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Letter

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SAR Studies of 3- or 4-Pyridine Derivatives of DS-6930

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KEYWORDS: DS-6930, benzoic acid, benzimidazole, PPARγ, partial agonist

ABSTRACT: Derivatization efforts were continued to discover backups for a potent selective PPARγ modulator, DS-6930. In this paper, the replacement of 2-pyridine ring in DS-6930 with 3- or 4-pyridyl group is reported. As the introduction of substituents on the pyridine ring did not provide potent partial agonists, modifications of benzimidazole ring were explored to discover potent intermediate agonists. 4'-Alkoxy substituted benzimidazoles failed to show potent efficacy in vivo, whereas 7'-fluoro benzimidazole **3g** (DS19161384) was found to result in robust plasma glucose reductions with excellent DMPK profiles.

Thiazolidinedione (TZD)-based PPARγ full agonists, pioglitazone hydrochloride (**I**, Figure 1) and rosiglitazone maleate (**II**, Figure 1) demonstrated to have robust pharmacological efficacy in clinical settings.[1] However, they attracted much attention owing to their adverse effects. The short-term usage of TZD drugs often causes peripheral edema.[2] It has also been reported that their long-term use is often associated with bone fracture, carcinogenicity, and cardiovascular risks.[3,4] Such adverse effects have limited their usage because of safety concerns.

Although it was reported that the inhibition of PPARγ phosphorylation by Cdk5 is the underlying mechanism of antidiabetic efficacy,[5] we believe there is still scope for the development of safer PPARγ modulators through the selective regulation of cofactors. Such a conventional approach led to the discovery of DS-6930 (**III**, Figure 1).[6] DS-6930 demonstrated potent plasma glucose (PG) reduction with fewer PPARγ-related adverse effects than rosiglitazone in preclinical studies.[6] Based on the co-crystal structure of **III** bound to PPARγ ligand binding domain (LBD), the avoidance of direct interactions with Tyr473 on helix 12 and the additional lipophilic interactions of dimethylpyridyl group are suggested to be related to the intermediate agonist activity of DS-6930.[6] The superior safety profile of DS-6930 was attributable to this distinct binding mode through the selective recruitment of cofactors.[6] We continued our exploration of structure-activity relationship (SAR) of this series of compounds to discover backup clinical candidates for DS-6930. Herein, we report SAR studies of 3- or 4-pyridines to identify novel PPARγ intermediate agonist **3g** (DS19161384), which demonstrated robust pharmacological efficacy with excellent DMPK properties in preclinical studies.

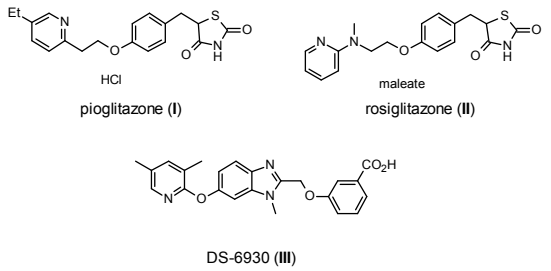


Figure 1. Chemical structures of pioglitazone hydrochloride (**I**), rosiglitazone maleate (**II**), and DS-6930 (**III**).

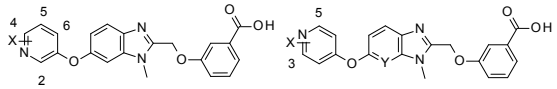
We reported that the high lipophilicity caused the elevation of liver enzyme activities, and the suppression of lipophilicity was achieved by the replacement of phenyl ring with 2-pyridyl group, which led to the discovery of DS-6930.[6] As the derivatization of 3- or 4-pyridines has generally been avoided owing to their poor potencies in vitro, we have focused on them as backups.

The SAR results of 3-pyridines with in vitro ADME profile are summarized in Table 1. Unsubstituted 3-pyridine **1a** possessed poor agonist potency. Unlike the previous SAR of 2-pyridine series,[6] the introduction of a methyl group did not result in good potency in vitro, despite the improvement of membrane permeability (compounds **1b–1e**). Compounds **1a–1e** exhibited comparable aqueous solubility and microsomal stability as those of **III**. Accordingly, further modifications were explored owing to the attractive in vitro ADME profile of **1a–1e**. When a chloro group was incorporated in each position of the pyridine ring, none of them had $EC_{50} < 1$ μM (data not shown). Improved in vitro potency was observed for 4- or 5-methoxy derivatives (**1g** and **1h**), whereas the introduction of 2-methoxy group did not result in high potency (compound **1f**). Although 4-methoxy analog **1g**

exhibited the best in vitro potency among 3-pyridines, **1g** lost partial agonist activity. Full agonists were also found in methyl analogs (**1c** and **1d**). Further, introduction of a substituent in **1f** or **1g** led full agonists **1i-1k**. In contrast, dimethyl derivative **1l** exerted modest potency, with partial agonist activity in vitro (E_{max} = 36%). In terms of PPARα selectivity, only **1k** showed relatively high PPARα activity.

We then focused on 4-pyridines (compounds **2** in Table 1). 3-Methyl derivative **2a** lost in vitro potency, whereas 3-ethyl analog **2b** showed tenfold higher potency. Further enhancement of potency was achieved by the introduction of an alkoxy group. 3-Methoxy and 3-ethoxy derivatives (**2c** and **2d**) exhibited EC_{50} = 188 and 182 nM, respectively. The 3-alkoxy group is essential for potency of 4-pyridine series, because 3-chloro and 3,5-dimethyl analog (**2e** and **2f**) lost their high potency in vitro. Although 3-methoxy-5-methyl derivative **2g** showed the best potency among the 4-pyridine series, full agonist activity was observed. The modification of benzimidazole ring of **2g** led to the discovery of intermediate agonist **2h** (E_{max} = 74%). Imidazopyridine **2h** exhibited adequate solubility and high microsomal stabilities against three species, with high PPARα selectivity.

Table 1. PPAR Transcriptional Activities and In Vitro ADME Profiles of 1 and 2



1a-1l **2a-2h**

Cmpd	X	Y	PPARγ EC_{50} (nM)[a]	PPARγ E_{max} (%)[a]	PPARα EC_{50} (nM)[a]	PPARα E_{max} (%)[a]	Log D	PAMPA P_{app} (10^{-6} cm/s)	Solubility (μg/mL)	MS (%, h/r/mon)[b]
1II			41 ± 10[d]	68 ± 8.0[d]	>10000	13 ± 2.0[d]	1.4	13 ± 3.4[d]	31	NT[c]/92/80
1a	H		6831	66	>10000	5	0.5	<2.0	23	100/NT[c]/NT[c]
1b	2-Me		>10000	77	>10000	3	1.0	2.6	54	98/NT[c]/NT[c]
1c	4-Me		543	110	>10000	4	0.8	5.9	71	87/NT[c]/NT[c]
1d	5-Me		779	104	>10000	5	1.0	2.4	43	NT[c]
1e	6-Me		>10000	45	>10000	9	0.9	4.1	13	100/NT[c]/NT[c]
1f	2-OMe		1193	59	>10000	8	0.8	3.0	46	NT[c]
1g	4-OMe		155	101	>10000	17	1.3	10.5	1.9	NT[c]
1h	5-OMe		231	86	>10000	5	0.9	2.8	58	NT[c]
1i	2-Me, 4-OMe		255	106	>10000	2	1.7	10.1	5.1	NT[c]
1j	2-OMe, 4-Me		436	131	>10000	12	1.4	10.4	39	NT[c]
1k	4-OMe, 5-Me		315	125	ND[e]	61	2.0	21.7	11	100/82/98
1l	2-Me, 4-Me		273	36	>10000	-2	1.3	4.2	46	100/100/100
2a	3-Me	CH	5947	44	>10000	3	0.9	<2.0	87	100/NT[c]/NT[c]
2b	3-Et	CH	509	99	>10000	3	1.3	4.2	71	88/NT[c]/NT[c]
2c	3-OMe	CH	188	110	>10000	9	1.3	6.8	38	98/100/100
2d	3-OEt	CH	182	83	>10000	4	1.8	12.6	21	94/NT[c]/NT[c]
2e	3-Cl	CH	5947	83	>10000	7	1.1	4.9	6.2	NT[c]
2f	3-Me, 5-Me	CH	2745	99	>10000	7	1.0	3.0	45	NT[c]
2g	3-OMe, 5-Me	CH	100	112	>10000	21	1.7	12.2	6.5	96/96/85
2h	3-OMe, 5-Me	N	166	74	>10000	20	1.2	8.5	18	91/98/100

[a]PPAR activity was assessed in COS-7 cells transfected with a chimeric human PPAR-Gal4 receptor expression plasmid and a pG5luc reporter plasmid. [b]Human/rat/monkey microsomal stability. [c]Not tested. [d]Values represented as mean ± S.E.M. Values on two independent experiments. [e]Not determined.

As described, the introduction of substituents on 3- or 4-pyridine ring enhanced in vitro potency to discover partial agonist **1l** and intermediate agonist **2h**. As the enhancement of in vitro potency is often associated with full agonist activity, other modifications were required.

X-ray crystal structure of PPARγ LBD complexed with **1l** was investigated to seek other chemical modifications. The binding mode of **1l** superimposed with DS-6930 is shown in Figure 2a. As expected, **1l** displayed the same binding mode as DS-6930.[6] As no direct interaction with Tyr473 on

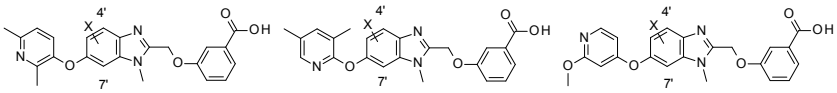
helix 12 and the lipophilic interactions of dimethylpyridyl group were confirmed, these interactions relates for **1l** to show partial agonist activity. A space around the 4'-positoin of benzimidazole ring surrounded by Phe264-Gly284-Arg288 was observed (Figure 2b). The existence of such a space urged us to introduce 4'-substituents on benzimidazole ring as shown in Table 2 (compounds **3**).

The introduction of 4'-methyl group in the bicyclic core structure led to disappointing results (compound **3a**), whereas 4'-methoxy derivative **3b** retained potency in vitro. Consequently, several 4'-alkoxy groups were incorporated. The in vitro potency was found to be correlated with the lipophilicity of molecules (**3b**–**3e**). For example, 4'-methoxy derivative **3b** had EC_{50} = 249 nM, whereas 4'-propoxy analog **3d** exhibited EC_{50} = 32 nM. This modification enhanced the activity by 7.8-fold, with an increase in Log D value by 1.0. Because the membrane permeability progressively increased, the improvement of membrane permeability might contribute to the high potency in vitro. This enhancement of PPARγ potency was not accompanied with the PPARα activation. Isopropyl analog **3e** exhibited high potency in vitro with enhanced aqueous solubility compared with that of **1l**. The improvement in solubility achieved was over tenfold, even though **3e** was more lipophilic than **1l**. Compound **3e** maintained robust stability against human liver microsomes. However, **3e** showed full agonist activity. In fact, all 4'-substituted analogs **3a-3e** showed full agonist activity (E_{max} = 94%-116%).

Accordingly, we sought another solution. Several small substituents were incorporated at 7'-position on benzimidazole ring due to the limited space around this position (Figure 2b). A methyl or fluoro group was introduced into this position, and both analogs retained in vitro potency. In particular, 7'-fluoro analog **3g** demonstrated intermediate agonist activity (E_{max} = 76%), with acceptable solubility and robust microsomal stability. The binding mode of **3g** is shown in Figure 2c. 7'-Fluoro analog **3g** exhibited the same binding mode as **1l**.

The introduction of substituents on the benzimidazole ring in **III** was then explored (compounds **4** in Table 2). 4-Pyridine **2c** was also modified (compounds **5** in Table 2). When 4'-alkoxy group was introduced in **III**, 4'-ethoxy and 4'-isopropoxy derivatives **4a** and **4b** retained high potency in vitro. However, the introduction of such substituents resulted in full agonist efficacy. The enhancement of in vitro potency was also achieved for 4-pyridines. When 4'-methyl, 4'-ethoxy, or 4'-isopropoxy group was introduced into benzimidazole ring, all compounds exerted high potency in vitro (compounds **5a**, **5b**, and **5c**). In particular, ethoxy analog **5b** demonstrated strong potency in vitro with an intermediate agonist activity (EC_{50} = 58 nM, E_{max} = 71%). Compound **5b** also exhibited improved aqueous solubility. The introduction of 7'-fluoro group resulted in full agonist **5d**.

Table 2. PPAR Transcriptional Activities and In Vitro ADME Profiles of 3, 4 and 5



Cmpd	X	PPARγ EC_{50} (nM)[a]	PPARγ E_{max} (%)[a]	PPARα EC_{50} (nM)[a]	PPARα E_{max} (%)[a]	Log D	PAMPA P_{app} (10^{-6} cm/s)	Solubility (μg/mL)	MS (%, h/r/mon)[b]
3a	4'-Me	811	116	>10000	4	1.7	6.0	3.2	100/NT[c]/NT[c]
3b	4'-OMe	249	99	>10000	1	1.2	2.7	50	NT[c]
3c	4'-OEt	104	103	>10000	5	1.6	4.8	130	100/NT[c]/NT[c]
3d	4'-OPr	32	94	>10000	1	2.2	11.8	34	NT[c]
3e	4'-O*i*-Pr	31	103	>10000	4	1.9	9.1	630	91/65/81
3f	7'-Me	244	92	>10000	10	1.8	7.0	14	NT[c]
3g	7'-F	246	76	>10000	3	1.6	9.2	28	100/100/100
4a	4'-OEt	58	84	>10000	2	1.7	18.6	12	100/NT[c]/NT[c]
4b	4'-O*i*-Pr	57	88	>10000	9	2.0	24.5	7.6	96/13/84
5a	4'-Me	57	83	>10000	13	1.7	12.6	36	100/NT[c]/NT[c]
5b	4'-OEt	58	71	>10000	5	1.7	15.5	120	100/NT[c]/NT[c]
5c	4'-O*i*-Pr	32	100	>10000	14	2.0	17.3	53	97/91/94
5d	7'-F	60	95	>10000	18	1.7	14.0	2.1	97/NT[c]/NT[c]

[a]PPAR activity was assessed in COS-7 cells transfected with a chimeric human PPAR-Gal4 receptor expression plasmid and a pG5luc reporter plasmid. [b]Human/rat/monkey microsomal stability. [c]Not tested.

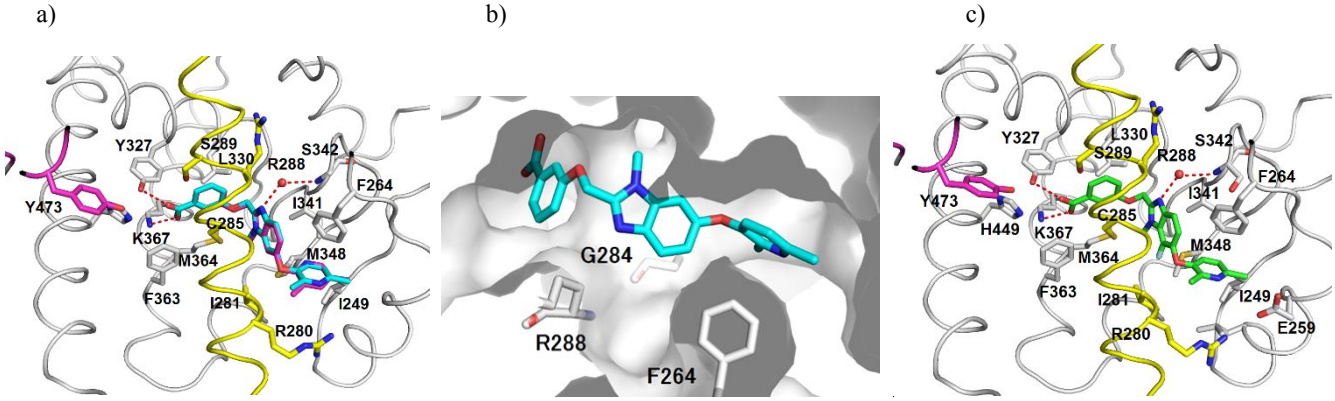


Figure 2. X-ray crystal structures of **1l** (PDB 6IZM) and **3g** (PDB 6IZN) bound to PPARγ-LBD. (a) Details of the binding mode of **1l** (blue) superimposed with DS-6930 (magenta). Hydrogen bonds are marked as red dotted lines. (b) Compound **1l** in PPARγ-LBD. PPARγ-LBD is shown in surface representation, and residues F264, G284, R288 and **1l** are shown in stick presentation. (c) Details of the binding structure of **3g** to PPARγ-LBD. Hydrogen bonds are marked as red dotted lines.

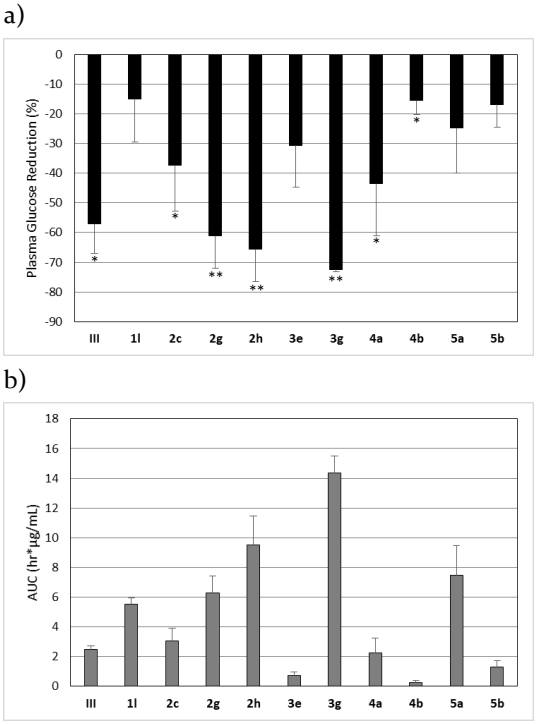


Figure 3. Pharmacological effects and PK parameters of PPARγ modulators. (a) PG reduction (% change in PG level vs vehicle control) in ZDF rats after the oral administration of 3 mg/kg of the test compounds in 0.5% methylcellulose on day 14 (n = 5). Data are represented as mean ± S.E.M. Statistical significance compared to vehicle treatment is denoted by *p < 0.05 and **p < 0.01. (b) $AUC_{0\text{-}24\,h}$ (h*μg/mL) was acquired by the administration of compounds to ZDF rats on Day 15 (n = 5). Each value is the mean ± S.D.

Several potent compounds were advanced to in vivo pharmacological profiling. These compounds were assessed for their ability to reduce PG in Zucker diabetic fatty (ZDF) rats at 3 mg/kg p.o. for 14 days as shown in Figure 3a. Plasma exposures of the test compounds (*AUC*) are shown in Figure 3b. DS-6930 exerted a statistically significant reduction in PG (57%, p < 0.05). 3-Pyridine **1l** exhibited poor efficacy in vivo owing to low potency in vitro, whereas better results were observed with full agonist **2c** (37% PG reduction, p < 0.05). Further enhancement of the efficacy was achieved in 4-pyridines **2g** and **2h** with statistical significance (p < 0.01). Compound **2g** exerted 61% reduction of PG, whereas 66% PG reduction was observed in imidazopyridine **2h**. Note that **2g** is a full agonist. Owing to the excellent plasma exposure, 7'-F substituted analog **3g** exhibited excellent efficacy (73% PG reduction, p < 0.01). Of 2-pyridines, 4'-ethoxy derivative **4a** showed modest efficacy, whereas 4'-isopropoxy analog **4b** lost the potent efficacy in vivo. As both compounds showed the same range of strong potency in vitro, the difference in the plasma exposure of the compounds resulted in such a pharmacological gap. 4'-Alkoxy substituted 4-pyridines, **5a** and **5b**, lost potent efficacy in vivo. The reasons for this poor efficacy are unclear, because **5a** showed sufficient plasma exposure with high potency in vitro. Overall, 4'-alkoxy substituted benzimidazoles tended to show lower efficacy in vivo. 4'-Alkoxy analog **3e** resulted in lower PG reduction than 7'-F analog **3g**, owing to the lower plasma exposure of the compound. Unsubstituted benzimidazole **III** exerted higher efficacy than 4'-alkoxy analogs **4a** and **4b**, and the same relationship was observed between unsubstituted analog **2c** and 4'-alkoxy derivatives (**5a** and **5b**).

Based on pharmacological results combined with ADME profile, **2h** and **3g** were selected as candidates for further evaluations. PK study of these compounds was performed by oral administration to male cynomolgus monkeys at 3 mg/kg as shown in Table 3. The compounds (1 mg/kg) were intravenously administered to the same monkey to calculate the total body clearance (*CL*), distribution volume at steady state (V_{ss}) and *F* value. 4-Pyridine **2h** retained excellent *CL* comparable to **III**. Further improvement of *CL* was achieved in 7'-fluoro derivative **3g**. 7'-Fluoro analog **3g** demonstrated excellent PK parameters, including the lowest *CL* as well as the highest *AUC* and *F* even compared to **III**. The PK parameters of **3g** in rodents at the same dose (3 mg/kg p.o., 1 mg/kg i.v.) are summarized (Table 3). 7'-Fluoro analog **3g** showed lower *AUC* and higher *CL* in rodents than in monkeys. Although

3g exerted the highest *CL* and the lowest bioavailability in mice, these PK parameters were acceptable for clinical candidate selection.

Table 3. Pharmacokinetic Parameters and Bioavailability of Compounds III, 2h and 3g at 3 mg/kg[a]

Cmpd	Species	C_{max} (μg/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{last} (h*μg/mL)	*F* (%)	*CL* (mL/min/kg)	V_{ss} (L/kg)
III	Monkey	2.25 ± 0.72[b]	5.00 ± 4.2[b]	13.5 ± 0.42[b]	23.5 ± 5.9[b]	89 ± 15[b]	2.06 ± 0.21[b]	0.36 ± 0.0071[b]
2h	Monkey	0.50 ± 0.37[b]	4.50 ± 4.9[b]	7.30 ± 2.8[b]	5.12 ± 2.4[b]	18 ± 8.7[b]	2.08 ± 1.1[b]	0.35 ± 0.049[b]
3g	Monkey	28.8 ± 10[b]	0.50 ± 0.0[b]	9.34 ± 3.3[b]	128 ± 73[b]	76 ± 34[b]	0.40 ± 0.23[b]	0.15 ± 0.042[b]
3g	Rat	3.49 ± 0.93[c]	2.25 ± 1.75[c]	3.45 ± 0.70[c]	28.0 ± 6.65[c]	74 ± 18[c]	1.29 ± 0.18[b]	0.27 ± 0.035[b]
3g	Mouse	1.29 ± 0.43[c]	0.50 ± 0.0[c]	4.35 ± 2.49[c]	2.07 ± 0.26[c]	21 ± 2.6[c]	4.91 ± 0.66[b]	0.62 ± 0.22[b]

[a]The test compounds in 0.5% methylcellulose were administered to male cynomolgus monkeys at 3 mg/kg (p.o.). Total body clearance (*CL*), distribution volume at steady state (V_{ss}), and *F* value were calculated after intravenous administration of the test compounds (1 mg/kg). Each value represents the mean ± S.D. [b]*n* = 2. [c]*n* = 3.

In summary, the 2-pyridine ring of DS-6930 was replaced with a 3- or 4-pyridyl group to identify backup clinical candidates for DS-6930. Although the introduction of substituents on 3- or 4-pyridine ring resulted in improvements of the in vitro potency, potent agonists showed full agonist activity. The introductions of 4'-substituent on benzimidazole ring also enhanced potency in vitro, while these compounds exhibited modest in vivo efficacy in ZDF rats. Most of 4'-substituted compounds including **3e** exerted full PPARγ agonist activity. Other modifications of the benzimidazole ring led to the discovery of 7'-fluoro analog **3g** and imidazopyridine **2h**, which demonstrated potent PG reduction in vivo with an intermediate agonist activity in vitro. Among them, 7'-fluoro analog **3g** (DS19161384) exhibited excellent DMPK profile.

ASSOCIATED CONTENT

Supporting Information

General synthetic procedure of all compounds; experimental procedures and characterization data of selected compounds; procedures for pharmacological activities. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ABBREVIATIONS

PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione; Cdk5, cyclin-dependent kinase 5; PG, Plasma glucose; LBD, ligand binding domain; SAR, structure activity relationship; PAMPA, parallel artificial membrane permeation assay; ZDF rat, Zucker diabetic fatty rat.

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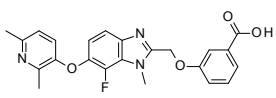

3g (DS19161384)
PPARγ EC_{50}: 246 nM
PPARγ E_{max}: 76%
73% PG reduction in ZDF rats (3 mg/kg)