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Discovery of BR102375, a new class of non-TZD PPARγ full agonist for the treatment of type 2 diabetes

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ABSTRACT

As a potential treatment of type 2 diabetes, a novel PPARγ non-TZD full agonist, compound 18 (BR102375) was identified from the original lead BR101549 by the SAR efforts of the labile metabolite control through bioisosteres approach. In vitro assessments of BR102375 demonstrated its activating potential of PPARγ comparable to Pioglitazone as well as the induction of related gene expressions. Further in vivo evaluation of BR102375 in diabetic rodent models successfully proved its glucose lowering effect as a potential antidiabetic agent, but the anticipated suppression of weight gain was not evident. The X-ray co-crystal analysis of BR102375-PPARγ LBD unexpectedly revealed binding modes totally different from those of BR101549, which was found, instead, closely resembled to those of TZD full agonists.

Since aging population has grown rapidly, the adequate control of chronic diseases has become major concern for the entire society not only to meet the needs of the aging population, but also to keep the potential economic burden from the medical expense as low as affordable. As a major culprit to threat the normal life style of, in particular, the senior population, the prevalence of diabetes has risen rapidly and it is reported to be the seventh leading cause of death in 2030.[1] Type 2 diabetes is a chronic disease of impaired blood glucose control either by insufficient secretion of insulin from the pancreatic beta-cells or decreased insulin sensitivity.[2] More seriously, type 2 diabetes also enables onset of scores of devastating complications including cardiovascular disease,[3] chronic kidney disease, stroke and blindness.[4] Besides the tremendous efforts to promote the life style to prevent the disease, the relentless efforts to expand the treatment options of type 2 diabetes still have been listed high priority in drug discovery research.

Among the many biological targets for the treatment of type 2 diabetes explored hitherto, a nuclear receptor peroxisome proliferator-activated receptorγ (PPARγ) could be listed as one of the most successful targets for which various effective modulators have been developed. Despite the target relevant adverse effects, some of them such as Rosiglitazone and Pioglitazone could reach the market.[5] All of the known PPARγ full agonists to this date are based on common scaffold called thiazolidinedione (TZD) which was deemed to contribute to the characteristic binding modes critical to draw the full effect of the protein.[6] However, the concerns from the toxicities unleashed in clinical application limited their therapeutic use by the Black Box Warning label or market withdrawal. To avoid the side effects suspected to be ascribed to the transcriptions caused by full agonism of TZD scaffold, studies to identify non-TZD PPARγ agonists produced a few promising candidates with partial agonism. Despite their weaker transcriptional activation, the selective PPARγ modulators (SPPARMs) indeed showed efficacy in animal models with even less adverse effects culminating in progress into clinical trials. However, partial agonism of PPARγ was eventually demonstrated not enough to show efficacy in the clinical settings and currently none of the non-TZD PPARγ agonists has achieved FDA approval.[7]

In our previous studies[8,9] to find additional therapeutic indications as part of the "Value Expansion" efforts of our original anti-hypertensive ARB (angiotensin receptor blocker) Fimasartan (brand name: Kanarb) which has been approved by Korean FDA in 2010, a potent PPARγ agonist (BR101549) has been identified (Fig. 1). Due to its ester moiety, BR101549 proved itself metabolically unstable releasing the corresponding carboxylic acid which was suspected to be further

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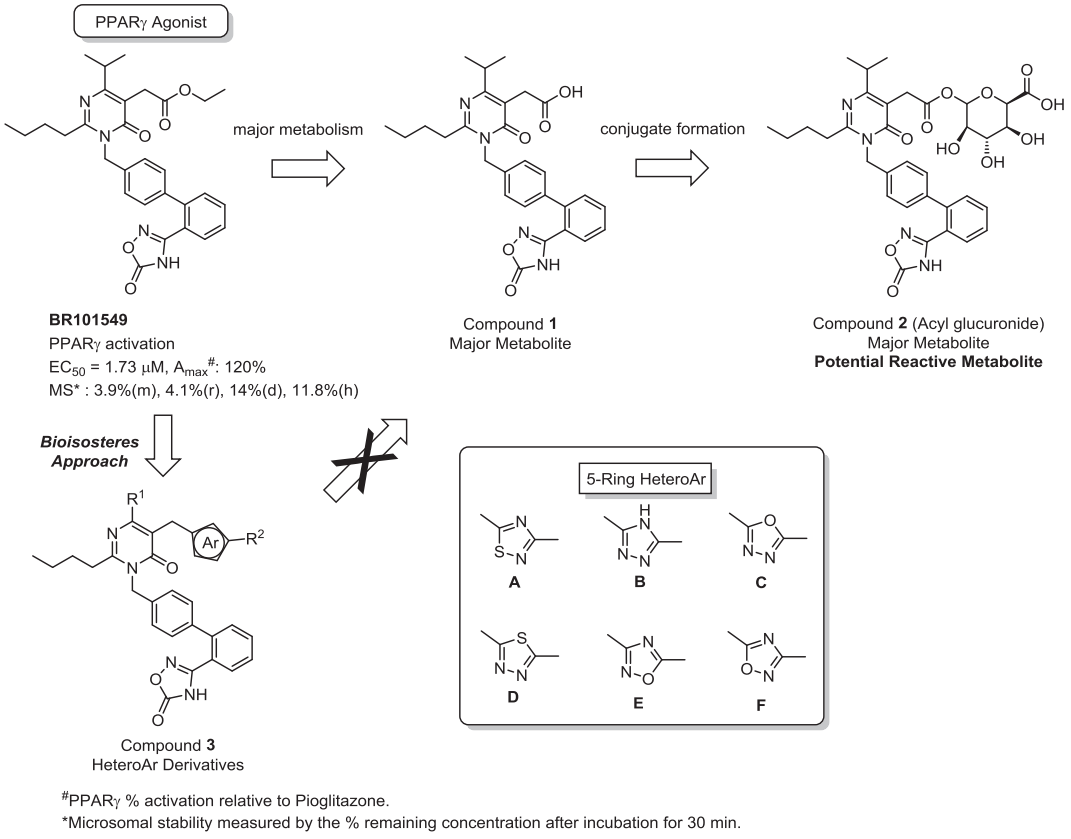


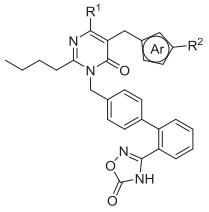
Fig. 1. Major metabolites of BR101549 and the bioisosteres approach.

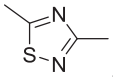
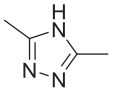
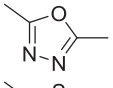
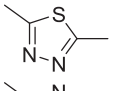
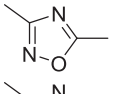
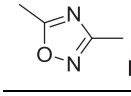
metabolized toward potentially toxic reactive acyl glucuronide. A series of Met ID studies indeed demonstrated the formation of acyl glucuronide from the carboxylic acid metabolite. To overcome the liability, SAR efforts were first focused on modification of ester alkyls hoping to suppress the degradation by sterically bulkier alkyl groups. Though there appeared some improved results, the intrinsic tendency prone to hydrolysis to the carboxylic acid seemed inevitable and subsequently the concern of toxic acyl glucuronide formation prohibited further exploration of the ester series. As an alternative and perhaps more reliable option to avoid the reactive acyl glucuronide formation, while maintaining the encouraging PPARγ activity of the ester derivatives, application of bioisosteres for ester functionality was explored.

5-Ring heteroaromatics have been used in a wide range of applications in medicinal chemistry to provide solutions of the issues faced in various discovery programs.[10] Among those applications, they have often proved themselves successful as bioisosteres of ester moiety mainly to avoid rapid hydrolysis, which attracted us to explore 5-ring heteroaromatics as a surrogate of ester functionality of BR101549. As shown in Fig. 1, a total of six 5-ring heteroaromatics containing three heteroatoms have been selected and assessed for the transcriptional activation of PPARγ relative to the partial agonist Telmisartan.[11,12] For the comparison of relative transcriptional effects, a few derivatives with representative alkyl substitutions were prepared for each series of 5-ring heteroaromatics.

As summarized in Table 1, 1,2,4-thiadiazoles, **A** (compounds **4**–**5**), 1,3,4-triazoles, **B** (compounds **6**–**7**), 1,3,4-oxadiazoles, **C** (compounds **8**–**9**), and 1,3,4-thiadiazoles, **D** (compounds **10**–**11**) demonstrated relatively weak activation versus Telmisartan regardless of substituents on R^1 (methyl, isopropyl) and R^2 (methyl, 4-fluorophenyl, 4-methoxyphenyl) with the exception of compound **12** (R^2 = t-Bu). Since compound **12** containing sterically demanding t-butyl group on R^2 unleashed exceptional activity, bulkier groups such as t-butyl and isopropyl have been applied to the next heteoaromatic motif, 1,2,4-

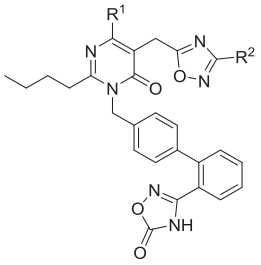
Table 1
Comparison of PPARγ activation of 5-ring heteroaromatics.



Ar	Comp. No	R^1	R^2	A_{max} of PPARγ vs. Telmisartan (%)†
 A	**4**	isopropyl	methyl	79
	5	methyl	methyl	93
 B	**6**	methyl	methyl	61
	7	methyl	4-fluorophenyl	71
 C	**8**	isopropyl	methyl	80
	9	isopropyl	4-methoxyphenyl	73
 D	**10**	isopropyl	methyl	79
	11	methyl	methyl	71
	12	isopropyl	t-butyl	180
 E	**13**	methyl	t-butyl	258
	14	methyl	isopropyl	233
	15	methyl	2-fluorophenyl	150
 F	**16**	isopropyl	methyl	207
	17	methyl	methyl	136
	18	methyl	t-butyl	331

† The A_{max} value is a percentage value calculated relative to Telmisartan.

Table 2
Activation of PPARγ with 1,2,4-oxadiazole derivatives.



Comp. No	R^1	R^2	EC_{50} (μM)†	A_{max} of PPARγ vs. Pioglitazone (%)†,‡
16	isopropyl	methyl	1.05	93
18	methyl	t-butyl	0.28	98
19	isopropyl	t-butyl	0.59	123
20	methyl	cyclopropyl	4.25	89
21	isopropyl	cyclopropyl	2.55	102
22	methyl	benzyl	1.75	105
23	isopropyl	benzyl	1.14	92
24	methyl	4-fluorobenzyl	2.41	81
25	isopropyl	4-fluorobenzyl	1.48	80
26	methyl	isopropyl	1.32	101
27	methyl	3-fluorobenzyl	1.39	82
28	methyl	3,5-di-fluorobenzyl	1.38	72
29	methyl	methoxyethyl	4.21	68
30	methyl	methoxymethyl	3.39	60

† EC_{50} and A_{max} were obtained through reporter gene analysis by measuring concentration dependent luciferase induction in cell lines (Indigo USA) transfected with PPRE and luciferase genes.

‡ The A_{max} value is a percentage value calculated relative to Pioglitazone.

oxadiazole, **E** (Fig. 1). As expected, compounds **13** and **14** disclosed excellent activation effects measured as A_{max} ratios of 258% and 233%, respectively. Even aromatic substitution on R^2 with 2-fluorophenyl revealed A_{max} ratio of 150% which is definitely superior to the similar analogs of other heteroaromatic series (compounds **7** and **9**). The encouraging results of 1,2,4-oxadiazole (**E**) spontaneously led us to exploit the reversed 1,2,4-oxadiazole (**F**) relative to the substitution pattern of R^1 and R^2. Indeed, even the subtle variation explicitly revealed the superior effects of reversed 1,2,4-oxadiazole (**F**) motif on PPARγ activation. Comparison of compound **16** (R^2 = Me, A_{max} ratio = 207%) and compound **18** (R^2 = t-butyl, A_{max} ratio = 331%) to the derivatives with same substituents on R^1 and R^2 in other heteroaromatic series clearly demonstrated the enhanced effect of the reversed 1,2,4-oxadiazole (**F**) motif. As such, the comparison of PPARγ activation among various 5-ring heteroaromatics apparently revealed superior activity of 1,2,4-oxadiazoles over the others. In particular, the series of 1,2,4-oxadiazole isomer **F** which seemed more potent than isomer **E** was chosen for further SAR evaluation. The potency improvement caused by the subtle configurational change derived by mutual exchange of hetero atoms (N and O) in isomer **F** was intrigued but found inexplicable via docking analysis.

Based on the results in Table 1 and our previous report,[9] the R^1 group was fixed to methyl and isopropyl and the agonist potential was measured as a ratio of activation versus Pioglitazone, a TZD full agonist (Table 2). As expected from the results shown in Table 1, compounds **16** and **18** indeed enabled to activate PPARγ to the level of Pioglitazone (93% and 98%, respectively). However, they disclosed more than 3-fold difference of potency, EC_{50}, as compound **18** revealed excellent EC_{50} value of 0.28 μM versus 1.05 μM of compound **16**. Subsequent R^1 replacement of methyl in compound **18** by isopropyl improved A_{max} in ca. 30% but with compromised EC_{50} of 0.59 μM (2-fold decrease) (compound **19**). On the contrary to the t-butyl (R^2) series (compounds **18** vs **19**), the other examples including the compounds **20–25** containing cyclopropyl, benzyl, and 4-fluorobenzyl groups on R^2 clearly demonstrated the positive effects of bulkier R^1 (isopropyl) on EC_{50}s, though the effects were found overall weaker than the t-butyl analogs. Regarding PPARγ activation, unlike the EC_{50}s, the series of compounds were unable to disclose clear SAR tendency with the exception of 4-fluorobenzyl derivatives which showed relatively weaker activation potential (compounds **24–25**). Continued tendency of weaker activation of 4-fluorobenzyl derivatives was also observed in the other electron deficient fluorobenzyl derivatives such as 3-fluorobenzyl and 3,5-difluorobenzyl compounds, **27** and **28**, respectively. Despite the cross substitutions of R^1 and R^2 relative to compound **16**, compound **26** remained its decent EC_{50} and A_{max} values similar to compound **16**. Additional hydrogen bonding acceptor represented by the ether functionalities of compounds **29** and **30** was not found beneficial to EC_{50}s as well as activation potentials. Overall, the potency (EC_{50}) seemed improved when R^1 is isopropyl versus methyl while no such tendency was observed on the efficacy (A_{max}). In terms of R^2 variations, alkyls, particularly branched ones proved their beneficial effects not only to the A_{max} but to the EC_{50} as well. Largely based on the submicromolar potencies as well as high activation potentials, compounds **18** (EC_{50} = 0.28 μM, A_{max} ratio = 98%) and **19** (EC_{50} = 0.59 μM, A_{max} ratio = 123%) were selected to proceed for further evaluation.

Further in vitro profiling (Table 3) and in vivo PK (Table 4) evaluation of compounds **18** and **19** revealed their similar properties in terms of CYP inhibitions, liver microsomal stabilities, and mouse PK, which were predictable from the similarity of the molecular structures. Compound **18** could maintain its edge to the compound **19** in the field of hERG inhibition. The fact that both compounds had unexpectedly low liver microsomal stabilities, particularly in rodent models, at least, seemed to have plausible correlation with the modest plasma exposure levels (Table 4) suggesting a tip helping to improve the poor exposure in later SAR attempts. Mostly due to the advantage in hERG profile (8.3% inhibition at 10 μM) versus compound **19** (16% inhibition at 10 μM), compound **18** was selected to proceed for further in vivo efficacy studies to complete proof-of-concept (POC) evaluation. Although

Table 4
Oral rodent PK of compounds **18** and **19**.

Comp. No.	Species (10 mpk)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)
18	Rat	1.78	0.30	1318	889
	Mouse	1.18	0.33	949	584
19	Mouse	0.82	0.33	547	581

Table 3
In vitro profiling of compounds **18** and **19**.

Comp. No	hERG (%)†	Microsomal stability (% remaining @30 min)				CYP inhibition (% remain activity @10uM)				
		M	R	D	H	1A2	2C9	2C19	2D6	3A4
18	8.3	11	12	11	17	88	57	84	93	64
19	16	24	13	13	12	92	33	78	89	50

† % inhibition at 10 μM.

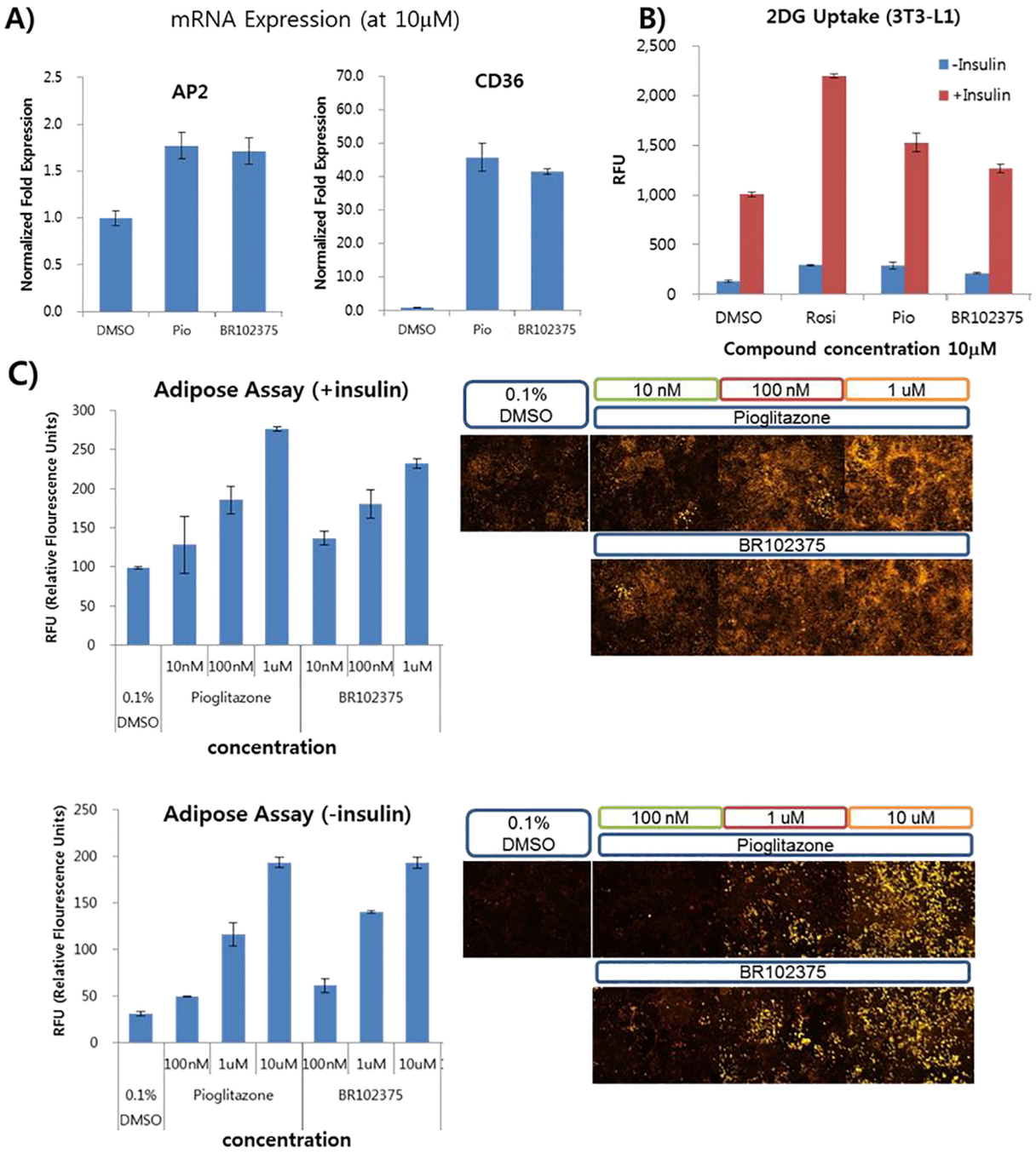


Fig. 2. Effects of compound **18** (BR102375) on mRNA expressions, glucose uptake, and adipocyte differentiation. (for experimental details, see Supporting Information)

the poor microsomal stability profiles and relatively low plasma concentrations were among concerns, the experiment was supported by the reasoning that higher dosage would enable to provide exposure coverage enough to show efficacious effect in comparison to the reference agent, Pioglitazone, for the purpose of POC.

Prior to the in vivo experiments, compound **18** (BR102375) was also evaluated in cell-based studies[13] with Pioglitazone as a reference compound. The gene expression levels relevant to PPARγ activation including AP2 and CD36 were indeed found significantly increased compared to the control, almost reaching to the level of full agonist, Pioglitazone (Fig. 2A).[14] In the study of insulin sensitizing potential of BR102375, the cell (3T3 L1 adipocyte) treated with BR102375 (10 μM) revealed enhanced glucose uptake comparable to Pioglitazone when stimulated by insulin (Fig. 2B).[15] Furthermore, the evaluation of PPARγ adipogenic capacity inducible by BR102375 has proved its concentration-dependent, insulin-sensitive effects on adipogenesis, which was found similar to the effect of Pioglitazone as evidenced in Fig. 2C.[16] In light of the cell based assessments carried out, it was inferred that BR102375 would be possibly a full agonist of PPARγ with comparable activation potential as Pioglitazone (A_{max} ratio = 98% of Pioglitazone, Table 2).

The anti-diabetic efficacy of compound **18** (BR102375) was assessed in genetically induced db/db mouse diabetes models.[17] In the 14-day BID study,[18] compound **18** (BR102375) (75 mpk, p.o., bid) has revealed significant suppressive effect on random blood glucose increase comparable to the effect of Pioglitazone (30 mpk, p.o., qd)

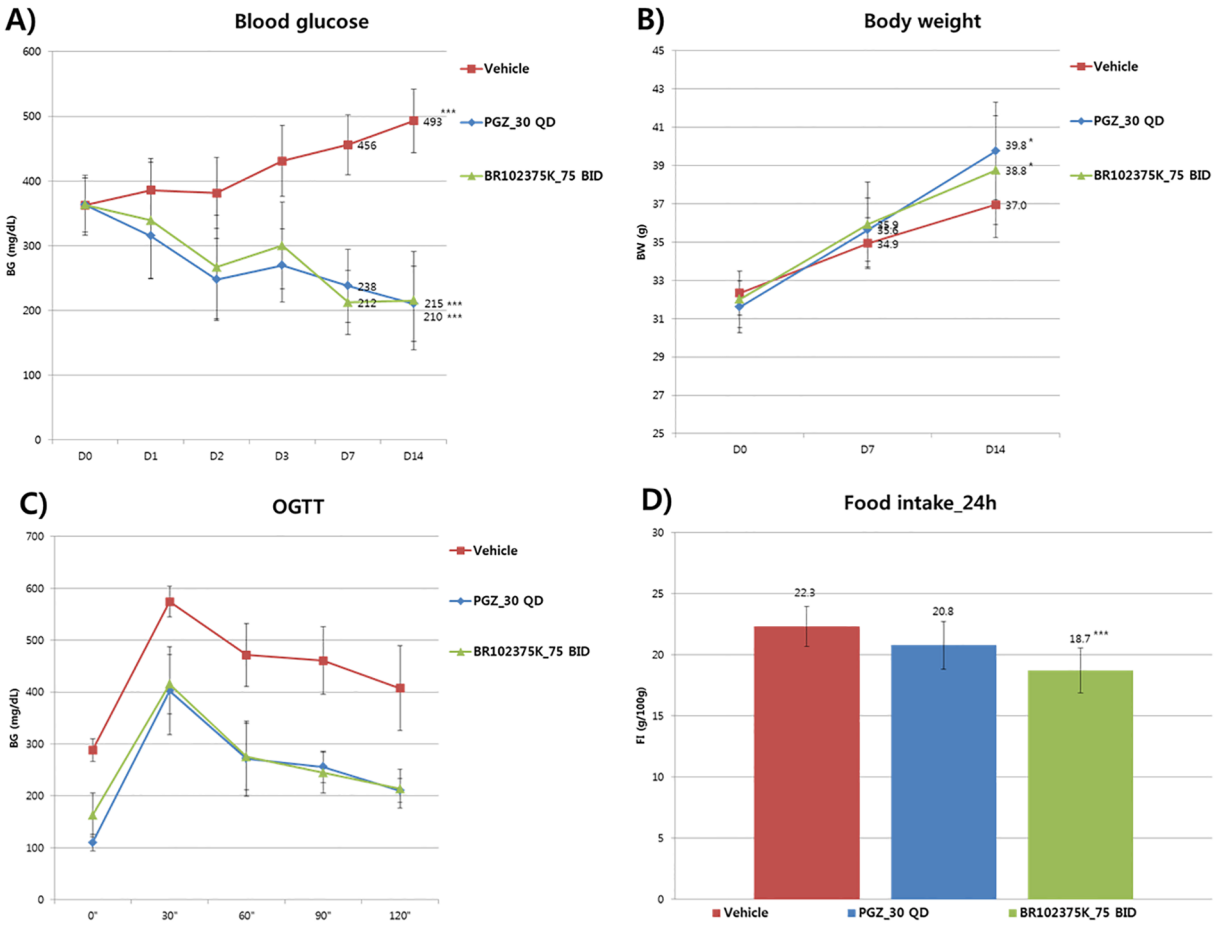


Fig. 3. In vivo efficacy study of compound **18** (BR102375) in db/db mouse model (75 mpk, bid, n = 9): A) Blood glucose lowering effect, B) Body weight increase, C) Oral glucose tolerance test (measured on day 14), D) Food intake (measured on day 7), (PGZ = Pioglitazone).

(Fig. 3A). In addition to the effect on glucose, compound **18** (BR102375) also disclosed similar findings in body weight gain with Pioglitazone on day 14 (Fig. 3B). Oral glucose tolerance test (OGTT) on day 14 also revealed decent effect of compound **18** (BR102375) on insulin resistance almost identical to Pioglitazone (Fig. 3C). On the other hand, the amount of food intake was found slightly diminished, however, which was not deemed significant enough to unleash a concern of potential toxic signal (Fig. 3D). The 2-week study indeed demonstrated the decent efficacy of BR102375 on mouse diabetes models, however the failure to suppress the body weight gain was disappointing in light of our proposed rational to leverage it as a distinguishable point from TZD drugs to overcome their clinical unmet need, as was discussed in our previous study.[9] The original lead BR101549 (Fig. 1) exhibited enhanced activation of PPARγ and animal efficacy with decent suppression of weight gain versus Pioglitazone.

In order to further interrogate the mechanism behind the enhanced activation potential of PPARγ, BR102375 has been subjected to co-crystal formation with PPARγ ligand binding domain (LBD) and the X-ray crystallography analysis. The study revealed, to our surprise, a totally different pattern of binding mode of BR102375 in the LBD stabilization from that of the precursor BR101549 (Fig. 4). On the contrary to BR101549, BR102375 in PPARγ LBD explicitly showed the strong interaction of its oxadiazoledione motif with the Tyr473 on helix 12 which has been widely recognized as a characteristic of full agonists enabling enhanced PPARγ activation.[19] The binding of BR102375 seems to be forked three-way with the pyrimidineone as a pivot aligned along the helix 3 (Fig. 4A). Most prominently, the oxadiazoledione motif is, through the biphenyl linker, projected toward the helix 12 enabling interactions with Tyr473 and His449, the key H-bonding interactions of TZD motif of TZD full agonists stabilizing AF2 residues. The t-butyl 1,2,4-oxadiazole motif is seemed to occupy the opposite site, where the oxadiazoledione of BR101549 was known to bind, perching on the helix-5 by hydrophobic interactions with Ile330, Ile326, and Met329 residues. No additional H-bonding interactions of the heteroatoms in the 1,2,4-oxadiazole ring were identified. Although it doesn't seem to be significant, the butyl branch of pyrimidinone ring seems approaching helix-6 to generate another hydrophobic interaction with M364 residue. Indeed, it was unexpected that the oxadiazoledione motifs in BR102375 and BR101549 were observed stabilizing completely different parts of the LBD and induced their discrete characteristic modes of binding (Fig. 4B). Although it's not verifiable yet, it might be inferred that the sterically bulkier *t*-butyl moiety on 1,2,4-oxadiazole of BR102375 versus relatively small ethyl ester of BR101549, was unable to fit into the pocket formed by helix-6 and helix-3. Instead, the t-butyl-1,2,4-oxadiazole could participate in the other side hydrophobic stabilization process which might be further facilitated by the interactions between the oxadiazoledione and Tyr473 and His449 of helix 12.

All the compounds enlisted in Tables 1 and 2 have been prepared according to the routes summarized in Scheme 1. Compounds containing heterocyclic motifs, **B,C,D** and **F** were prepared in 2–3 steps from the carboxylic acids **35** obtained by hydrolysis of the corresponding esters **34** whose syntheses have been reported in our previous publication[8]. The acids **35** were converted to the desired 1,2,4-oxadiazole system **F** derivatives by refluxing with $SOCl_2$ in pyridine in the presence of hydroxylamidines **33** with varied R^2, which were prepared

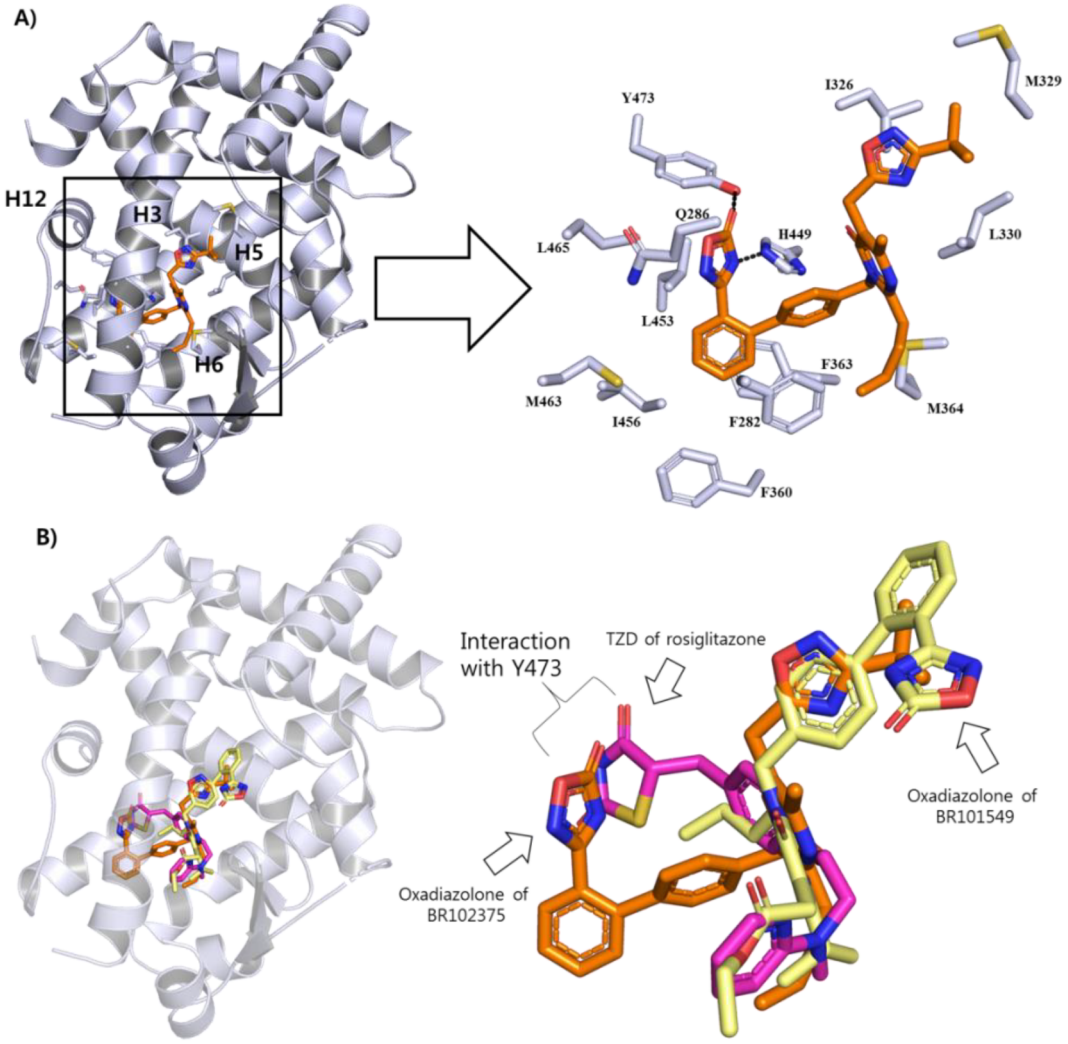
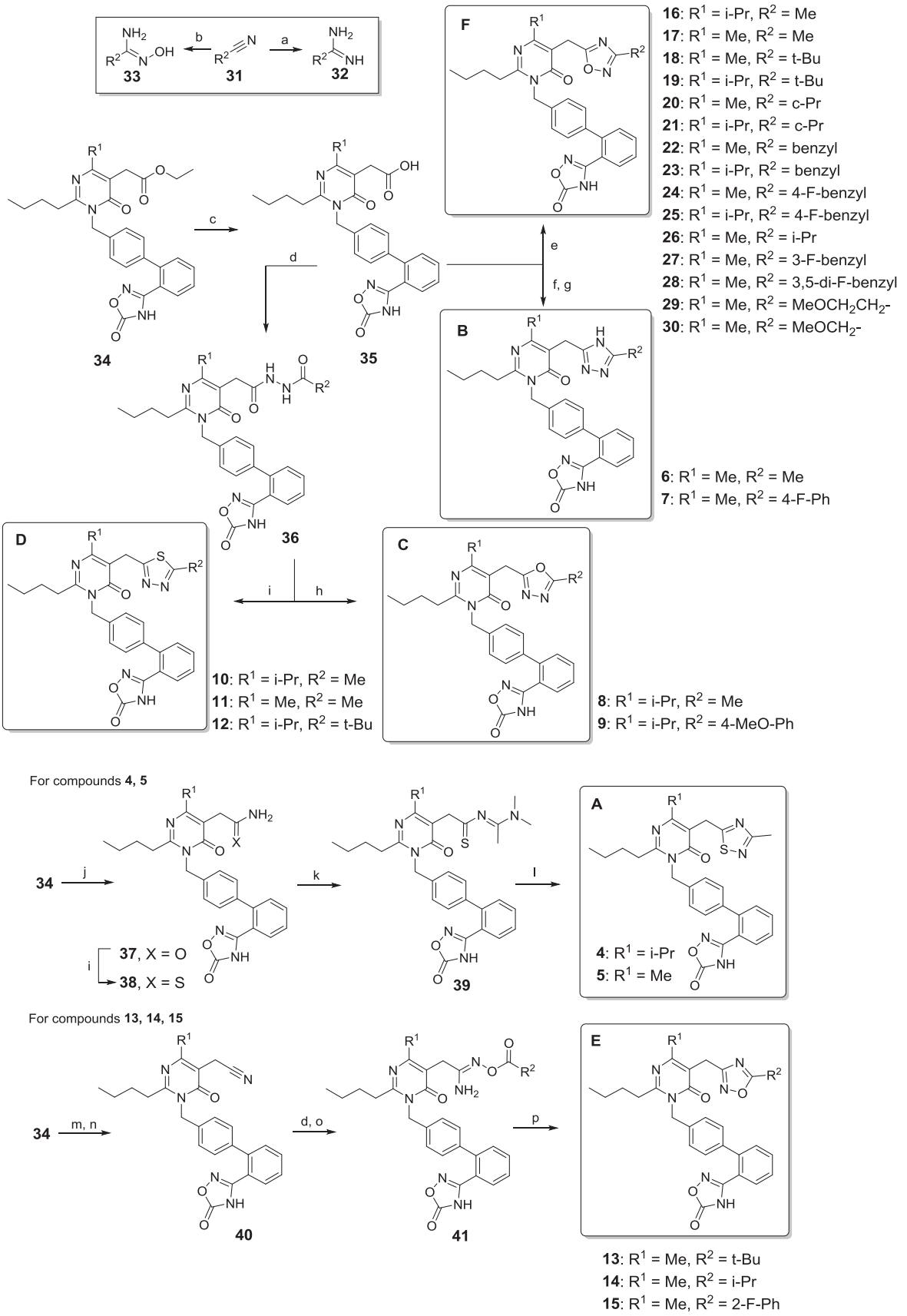


Fig. 4. A) Crystal structure of PPARγ ligand binding domain (LBD, in sky blue cartoon) with BR102375 (sticks colored orange) in the presence of SRC-1 coactivator peptide, and its zoomed in view showing interacting residues. B) Overall structure of BR102375 (in orange) in the PPARγ LBD (in white cartoon). BR101549 (in yellow) and Rosiglitazone (in magenta) are superimposed on the structure. (PDB ID 6ICJ, Diffraction resolution: 2.48 Å).

from the corresponding nitriles **31**. Conversion of nitriles **31** into the amidines **32** was achieved by the treatment of trimethylaluminum and NH_4Cl in toluene at room temperature. Coupling of resulting amidines **32** with the acids **35** using DIPEA and HBTU in DMF followed by cyclization with hydrazine gave the desired triazole compounds **6** and **7**. The acid intermediates **35** were also reacted with the acylhydrazines with varied R^2 to provide the corresponding acylhydrazide derivatives **36** which were cyclized with Lawesson's reagent in THF when heated to 70 °C resulting in the 1,3,4-thiadiazole derivatives **10–12**. The oxygen analogs, 1,3,4-oxadiazoles **8** and **9** could be obtained by the reaction of the acylhydrazides **36** with $POCl_3$ in refluxing toluene. For the synthesis of 1,2,4-thiadiazole derivatives **4** and **5**, the thioamide intermediates **38** prepared from the esters **34** by the sequence of amide formation and thiolation reacted with DMF-DMA in MeOH affording the thioacylamidine derivatives **39**, which were next cyclized in the presence of hydroxylamine and acetic acid in dioxane at 90 °C.[20] Another 1,2,4-oxadiazole isomer ring system **E** including compounds **13–15** was installed by the cyclization of the acyloxyamidine intermediate **41** prepared from the ester **34** in 4 steps. Amination of **34** by treatment with ammonia water, followed by $POCl_3$ induced dehydration gave the desired nitriles **40**, which were converted to acyloxylamidines in two steps via hydroxylamines including aqueous hydroxylamine refluxing and coupling with the R^2-carboxylic acids under EDCI-HOBt condition. The final cyclization by refluxing with K_2CO_3 in toluene provided the derivatives containing 1,2,4-oxadiazole isomer **E**.[21]

In summary, a new class of non-TZD PPARγ full agonist, BR102375 (compound **18**), has been identified through the efforts to overcome potential reactive metabolites formation by successfully replacing the metabolically labile ester moiety of BR101549 with its bioisostere, 1,2,4-oxadiazole motif. BR102375 has exhibited excellent potency in terms of EC_{50} and A_{max}, in particular, the activation potential of the protein was found comparable to the full agonist, Pioglitazone, which was further evidenced by the mRNA expression patterns and the characteristic binding interactions uncovered by the X-ray co-crystal analysis. Despite its relatively undesired mouse PK exposure, BR102375 was found efficacious in preclinical diabetic mouse models when assessed in high-dose oral settings. However the beneficial effect of efficacy was compromised by absence of the anticipated effect of suppressing body weight gain, which could be ascribed to the indifferent profiles observed in cell based assessments and the key binding interactions of BR102375 in PPARγ LBD, compared to those of the TZD full agonists. Also noteworthy is the finding of substantial change in binding modes induced by the replacement of ethyl ester of BR101549 with t-butyl-1,2,4-oxadiazole motif of BR102375.



Scheme 1. General synthetic scheme, a) trimethylaluminum, NH_4Cl, toluene, 25 °C, b) NH_2OH in H_2O, EtOH, reflux, c) 2.5 M NaOH in H_2O, EtOH, 25 °C, d) EDCI, HOBt, TEA, acylhydrazide, $CHCl_3$, 25 °C, e) **33**, $SOCl_2$, pyridine, reflux, f) **32**, DIPEA, HBTU, DMF, 25 °C, g) hydrazine, AcOH, reflux, h) $POCl_3$, toluene, reflux, i) Lawesson's reagent, THF, reflux, j) 1 M ammonia in MeOH, 50 °C, k) DMFDMA, MeOH, 25 °C, l) NH_2OH, 1,4-dioxane, 90 °C, then AcOH, m) 28% ammonia in H_2O, 25 °C, n) $POCl_3$, acetonitrile, reflux, o) HOBt, EDCI, TEA, carboxylic acid, CH_2Cl_2, 25 °C, p) K_2CO_3, toluene, reflux.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2019.06.027.

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13. For experimental details, see “Supporting Information”.
14. Takazawa T, Yamauchi T, Tsuchida A, et al. *J Biol Chem.* 2009;284(44):30049.
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18. Seven-week-old male db/db mice were obtained from Central Lab Animal Co. (Seoul, Korea) and were acclimated to the laboratory condition for 1 week. To investigate the anti-diabetic effect so BR102375K (potassium salt), the mice were assigned into three groups (n = 9/group) by blood glucose level and weight Mice were treated once or twice daily by gavage with BR102357K (75 mg/kg/day), poiglitazone (30 mg/kg/day) or vehicle (0.5 CMC in 1% Tween 80) for 2 weeks. Blood samples were collected from tail vein and blood glucose levels were measured by Accu-Check (Roche) once each week. Body weight and food intake were also measured once each week. To confirm anti-diabetic effects of BR102357, oral glucose tolerance test was carried out after 12 h fasting. A glucose solution (1 g/kg of body weight) was administered by orally gavage. At the time points indicated, blood glucose levels were measured with an Accu-Check (Roche) before (0 min) and after (30, 60, 90, and 120 min) the glucose gavage.
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