Bioorganic & Medicinal Chemistry Letters 20 (2010) 1399–1404

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and biological activities of novel indole derivatives as potent and selective PPARγ modulators

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ARTICLE INFO

Article history:
Received 12 November 2009
Revised 24 December 2009
Accepted 29 December 2009
Available online 4 January 2010

Keywords:
PPARγ
Peroxisome proliferator-activated receptor
Telmisartan
Diabetes
Modulator

ABSTRACT

Starting from the structure of Telmisartan, a new series of potent and selective PPARγ modulators was identified. The synthesis, in vitro and in vivo evaluation of the most potent compounds are reported and the X-ray structure of compound **7b** bound to the PPARγ ligand binding domain is described.

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily. When activated by natural or synthetic ligands, the PPARs form heterodimers with 9-cis retinoic acid receptor (RXR), yielding a complex that binds to specific peroxisome proliferator response elements (PPRE) which regulates expression of several genes.[1]

The PPAR subtypes (PPARα, PPARδ, and PPARγ) have been the focus of extensive research during the last decade.[2] Glitazones (Rosiglitazone and Pioglitazone) are pharmaceutical agents that activate the PPARγ receptor and are currently marketed for treatment of type II diabetes. Indeed in human, Glitazones are insulin sensitizers and lower glucose levels. In addition, Pioglitazone increases HDL levels (5–10%) and Rosiglitazone gives a moderate decrease of TG levels (15–20%).[3] However Glitazones induce weight gain as a major side effect and in rare cases promote fluid retention.[4,5]

Recently, new classes of PPARγ ligands, the so called 'modulators', have been reported.[6] These compounds profile as partial agonists in a GAL-4 luciferase assay[7] and are suspected to display a different binding mode in the PPARγ subunit compared to the Glitazones, differential cofactor recruitment/displacement have also been demonstrated.

A different PPARγ binding mode leading to a different cofactor recruitment profile may account for a unique gene expression patterns compared to full agonists (Glitazones).[8,9] Interestingly, partial agonists are reported to show in preclinical models fewer side effects while retaining pharmacodynamic effects equivalent to the Glitazones.[6]

During the past decade, Telmisartan **1** (Fig. 1), a highly selective angiotensin II AT1 receptor blocker (ARB) (IC_{50} AT1 = 3 nM) has been widely used for treatment of hypertension.[10]

In addition to its AT1 receptor antagonist activity, Telmisartan has been reported to function as PPARγ partial agonist (EC_{50} PPARγ = 4.5 μM (25–30%)).[11,12]

In fact, a recently published binding model suggests that Telmisartan binds PPARγ in a different way than does Rosiglitazone.[12] In addition, Telmisartan demonstrated a specific cofactor recruitment profile compared with the Glitazones which translated into a different gene expression pattern.[13]

Despite these preclinical data suggesting PPARγ modulator activity, in human Telmisartan has not demonstrated any benefit resulting from PPARγ-related effects, probably due to the fact that typical plasma concentrations of Telmisartan (0.54 μM) are 10-fold lower than the PPARγ EC_{50}.

Thus, starting from the chemical structure of Telmisartan, we were aiming to design new potent PPARγ modulators. Recent publications have reported SAR studies around the Telmisartan

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doi:10.1016/j.bmcl.2009.12.107

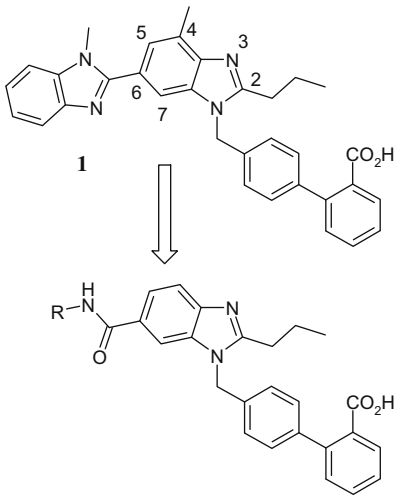


Figure 1. Replacement of methylbenzimidazole of Telmisartan.

scaffold, the best compounds profiled as partial agonist exhibited EC_{50} around 0.3 μM.[14,15]

We first focussed our effort on modifications of the C-6 substitution of the benzimidazole ring (Fig. 1).

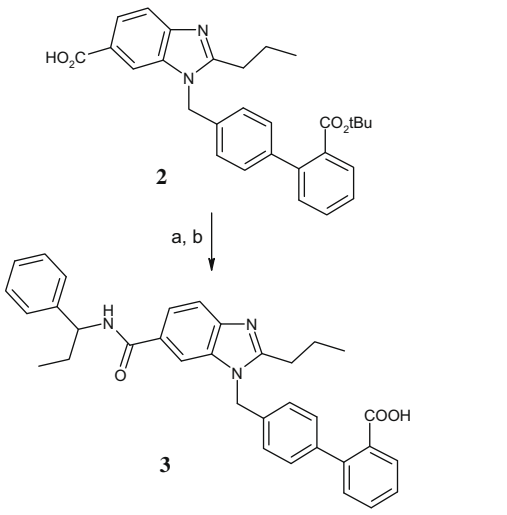
The 1-methylbenzimidazole group of Telmisartan in position 6 can be considered as bioisostere of an amide function (Fig. 1). In a similar manner to previous reports,[16] we replaced the benzimidazole group by a range of easily accessible carboxamides using array chemistry strategy (Scheme 1). Initial results showed only a slight improvement of in vitro activity and from a total number of 65 analogues prepared, only compound **3** demonstrated encouraging potency (Table 1). Both enantiomers were synthesised and were shown to be equipotent with **3** on PPARγ.

From published Telmisartan structure–activity relationship, it was clear that the amides would retain AT1 antagonist activity.[17] However, a dramatic decrease in AT1 affinity has been reported for Telmisartan analogues bearing an indole as central core instead of a benzimidazole ring.[18] In addition, compounds bearing an indole scaffold have been previously reported in literature as PPARγ partial agonists.[19–24]

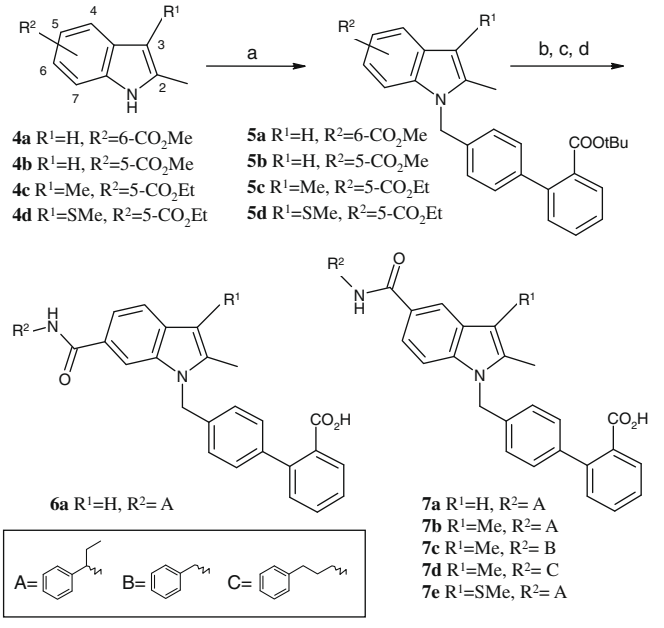
Thus, in an attempt to gain increased PPARγ potency and to abolish the AT1 antagonist activity, we replaced the benzimidazole central core by an indole. Compounds were synthesized using the chemical route shown in Scheme 2.

Variation of carboxamide side chain has been performed on positions 5 and 6 of the indole ring. Derivatives **6a** and **7a–e** were prepared from methyl 1*H*-indole-6-carboxylate **4a** or alkyl 1*H*-indole-5-carboxylate **4b–d** (Scheme 2). Intermediates **5a–d** were synthesized via alkylation with *tert*-butyl 4′-(bromomethyl)-2-biphenylcarboxylate in the presence of sodium hydride. Compounds **6a**, **7a–e** were synthesized by saponification of the ester group followed by standard peptide coupling methodology and *tert*-butyl ester cleavage.

Indole **6a** was found to be more potent on human PPARγ compared with the benzimidazole derivative **3**, but both compounds behaved as partial agonists. Substitution at C-5 gave compound **7a** which showed a very significant improvement in PPARγ



Scheme 1. Reagents and conditions: (a) α-ethylbenzylamine, HOBt, EDCI, Et_3N, CH_2Cl_2, rt; (b) TFA, CH_2Cl_2, rt.



Scheme 2. Reagents and conditions: (a) *tert*-butyl 4′-(bromomethyl)-2-biphenylcarboxylate, NaH, DMF, rt; (b) NaOH 1 N, EtOH, reflux; (c) amine, HOBt, EDCI, Et_3N, CH_2Cl_2, rt; (d) TFA, CH_2Cl_2, rt.

Table 1
In vitro evaluation of PPAR agonists on both murine (m) and human (h) receptors

Compound	EC_{50}[a] (μM) h PPARγ (%activation)[b]	EC_{50}[a] (μM) h PPARα (%activation)[b]	EC_{50}[a] (μM) h PPARδ (%activation)[b]	EC_{50}[a] (μM) m PPARγ (%activation)[b]	EC_{50}[a] (μM) m PPARα (%activation)[b]	EC_{50} (μM)[a] m PPARδ (%activation)[b]
1	2.02 (49)	>10	>10	4.06 (45)	>10	>10
3	0.90 (34)	>10	>10	1.69 (29)	>10	>10

[a] Data generated using cell based transient transfection assays.[25]

[b] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARγ activity, the reference was Rosiglitazone. For the PPARδ and PPARα activities, the reference compounds were GW516[26] and GW735,[27] respectively.

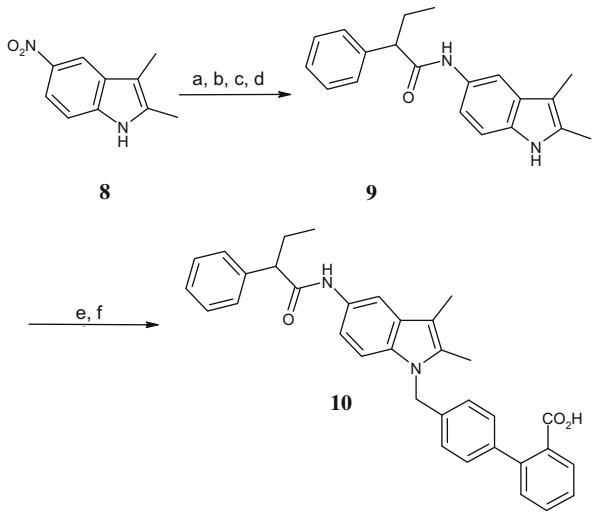
Table 2
Indole series: In vitro evaluation of human PPAR potency and selectivity

Compound	EC_{50}[a] (μM) h PPARγ (%activation)[b]	EC_{50}[a] (μM) h PPARα (%activation)[b]	EC_{50}[a] (μM) h PPARδ (%activation)[b]	IC_{50}[c] (μM) h PPARγ	IC_{50}[c] (μM) h PPARα	IC_{50}[c] (μM) h PPARδ
1	**2.02 (49)**	>10	>10	**12.2**	>10	>10
3	**0.90 (34)**	>10	>10	ND	ND	ND
6a	**0.163 (26)**	>10	>10	**0.321**	>10	>10
7a	**0.017 (43)**	4.96 (114)	>10	**0.018**	7.04	>10
7b	**0.0008 (31)**	>10	>10	**0.008**	>10	>10
7c	**0.047 (28)**	>10	>10	**0.041**	>10	>10
7d	**0.022 (37)**	>10	>10	**0.018**	>10	>10
7e	**0.001 (36)**	>10	>10	**0.012**	>10	>10

ND = Not determined.
[a] Data generated using cell based transient transfection assays.[25]
[b] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARγ activity, the reference was Rosiglitazone. For the PPARδ and PPARα activities, the reference compounds were GW516[26] and GW735,[27] respectively.
[c] Binding affinities were measured using radioligands following published procedures.[25]

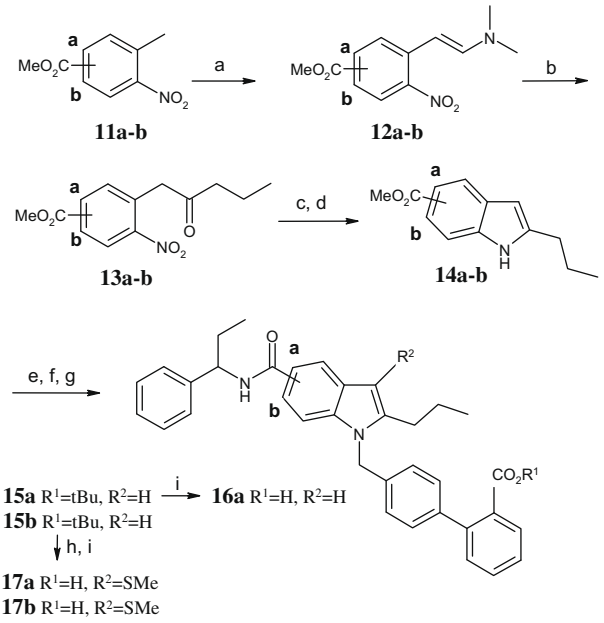
potency in both transactivation and binding assays, although weak PPARα activity was observed as well (Table 2).

Introduction of methyl or thiomethyl groups on the C-3 position of the indole gave **7b** and **e**, respectively, two partial agonists showing nanomolar potency in the transactivation assay, selectivity over δ and α subtypes and a high affinity in the binding assay (Table 2). Removing the ethyl group of the ethylbenzylamine (compound **7c**) as well as increasing the length of the chain with the (3-phenylpropyl)amine (compound **7d**) produced a small decrease in PPARγ potency compared with **7b** (Table 2).



Scheme 3. Reagents and conditions: (a) Boc_2O, DMAP, THF, rt; (b) NH_4COOH, Pd/C 10%, EtOH, 40 °C; (c) 2-phenylbutyryl chloride, Et_3N, THF, rt; (d) TFA, CH_2Cl_2, rt; (e) *tert*-butyl 4′-(bromomethyl)-2-biphenylcarboxylate, NaH, DMF, rt; (f) $HCl_{(g)}$, AcOEt, rt.

Compound **10**, the reverse amide analogue of compound **7b,** was synthesized following a six step strategy starting from 2,3-dimethyl-5-nitroindole **8** (Scheme 3). Amide inversion, however, induced a dramatic fall in potency (cf. **7b** and **10**) (Table 3).



Scheme 4. Reagents and conditions: (a) DMA–DMF, DMF, 130 °C; (b) butyryl chloride, pyridine, CH_2Cl_2, rt then dioxane–water, reflux; (c) H_2, Pd/C 10%, EtOH–THF, rt; (d) Zn powder, AcOH, reflux; (e) *tert*-butyl 4′-(bromomethyl)-2-biphenylcarboxylate, KOH, EtOH or DMF, rt; (f) NaOH 1 N, EtOH, reflux; (g) α-ethylbenzylamine, HATU, Et_3N, CH_2Cl_2, rt; (h) N-(methylthio)phtalimide, LiCl, DMAc, 80 °C; (i) $HCl_{(g)}$, AcOEt, rt.

Table 3
Indole series: In vitro evaluation of human PPAR potency and selectivity

Compound	EC_{50}[a] (μM) h PPARγ (%activation)[b]	EC_{50}[a] (μM) h PPARα (%activation)[b]	EC_{50}[a] (μM) h PPARδ (%activation)[b]	IC_{50}[c] (μM) h PPARγ	IC_{50}[c] (μM) h PPARα	IC_{50}[c] (μM) h PPARδ
7b	**0.0008 (31)**	>10	>10	**0.008**	>10	>10
10	**0.338 (37)**	**6.14 (45)**	ND	**0.574**	>10	>10

ND = Not determined.
[a] Data generated using cell based transient transfection assays.[25]
[b] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARγ activity, the reference was Rosiglitazone. For the PPARδ and PPARα activities, the reference compounds were GW516[26] and GW735,[27] respectively.
[c] Binding affinities were measured using radioligands following published procedures.[25]

Table 4
Indole series: In vitro evaluation of human PPAR potency and selectivity

Compound	EC_{50}[a] (μM) h PPARγ (%activation)[b]	EC_{50}[a] (μM) h PPARα (%activation)[b]	EC_{50}[a] (μM) h PPARδ (%activation)[b]	IC_{50}[c] (μM) h PPARγ	IC_{50}[c] (μM) h PPARα	IC_{50}[c] (μM) h PPARδ
7b	**0.0008 (31)**	>10	>10	**0.008**	>10	>10
16a	**0.002 (65)**	>10	ND	**0.026**	>10	>10
17a	**0.003 (32)**	>10	>10	**0.036**	>10	>10
17b	**0.201 (48)**	>10	ND	**0.490**	>10	**6.95**

ND = Not determined.
[a] Data generated using cell based transient transfection assays.[25]
[b] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARγ activity, the reference was Rosiglitazone. For the PPARδ and PPARα activities, the reference compounds were GW516[26] and GW735,[27] respectively.
[c] Binding affinities were measured using radioligands following published procedures.[25]

The influence of the C-2 indole alkyl side chain has also been investigated (Scheme 4). Modified Batcho–Leimgruber methodology[28] was used to prepare indole derivatives **14a–b**. Compound **16a** was obtained using the synthetic pathway described above. Introduction of thiomethyl substitution at the C-3 indole position led to compounds **17a–b**,[29] two highly potent and selective PPARγ partial agonists (Table 4).

Modification of the alkyl side chain on the C-2 position of the indole ring and/or introduction of the thiomethyl moiety on C-3 gave compounds showing similar potency (**16a** vs **7a** and **17a** vs **7e**) (Table 4). It is noteworthy that all indole derivatives synthesized were found inactive in the AT1 antagonism assay, as anticipated.

To determine the binding mode of this new series, compound **7b** was co-crystallized with PPARγ ligand-binding domain (Fig. 2). Interestingly, the acid moiety of **7b** does not form hydrogen bonds with the Tyr-473, His-323, and His-449 triad, as does the acid isostere thiazolidinedione of Rosiglitzaone.[30] Instead, the carboxylic acid of **7b** binds at the opposite end of the active site and hydrogen bonds with Arg-288 and Ser-342. This flipped orientation places the amide of **7b** near the triad, allowing the amide to donate and accept hydrogen bonds to Ser-289 and Tyr-327, respectively (not shown). Thus, the crystal structure of the partial agonist **7b,** bound to the PPARγ ligand binding domain exemplifies a new binding mode that differs from the crystal structure of a full agonist containing a thiazolidinedione and from the previously hypothesized model of bound Telmisartan.[12]

Compound **7b**, a highly potent PPARγ partial agonist on both the human and the murine isoforms (Table 5), was considered for in vivo evaluation.

The rat pharmacokinetic profile showed that compound **7b** was suitable for chronic administration (Table 6). Following a single oral dose of compound **7b** at 5 mg/kg, the plasma AUC was found to be 1152 ng h/mL and the oral bioavailability was determined as 52%.

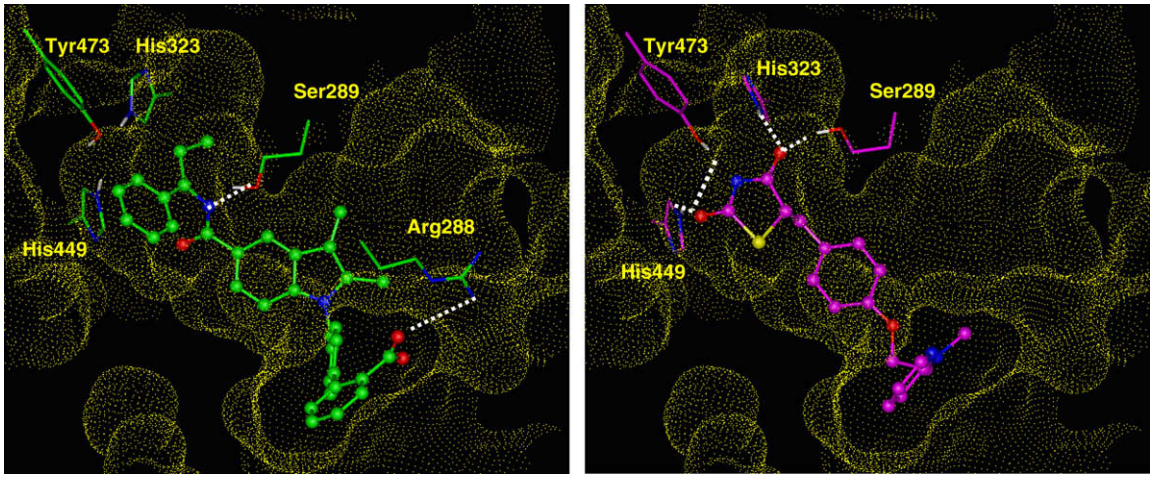


Figure 2. X-ray crystal structure of **7b**[31] (left, PDB access code: 3KMG) and **Rosiglitazone** (right, PDB access code: 2PRG) complexed with the PPARγ ligand binding domain. The molecular surface of the binding site is represented by yellow dots. Some interactions of the amino acids with the ligands are shown as white dotted lines.

Table 5
In vitro evaluation of **7b** vs human (h) and murine (m) PPARs

Compound	EC_{50}[a] (μM) h PPARγ (%activation)[b]	EC_{50}[a] (μM) h PPARα (%activation)[b]	EC_{50}[a] (μM) h PPARδ (%activation)[b]	EC_{50}[a] (μM) m PPARγ (%activation)[b]	EC_{50}[a] (μM) m PPARα (%activation)[b]	EC_{50}[a] (μM) m PPARδ (%activation)[b]
7b	**0.0008 (31)**	>10	>10	**0.002 (30)**	**5.51 (79)**	>10

[a] Data generated using cell based transient transfection assays.[25]
[b] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARγ activity, the reference was Rosiglitazone. For the PPARδ and PPARα activities, the reference compounds were GW516[26] and GW735,[27] respectively.

Table 6
Pharmacokinetic data for compound **7b** in CD rat[a]

F%	Cl (mL/min/kg)	C_{max} (ng/mL)	Vd_{ss} (L/kg)	$T_{1/2}$ (h)	AUC_{po} (ng h/mL)
52	40	319	17	4.58	1152

[a] IV dose: 1 mg/kg (10% DMSO/25% PEG200/65% Phosphate buffer 30 MM pH 9.3; PO dose: 5 mg/kg (0.5% HPMC K15 M/0.1% Tween80/water).

Table 7
PPAR potencies and oral exposure for compounds **7b** and **GW1929** in Zucker fa/fa rat[a]

Compound	AUC_{po} (ng h/mL)	EC_{50}[b] (μM) h PPARγ (%activation)[c]	EC_{50}[b] (μM) m PPARγ (%activation)[c]
7b	1329	0.0008 (31)	0.002 (30)
GW1929	16525	0.006 (72)	0.013 (84)

[a] PO dose: 5 mg/kg (0.5% HPMC K100/0.1% Tween80/Phosphate buffer 60 MM pH 7).
[b] Data generated using cell based transient transfection assays.[25]
[c] % of maximal activation of all compounds was compared to reference compounds normalized to 100%. For the PPARγ activity, the reference was Rosiglitazone.

Given that we proposed to use the Zucker fa/fa rat as pharmacodynamic model the pharmacokinetic profile of **7b** was also evaluated in this strain. The standard PPARγ full agonist, **GW1929**[32] was also evaluated for comparison purposes (Table 7).

We anticipated that PK/PD relationship could be different between a modulator and a full agonist. Thus we did not try to draw a strict correlation between plasma AUC and in vitro potency in determining the doses of compound **7b** to be administered to the Zucker fa/fa rat. Taking into account that **7b** is approximately ten fold more potent in the transactivation assay and displays approximately a 10-fold lower AUC versus the full agonist **GW1929**, we should have selected the same doses of compounds **7b** and **GW1929** for in vivo experiment in Zucker fa/fa rat. However, as **7b** was a partial agonist we decided to administer **7b** twice a day for 5 days at 10 and 40 mg/kg compared to a standard in vivo experiment with **GW1929**, tested at 1 and 10 mg/kg in the same protocol (Fig. 3).

Compound **7b** efficiently decreased plasma glucose level by 25% and triglycerides by 49% at 40 mg/kg. Similar effects on glucose and triglycerides were observed with **GW1929** at 10 mg/kg (21% decrease of plasma glucose and 54% fall in triglycerides). For an identical effect on glucose/TG, weight gain was more pronounced in the group treated with **GW1929** than in that treated with compound **7b**. Hematocrit level was decreased by 15% with **GW1929** (10 mg/kg), versus 10% observed with compound **7b** (40 mg/kg).

Overall, **7b** (40 mg/kg), displayed similar pharmacological effects as **GW1929** (10 mg/kg) but showed a lower degree of the side effects traditionally associated with full PPARγ agonists.

In summary, starting from the angiotensin II receptor antagonist Telmisartan which showed weak potency on PPARγ, we have developed a new series of selective and very potent PPARγ modulators. A crystal structure revealed that compound **7b**, one of the most potent modulators in the series, displays a novel binding mode in PPARγ ligand binding domain. Compound **7b** demonstrated similar effects on glucose and triglycerides in comparison to a full PPARγ agonist with fewer side effects as assessed by in vivo experiments in the Zucker fa/fa rat.

Acknowledgements

We thank Bruce Wisely for cloning and Jane Bynum for replenishing the stock of purified protein used to produce the crystal structure of PPARγ bound with compound **7b**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.12.107.

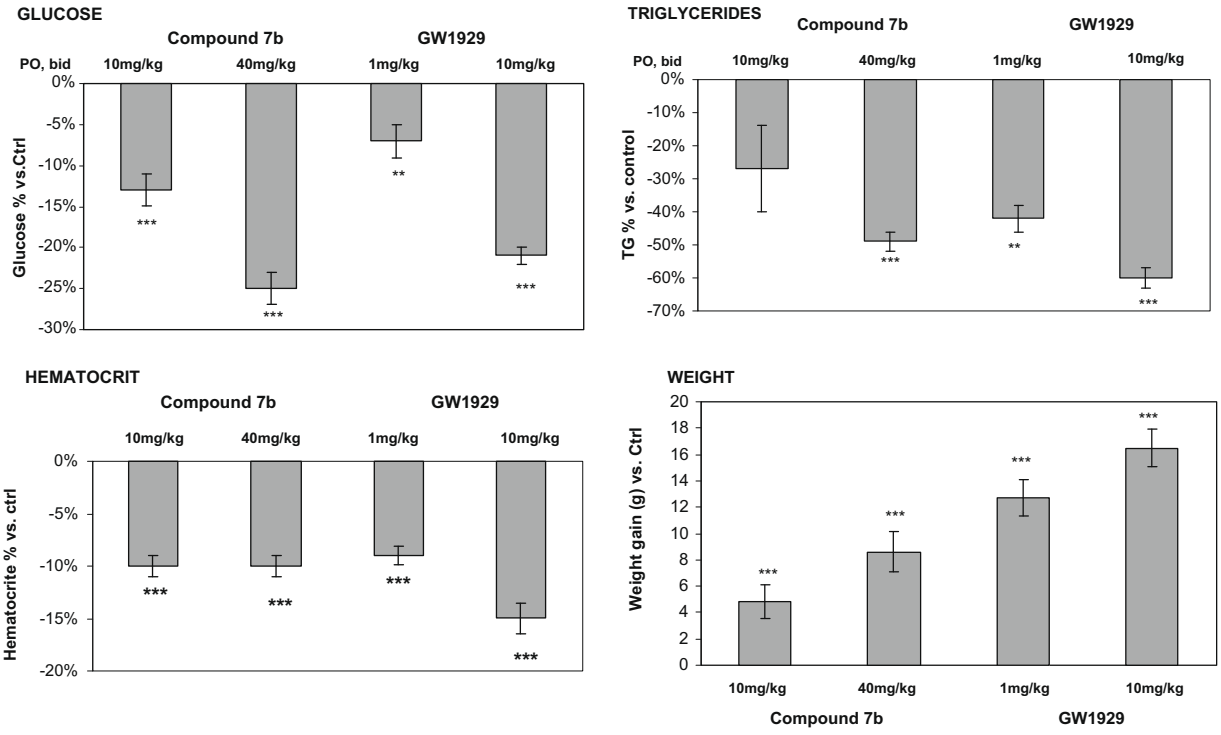


Figure 3. Effects of compound **7b** and **GW1929** on glucose, triglycerides, hematocrit and weight gain in male Zucker fa/fa rat.

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