This in vivo efficacy was greater than that of pioglitazone at the same dose. On the other hand, body weight gain caused by **9Na** as PPARγ mechanism-based side effect was significantly smaller than that caused by pioglitazone. No difference in food intake was observed between the mice treated with **9Na** or pioglitazone and those treated with the vehicle. Although activation of PPARα has been reported to reduce body weight,[16] **9** possesses weak mouse PPARα agonistic activity compared to its activation of PPARγ (13-fold). In contrast, PPARγ partial agonists or modulators have been reported to cause little or no change in body weight.[17] Therefore, we assume that PPARα agonistic activity of **9** as well as its PPARγ partial agonistic activity would contribute to attenuation of body weight gain as a side effect.

In summary, we explored in this study the structure–activity relationships of a series of benzoylazole-based carboxylic acids and identified benzimidazole analogs as potent PPARα/γ agonists. In particular, compound **9** displayed potent PPARγ partial agonistic activity with modest activation of PPARα. The anti-diabetic and lipid-lowering effects of **9Na** were superior to those of pioglitazone in rodent models of type 2 diabetes with no serious body weight gain. Unlike the marketed thiazolidinediones, **9** was found to be a PPARγ partial agonist as evidenced by the results of a transactivation assay, those of X-ray crystal structure of the complex of **9**, and those of an in vivo efficacy study. These unique pharmacological properties of compound **9** would make it an attractive candidate for the treatment of type 2 diabetes.

Acknowledgments

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11. Transactivation assay: COS-1 cells were inoculated in 24-well plates (5×10^4 cells/well) and cultured for approximately 24 h in Dulbecco's modified Eagle's essential medium (DMEM) supplemented with 10% charcoal-treated fetal calf serum in 5% CO_2 at 37 °C. The cells were transfected with each expression plasmid for a fusion protein of the ligand binding domain of PPAR and GAL4, and a GAL4-responsive luciferase reporter plasmid by lipofection, using Lipofectamine™ and Plus™ Reagent. Culture medium was removed 4 h after the initiation of transfection, followed by addition of medium containing the test substance (1 mL/well), and the cells were then cultured in a CO_2 incubator at 37 °C with 5% CO_2. No drug control cells were added with DMSO concentration of 0.1% as final. After 24 h, cells were lysed and the luciferase activity was measured in a luminometer.
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