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Discovery of novel indazole derivatives as dual angiotensin II antagonists and partial PPARγ agonists

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Centre de Recherches François Hyafil, GlaxoSmithKline R&D, 25 avenue du Québec, 91140 Villebon-sur-Yvette, France.

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Abstract : Identification of indazole derivatives acting as dual angiotensin II type 1 (AT_1) receptor antagonists and partial peroxisome proliferator-activated receptor-γ (PPARγ) agonists is described.
Starting from Telmisartan, we previously described that indole derivatives were very potent partial PPARγ agonists with loss of AT_1 receptor antagonist activity.
Design, synthesis and evaluation of new central scaffolds led us to the discovery of pyrrazolopyridine then indazole derivatives provided novel series possessing the desired dual activity.
Among the new compounds, **38** was identified as a potent AT_1 receptor antagonist (IC_{50} = 0.006 μM) and partial PPARγ agonist (EC_{50} = 0.25 μM, 40% max) with good oral bioavailability in rat.
The dual pharmacology of compound **38** was demonstrated in two preclinical models of hypertension (SHR) and insulin resistance (Zucker fa/fa rat).

Keywords
Telmisartan
PPARγ
Peroxisome proliferator-activated receptor
Angiotensin

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Metabolic syndrome refers to a cluster of metabolic disorders such as high blood pressure, obesity, insulin resistance, and dyslipidaemia that constitutes a major risk factor for cardiovascular diseases.[1-2] A drug that could simultaneously address several of these diseases would have a significant health benefit effect. The angiotensin II receptor antagonist (AT_1 receptor antagonist) Telmisartan (Micardis®) (Fig. 1), a marketed blood pressure reducing drug was found to exhibit unexpected beneficial metabolic properties on serum glucose levels, serum triglycerides and insulin.[3] *In vitro* and preclinical *in vivo* studies have demonstrated PPARγ activation to be directly linked to these benefits.[4-6] More recently, the partial PPARγ agonist properties of Telmisartan was explained by an unique binding mode in PPARγ ligand binding domain.[7]

The identification of essential structural components of Telmisartan for PPARγ receptor activation has already been disclosed.[8] These reports highlighted the importance of the alkyl side chain at position 2 of the benzimidazole ring[9] and the influence of the lipophilic moiety at position 5 and 6[10] on potency, efficacy and co-factor recruitment.[11]

Telmisartan analogues have been designed and reported as dual angiotensin II type 1 receptor antagonists and partial PPARγ agonists.[12–14] More recently, Casimiro-Garcia et al. showed that modification of the central scaffold could lead to compounds with dual *in vitro* activity (imidazo[4,5-*c*]pyridin-4-one series)[15] and *in vivo* pharmacological effects (imidazo[4,5-*b*]pyridine series)[16] in two different rodent models (Spontaneously Hypertensive Rats (SHR) and Zucker fa/fa rats).

In a previous report,[17] our group confirmed that the replacement of the methylbenzimidazole moiety of Telmisartan with a carboxamide at the 6-position of the benzimidazole central core (compound **2**) (Fig.1), increased the affinity for PPARγ while maintaining an acceptable AT_1

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receptor antagonist activity. Analogue compound substituted at the 5-position (compound **1**) was a less potent PPARγ agonist.

FIGURE 1

Having established that PPARγ activity of Telmisartan could be enhanced while retaining some AT_1 receptor inhibiting activity, we explored novel related scaffolds in order to increase potency at both PPARγ and AT_1 receptors.

In our previous report,[17] we demonstrated that the replacement of Telmisartan's benzimidazole central core by indole central scaffold (compound **3**, Fig. 1) revealed a very potent PPARγ partial agonist. The crystal structure of compound **3** displayed a novel binding mode in PPARγ ligand binding domain. This compound demonstrated a similar pharmacological effect compare to a full PPARγ agonist **GW1929**[18] albeit with fewer side effects as assessed by *in vivo* experiments in the Zucker fa/fa rat. Unfortunately, compound **3** was totally inactive on AT_1 receptor.

Cruciani et al.[19] have thoroughly discussed the SAR for AT_1 receptor inhibition, emphasizing the importance of the nitrogen at position 3 on the benzimidazole as a H-bond acceptor key for AT_1 receptor pharmacophore. We therefore focused our efforts on chemical scaffolds that allow the crucial H-bonding interaction lacking in the indole series.

New ligands where a nitrogen atom is acting as H-bond acceptor (Fig. **2**) were design with the aim to maintain PPARγ agonist activity while restoring AT_1 receptor antagonism.

FIGURE 2

The synthetic route of reverse indole series is depicted in Scheme 1. Methyl-4-methyl-3-nitrobenzoate **4a** and methyl-3-methyl-4-nitrobenzoate **4b** were submitted to Batcho-

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Leimgruber conditions, then sequentially acylated and alkylated to give the corresponding ketones **6a-b**. Reductive cyclization using Pd/C followed by alkylation with methyl iodide led to compound **9b** while zinc-mediated reduction in acetic acid followed by alkylation or *tert*-butylcarbamate protection gave compounds **7a** and **8a**. Saponification, acylation and deprotection steps afforded compounds **13a**, **14a**, **15b** and **16b**.

SCHEME 1

Reverse indoles substituted in position 6 (**13a**, **14a**) act as potent partial PPARγ agonists (Table 1). Compounds substituted in position 5 (**15b**, **16b**) were more potent PPARγ agonists than benzimidazole derivative **2**. Despite its ability to act as an H-bond acceptor, indole **15b** showed no AT_1 receptor activity. Not surprisingly, indoles **14a** and **16b** which nitrogens are H-bond donors were inactive on AT_1 receptor.

TABLE 1

The synthesis of pyrazolopyridine (compounds **22**, **26** and **27**) is described in Scheme 2. Compound **18** was synthesized in two steps from 4-bromobenzoic acid **17** using Weinreb methodology. Intermediate **18** underwent a 1,3-dipolar cycloaddition reaction with compound **19** to give expected pyrazolopyridine ring **20**. Methyl ester was saponified using lithium hydroxide to afford compound **21**. On one hand, a Suzuki reaction followed by a standard peptide coupling procedure, saponification of the methyl ester using lithium hydroxide and carbonyl function reduction followed by deshydroxylation under acidic conditions led to compound **22**. On the other hand, compound **23** was prepared by carbonyl function reduction and deshydroxylation followed by acylation and dehydratation using Eaton reagent. Introduction of appropriate substituted benzeneboronic acid by Suzuki coupling and conversion to the corresponding carboxylic acid and tetrazole led respectively to compounds **26** and **27**.

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SCHEME 2

The modification of central scaffold from reverse indole to pyrazolopyridine ring led to a similar PPARγ activity (compound **16b** vs. **22**). However, nitrogen atom acting as H-bond acceptor in the desired region restored AT_1 receptor antagonist activity. Modification of the left hand side moiety (**22** vs. **26**) showed a 20-fold improvement on AT_1 receptor with similar potency and efficacy on PPARγ. The replacement of the carboxylic acid **26** to the tetrazole bioisostere **27** not only improved both AT_1 receptor and PPARγ activities, but also led to the loss of partial agonism.

TABLE 2

The hypothesis to restore AT_1 receptor activity proved to be accurate. Thus, we decided to continue our efforts to discover a molecule with a more attractive dual profile. We decided to change the central scaffold from pyrazolopyridine to 2H-indazole ring (Fig. 2).

SCHEME 3

The synthetic route of 2H-indazole series is illustrated in Scheme 3. The indazole ring was prepared via diazotation and cyclization from methyl 4-amino-3-methylbenzoate **28** and converted to compound **29** by iodination. The compound **29** was then transformed using iodine-magnesium exchange and the resulting magnesiated species was trapped with *tert*-butyl-4'-formyl-2-biphenylcarboxylate **A** to afford compound **30**.[21-22] The compound obtained was then saponified and subjected to peptide-coupling conditions to introduce the lipophilic left hand side group. Finally, the use of triethylsilane and trifluoroacetic acid in dichloromethane allowed dehydroxylation and deprotection leading to compound **31**.

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Compound **35** (R^1 = tetrazole) was prepared using an analogous general methodology. For compounds **37** and **38**, the carboxamide moiety was replaced by a butyl-benzimidazole substituent.

TABLE 3

The replacement of the pyrazolopyridine by an indazole led to a more attractive dual profile (**22** vs. **31**). Compound **31** was a more potent AT_1 receptor antagonist and an attractive partial PPARγ agonist. The replacement of carboxylic acid to tetrazole (**31** vs. **35**) confirmed the improvement in AT_1 receptor antagonist activity (10-fold more potent).

The replacement of carboxamide by butylbenzimidazole (**35** vs. **38**) led to a very interesting dual compound (nanomolar range on AT_1 receptor and a partial PPARγ agonist activity compared to Telmisartan).

Compound **38** was also screened on murine PPARα and PPARδ receptors and was found selective (>10 μM) in a transactivation assay over these two receptor subtypes.

Compound **38**, a very interesting dual AT_1 receptor and partial PPARγ agonist was then administered to Zucker fa/fa rats by oral and intravenous routes to determine its pharmacokinetic profile (Table 4).

TABLE 4

Compound **38** showed a good oral bioavailability (78%) and exhibited a moderate *in vivo* clearance (11 mL/min/kg). The pharmacokinetic properties illustrate that compound **38** was suitable for chronic oral administration allowing it was thus progressed into Zucker fa/fa and SHR models.

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Compound **38** was chronically administrated *per os* daily for 12 days at 10 mg/kg in SHR (Fig. 3). During the treatment phase, the systolic and diastolic blood pressure significantly decreased compared to baseline value and vehicle-treated animals. At the end of the treatment phase, a wash out period showed that blood pressure in compound **38**-treated group was similar to the vehicle-treated control group, thus confirming *in vivo* efficacy of compound **38** on blood pressure through AT_1 receptor antagonism.

FIGURE 3 / FIGURE 4

Compound **38** was administrated *per os* to Zucker fa/fa rats for 5 days at 75 mg/kg once daily and compared to a PPARγ full agonist **GW1929**[18] dosed at 1 and 10 mg/kg in the same study (Fig. 4). The dose chosen for this experiment was deliberately high in order to check that compound **38** was really acting as a partial PPARγ agonist and to demonstrate potential side effects.

Compound **38** (75 mg/kg) substantially lowered plasma levels of free fatty acids, insulin and triglycerides, indicating significant insulin sensitizing activity compared to vehicle-treated group. The pharmacological effect of compound **38** was found similar when comparing to the full PPARγ agonist **GW1929** administered at 1 mg/kg. However, compound **38** did not change body weight gain during the study when compared to vehicle group, while a significant increase in body weight gain was observed in the group treated with the full PPARγ agonist **GW1929** (Fig. 4).

In summary, compound **38** was identified as a potent and selective dual AT_1 receptor antagonist and partial PPARγ agonist. It was found active at 10 mg/kg on blood pressure in the SHR model. At the dose of 75 mg/kg, compound **38** demonstrated similar effects on insulin, NEFA and triglycerides compared to a full PPARγ agonist but with no weight gain as assessed by *in vivo* experiments in the Zucker fa/fa rats.

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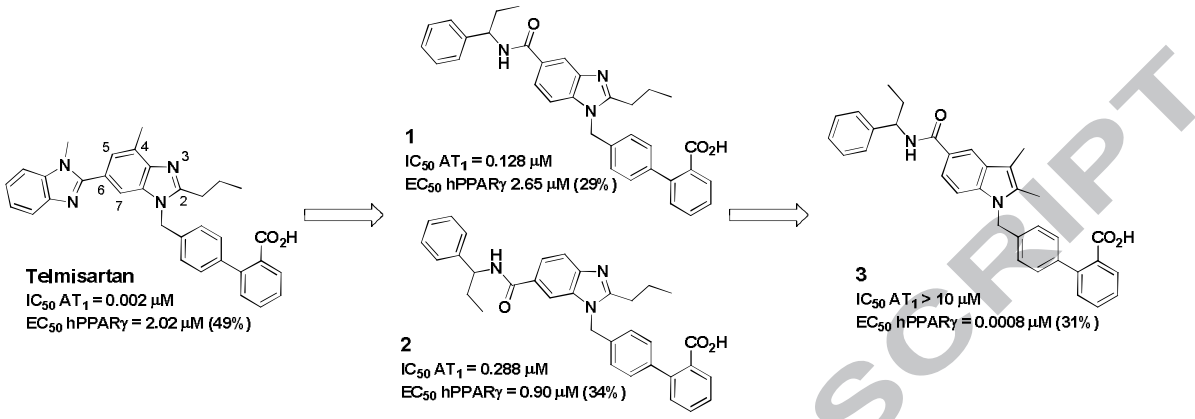

Figure 1. Starting from **Telmisartan**, a very potent PPARγ modulator was previously identified.

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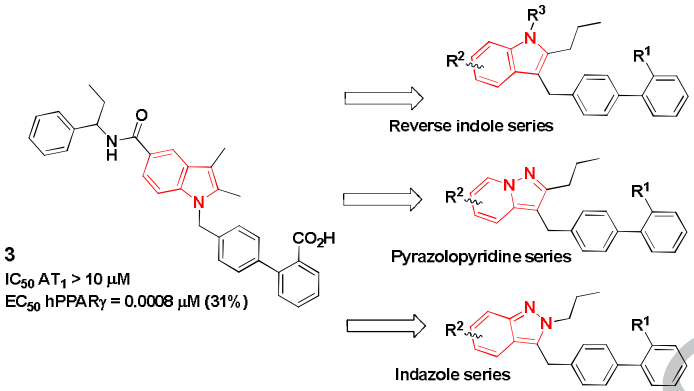

Figure 2. Design of new central scaffolds to restore AT_1 receptor antagonist activity.

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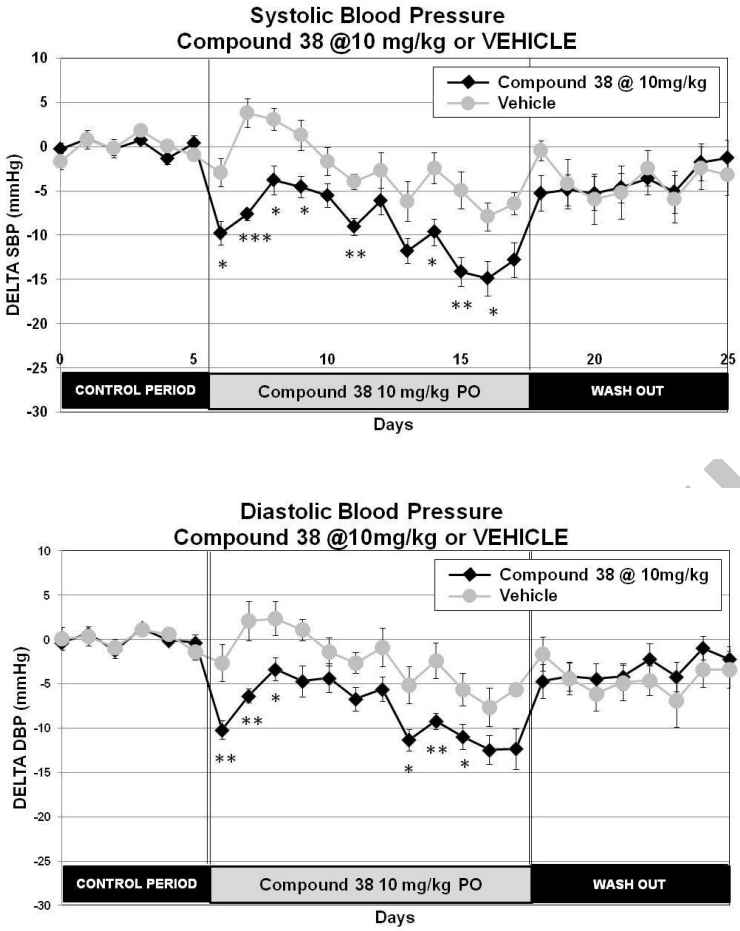

Figure 3. Effect of Compound **38** at 10 mg/kg/day or Vehicle on systolic and diastolic blood pressures in SHR.

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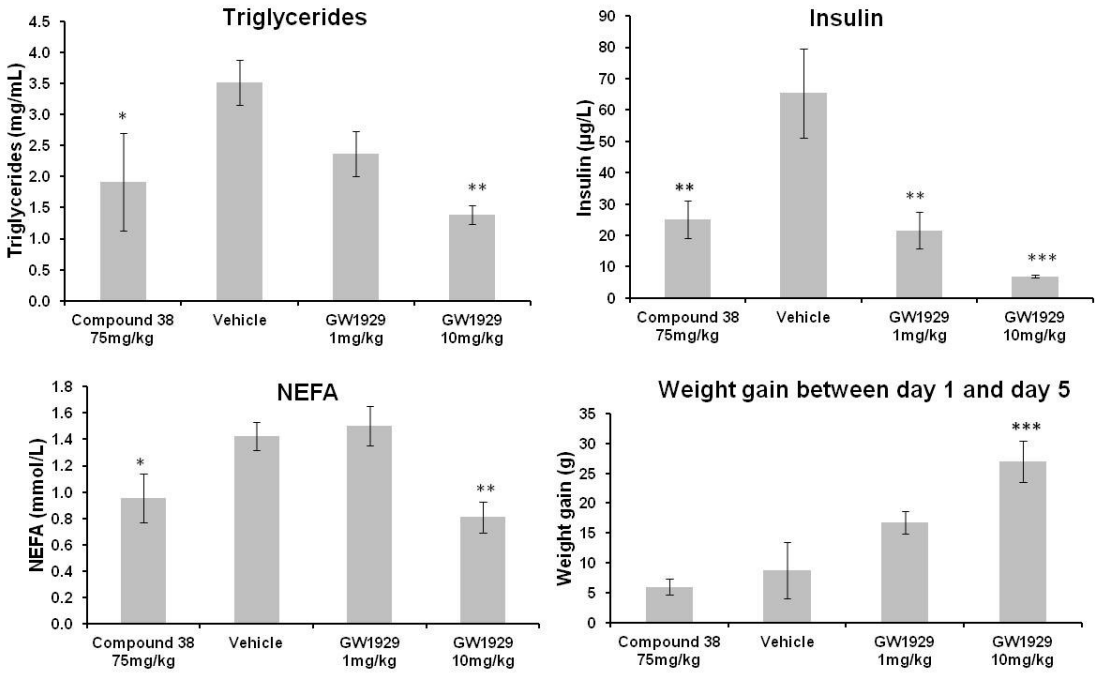

Figure 4. Effect of Compound **38** (75 mg/kg per os – once daily) and **GW1929** on triglycerides, insulin, NEFA and weight gain in male Zucker fa/fa rats after a 5 day oral dosing. (* $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$)

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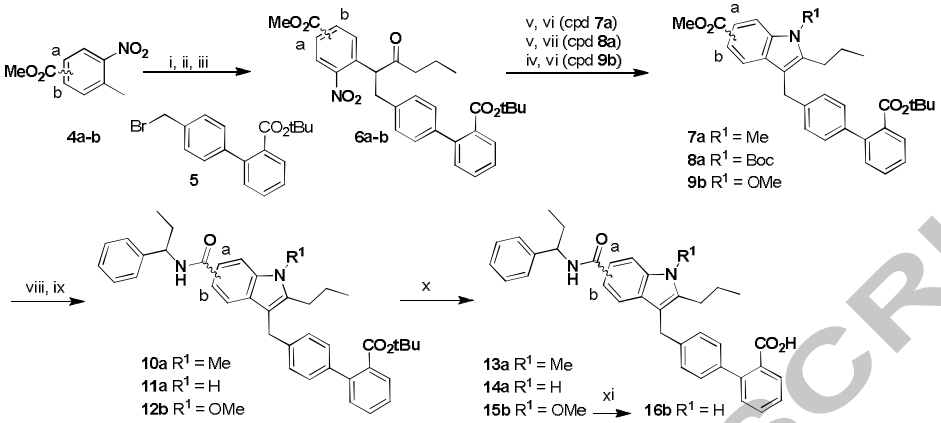

Scheme 1. Reagents and conditions: (i) DMF-DMA, DMF, 130°C; (ii) Butyryl chloride, pyridine, DCM, RT; (iii) NaH, KI, 0°C then **5**, reflux; (iv) H_2, Pd/C, EtOH/THF, RT; (v) Zn, AcOH, 80°C; (vi) NaH, MeI, DMF, 0°C to RT; (vii) Boc_2O, DMAP, THF, RT; (viii) NaOH, dioxane, 80°C or reflux; (ix) 1-phenylpropan-1-amine, HATU, Et_3N, DCM, RT; (x) $HCl_{(g)}$, EtOAc, RT; (xi) H_2, Pd/C, MeOH, RT.

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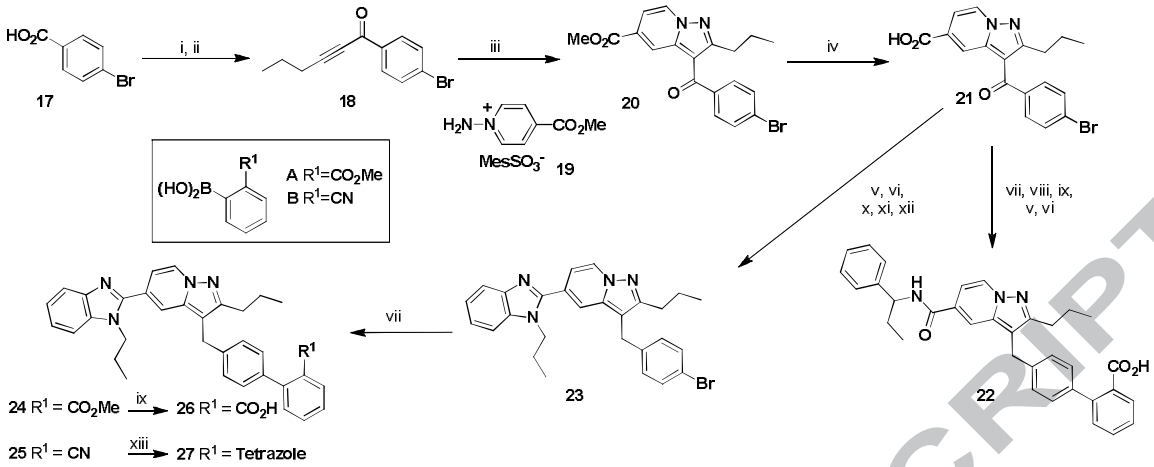

Scheme 2. Reagents and conditions: (i) *N,O*-Dimethylhydroxylamine hydrochloride, EDCI, HOBt, Et_3N, DMF, RT; (ii) Pent-1-yne, *n*-BuLi, THF, -78°C to RT; (iii) K_2CO_3, DMF, 0°C to RT; (iv) LiOH 1N, THF/MeOH, 70°C; (v) $NaBH_4$, THF/MeOH, RT; (vi) TFA, Et_3SiH, DCM, RT; (vii) boronic acid **A** or **B**, $Pd(PPh_3)_4$, Cs_2CO_3 or Na_2CO_3 or CsF, DME, 110°C; (viii) 1-phenylpropan-1-amine, EDCI, HOBt, Et_3N, DMF, RT; (ix) LiOH, THF/MeOH, reflux; (x) 1,2-benzenediamine, HATU, Et_3N, DMF, RT; (xi) Eaton reagent, RT to 120°C; (xii) n-PrI, Cs_2CO_3, DMF, 70°C; (xiii) Azidotributyltin, 165°C.

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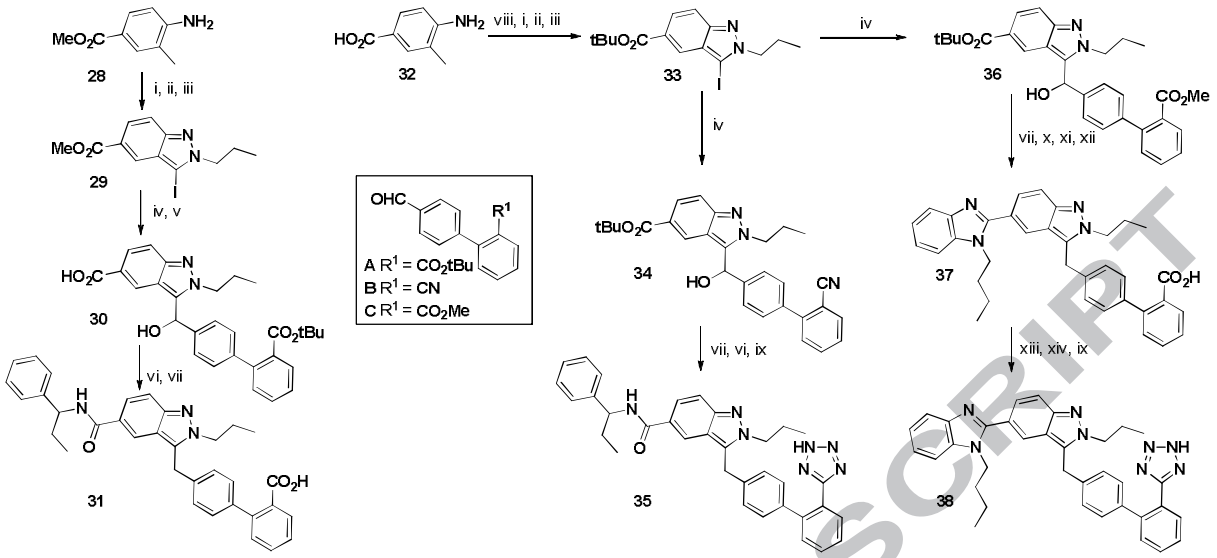

Scheme 3. Reagents and conditions: (i) a) NH_4BF_4, HCl 37%, $NaNO_2$, H_2O, 0°C to RT; b) KOAc, 18-Crown-6, $CHCl_3$, RT ; (ii) PrI, K_2CO_3, DMF, 60°C; (iii) NIS, AcOH, 80°C; (iv) iPrMgCl, 40°C to -20°C, THF/NMP (10/1), then aldehyde **A-C** to RT; (v) NaOH 1N , dioxane, 80°C; (vi) 1-Phenylpropan-1-amine, HATU, Et_3N, DMF, RT ; (vii) TFA, Et_3SiH, DCM, reflux; (viii) EDCI, tBuOH, reflux; (ix) Azidotributyltin, 165°C; (x) N^1-butylbenzene-1,2-diamine, HATU, Et_3N, THF, RT; (xi) Acetic acid, 80°C; (xii) NaOH 1N, MeOH, reflux ; (xiii) Ammonium chloride, HATU, Et_3N, DCM/DMF, RT; (xiv) 2,2,2-Trichloroacetyl chloride, Et_3N, DCM, 0°C.

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Table 1. Reverse indole series: *In vitro* evaluation on human (h) and murine (m) PPARγ[a] and AT_1 receptors.

Compound	R^1	Substituent position	EC_{50} (μM) h PPARγ (%activation)[b]	EC_{50} (μM) m PPARγ (%activation)[b]	IC_{50} AT_1 (μM)
13a	Me	6	0.002 (52)	0.003 (42)	>10
14a	H	6	0.006 (47)	0.009 (36)	>10
15b	OMe	5	0.09 (29)	0.20 (17)	>10
16b	H	5	0.35 (39)	0.51 (24)	>10

[a] Data generated using cell based transient transfection assays.[19] PPAR EC_{50} values are means of 2 independent experiments. AT_1 IC_{50} values were assessed once.

Compound **13a** and **14a** displayed respectively EC_{50} of 0.17 μM (90%) and 0.79 μM (71%) on murine PPARα isoform. Compounds **15b** and **16b** were found inactive (>10 μM) on murine PPARα. Compounds **13a**, **14a** and **16b** were not evaluated on murine PPARδ isoforms. Compounds **15b** was found inactive (>10 μM) on murine PPARδ.

[b] % of maximal activation for all compounds was compared to the reference compound rosiglitazone normalized to 100%.

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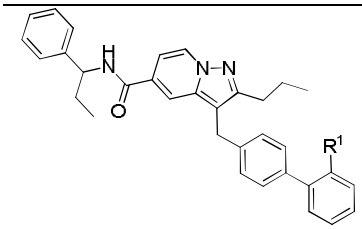
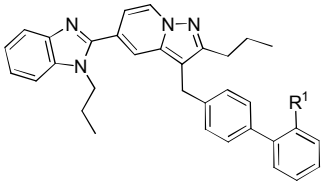
Table 2. Pyrazolopyridine series: *In vitro* evaluation on human (h) and murine (m) PPARγ[a] and AT_1 receptors.

Structure	R^1 Cpd number	EC_{50} (μM) h PPARγ (%activation)[b]	EC_{50} (μM) m PPARγ (%activation)[b]	IC_{50} AT_1 (μM)
	-COOH **22**	0.39 (37)	1.02 (32)	1.69
	-COOH **26**	0.28 (43)	0.38 (27)	0.085
	-Tetrazole **27**	0.08 (81)	0.13 (60)	0.023

[a] Data generated using cell based transient transfection assays.[19] PPAR EC_{50} values are means of 2 independent experiments. AT_1 IC_{50} values were assessed once.

All compounds were found inactive (>10 μM) on murine PPARα and PPARδ isoforms.

[b] % of maximal activation for all compounds was compared to the reference compound rosiglitazone normalized to 100%.

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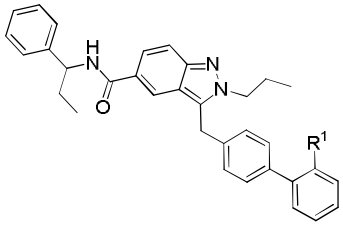
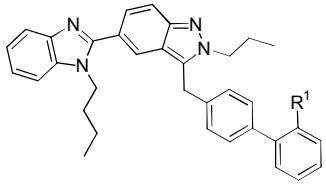
Table 3. Indazole series: *In vitro* evaluation on human (h) and murine (m) PPARγ[a] and AT_1 receptors.

Structure	R^1 Cpd number	EC_{50} (μM) h PPARγ (%activation)[b]	EC_{50} (μM) m PPARγ (%activation)[b]	IC_{50} AT_1 (μM)
	-COOH **31**	0.13 (24)	0.25 (19)	1.0
	-Tetrazole **35**	0.18 (21)	0.25 (9)	0.097
	-COOH **37**	0.64 (40)	1.39 (37)	0.06
	-Tetrazole **38**	0.25 (40)	0.27 (18)	0.006

[a] Data generated using cell based transient transfection assays.[19] PPAR EC_{50} values are means of 2 independent experiments. AT_1 IC_{50} values were assessed once.

All compounds were found inactive (>10 μM) on murine PPARα and PPARδ isoforms.

[b] % of maximal activation for all compounds was compared to the reference compound rosiglitazone normalized to 100%.

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Table 4. Pharmacokinetic parameters of **38** in ZDF rat[a]

Route	Dose (mg/kg)	AUC_{po} (ng.h/mL)	$T_{1/2}$ (h)	Vd_{ss} (L/kg)	Cl (mL/min/kg)	F (%)
IV	5.2	8011	14.00	7.8	11	
PO	30	36325				78

[a] IV: DMSO/Hydroxypropyl-β-Cyclodextrin 20% in phosphate buffer 60MM pH 7; PO: HPMC K100 0.5%/TWEEN 80 0.1% IN PHOSPHATE BUFFER 60MM PH 7.

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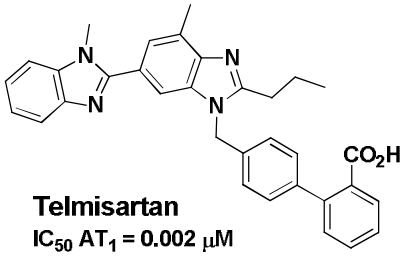
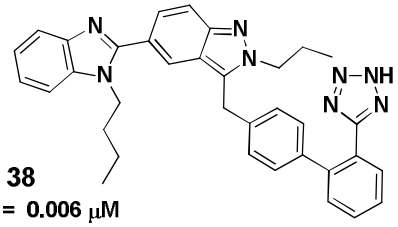


Telmisartan

IC_{50} AT_1 = 0.002 μM

EC_{50} hPPARγ = 2.02 μM (49%)



38

IC_{50} AT_1 = 0.006 μM

EC_{50} hPPARγ = 0.025 μM (40%)

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