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Discovery of a novel class of PPARδ partial agonists

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ABSTRACT

Anthranilic acid GW9371 was identified as a novel class of PPARδ partial agonist through high-throughput screening. The design and synthesis of SAR analogues is described. GSK1115 and GSK7227 show potent partial agonism of the PPARδ target genes CPT1a and PDK4 in skeletal muscle cells.

The peroxisome proliferator activated receptors (PPARs) are important members of the nuclear receptor superfamily. These receptors are ligand activated transcription factors known to play a key role in the catabolism and storage of dietary fats. Three receptor subtypes, PPARα, PPARγ, and PPARδ, exhibiting distinct tissue expressions have been identified, and represent attractive therapeutic targets with promising clinical potential.[1] The fibrate class of drugs including clofibrate, fenofibrate, and bezafibrate are known PPARα activators that have been used for decades in the clinic as hypolipodemic agents.[2] PPARγ agonists enhance insulin sensitivity, and lower plasma glucose and fatty acid levels.[3] Rosiglitazone (Avandia) and pioglitazone (Actos) are PPARγ agonists currently used for the clinical treatment of type 2 diabetes. PPARδ remains the least understood PPAR subtype and currently no marketed PPARδ drugs exist. However, evidence implicating PPARδ as a key regulator of lipid homeostasis and glucose disposal is growing.[4] The PPARδ agonist GW501516 has been shown to improve insulin resistance and reduce plasma glucose in rodent models of type 2 diabetes and correct the metabolic syndrome in obese primates.[5] Most notably, it has also been recently shown that GW501516 reduces serum triglycerides and prevents the decrease of HDL-c and apoA-1 levels in sedentary human volunteers.[6] These positive results suggest that PPARδ is a promising target for the novel treatment of metabolic diseases.

The development of selective small molecule regulators of the PPAR family has been instrumental in deciphering the biological pathways regulated by these receptors. A number of PPAR agonists have been described in the literature. The availability of PPARδ specific compounds, however, is limited. Recently, a selective PPARδ partial agonist was reported to correct plasma lipid parameters and improve insulin sensitivity in a high fat fed ApoB100/CETP-Tgn mouse model, highlighting the therapeutic potential of PPARδ partial agonists as a novel treatment of dyslipidemia.[7] Additional chemical tool compounds with a range of functional activity profiles are still needed to further elucidate the biological roles of PPARδ and provide new insights into potential therapeutic utilities.

We recently reported a novel selective PPARδ antagonist ligand for use as a research tool.[8] As part of our continuing efforts to identify additional PPARδ tool compounds, we executed a high-throughput screen of our compound collection. Anthranilic acid **GW9371** was identified as a chemically unique PPARδ ligand. Structurally, **GW9371** resembles the anthranilic acid **BVT.762** (Fig. 1) reported by Biovitrum as a PPARα/γ partial agonist.[9,10] **GW9371**, however, has a distinct PPARδ selectivity profile.

The PPARδ binding affinity and subtype selectivity was measured in an in vitro ligand displacement assay.[11] **GW9371** is a potent and selective PPARδ ligand ($pIC_{50} = 6.9$) without appreciable

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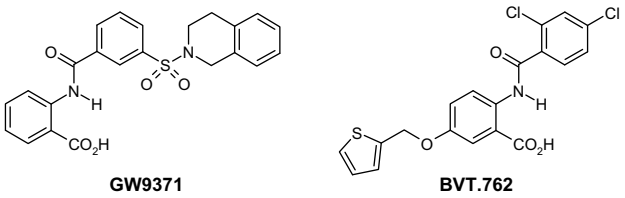


Figure 1. Structure of anthranilic acid-derived PPAR ligands.

affinity for either PPARα or PPARγ (pIC_{50}'s < 5). The functional PPARδ activity of **GW9371** was assessed in a standard Gal4 chimera cell-based reporter assay,[12] and it was found to be a weak partial agonist (pEC_{50} = 5.9,% max = 61 compared to full agonist **GW501516**).

Using **GW9371** as a lead, we initiated an effort to develop a novel series of PPARδ partial agonists. Most PPAR agonists have an acidic group and previous ligand bound crystal structures[13] have shown that the acidic group usually forms hydrogen bonds with Tyr473 (in the AF2 helix), His323, and/or His449 (all residue numbers given in PPARγ numbering). Partial agonists sometimes bind differently, and **BVT.762** binds to PPARγ with its carboxylate directed away from the AF2 helix, forming a hydrogen bond instead with the backbone NH of Ser342.[10] In an effort to understand the key receptor binding interactions of our anthranilic acid template with PPARδ, **GW9371** was co-crystallized with the ligand binding domain (LBD) of the hPPARδ receptor. The crystal structure, solved at 2.9 Å resolution (R = 21%, R_{free} = 24%, PDB code 3DY6), shows that the **GW9371** anthranilate group binds similarly to **BVT.762** between helix-3 and the β-sheet, with the carboxylate directed away from the AF2 helix (Fig. 2). The carboxylate makes a possible hydrogen bond with Thr288 (2.8 Å O–O distance), and makes additional interactions with the side chains of Arg284 and Trp264, and the backbone NH of Ala342 with O-H distances of 4.2, 4.6 and 4.2 Å, respectively. Thr288 is conserved in PPARα but not in PPARγ, while Arg284 and Trp264 are unique to PPARδ. All three of these side chain interactions are different from those in the PPARγ/**BVT.762** structure, and tend to promote PPARδ selectivity. The carboxylate is further stabilized by an intramolecular hydrogen bond with the ligand amide NH group, which serves to rigidify the core structure within the binding pocket. The sulfonamide adopts a conformation that directs the tetrahydroisoquinoline group toward Tyr473, His323 and His449 (heavy atom distances of 3.2, 4.1, and 3.4 Å, respectively). With the acid binding site occupied by the lipophilic tetrahydroisoquinoline group, Tyr473 shifts slightly to make hydrogen bonds with His323 and His449. The X-ray structure reveals a small vacant lipophilic pocket below the anthranilic acid headgroup with a second narrow lipophilic pocket available near the tetrahydroisoquinoline region.

The structure of **GW3971** bound within the PPARδ LBD suggests that the potency of this series could be improved by optimizing the interactions within one or both of the vacant lipophilic pockets. In addition, we surmised that appropriate structural modifications to the tetrahydroisoquinoline fragment could be designed to interact with the AF-2 helix and influence the activity profile. Using the PPARδ bound structure of **GW9371** as a guide, we synthesized a series of compounds to explore the SAR of this new class of PPARδ ligand. Our initial efforts focused on the anthranilic acid region. The synthesis of these compounds is detailed in Scheme 1. The coupling reaction of commercially available 3-(chlorosulfonyl)benzoic acid with 1,2,3,4-tetrahydroiso-quinoline in acetone provided sulfonamide **1**. Refluxing intermediate **1** in thionyl chloride followed by reaction of the crude acid chloride with substituted anthranilic esters and saponification gave the final targets **2–9** in good yields.

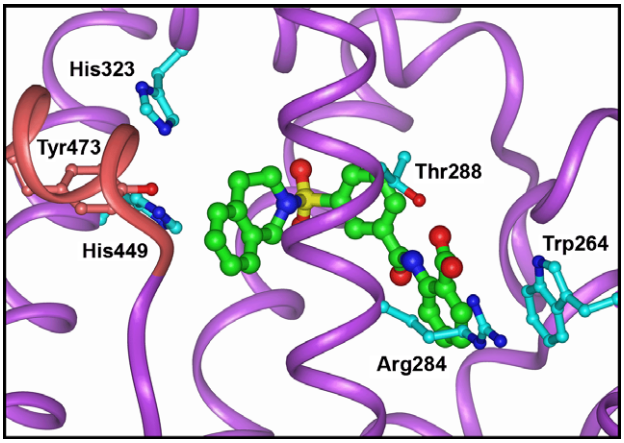
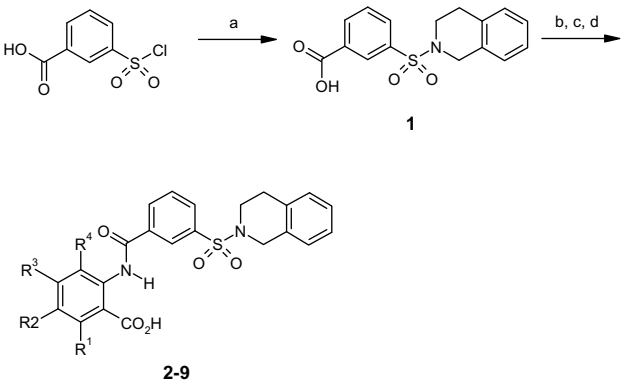


Figure 2. Crystal structure of GW9371 bound to the ligand binding domain of PPARδ, PDB code 3DY6. Carbon atoms in the ligand, PPARδ, and the PPARδ AF2 are shown in green, light blue, and pink, respectively. Nitrogen, oxygen, and sulfur are shown in dark blue, red, and yellow, respectively. The PPARδ backbone is depicted with a tube, colored pink for the AF2 helix.



Scheme 1. Reagents and conditions: (a) 1,2,3,4-tetrahydroisoquinoline, Et_3N, acetone; (b) thionyl chloride, reflux; (c) substituted methyl anthranilate, DIEA, $CHCl_3$, 45 °C; (d) NaOH, THF/H_2O, 50 °C.

The ability of these compounds to bind to each of the PPAR subtypes was measured in vitro in a ligand displacement assay.[11] Functional PPARδ activity was assessed in a standard cell-based Gal4 chimera reporter assay.[12] These results are summarized in Table 1. Data for PPARδ agonist **GW501516 (GW1516)** are included for comparison. Substitution of the anthranilic acid ring had significant effects upon potency. Placement of a substituent ortho to either the carboxylic acid (**2**, R^1 = Me) or nitrogen (**9**, R^4 = Me) resulted in inactive compounds. Based upon the PPARδ bound structure of **GW9371**, placement of the methyl group ortho to the acid as in compound **2** creates unfavorable steric interactions with the receptor, most notably with the indole ring of Trp264 and to a lesser extent with a side chain carbon of Arg284. Movement of the receptor to relieve the unfavorable steric interaction between the methyl substituent and Trp264 would weaken any hydrogen bonding interaction between the acid group of compound **2** and the indole NH group thereby reducing binding affinity. In the case of compound **9**, placement of a methyl group ortho to the amide group does not appear to create detrimental steric interactions with any receptor residues. However, significant steric interaction between the methyl substituent and the adjacent amide oxygen could force the amide considerably out of the plane of the anthranilic acid ring. Ultimately, this would disrupt the intramolecular hydrogen bond between the amide NH and adjacent carboxylic

Table 1
Human PPAR binding and functional potency of substituted anthranilic acids[a]

Compound	R^1	R^2	R^3	R^4	hPPAR binding pIC_{50}[a]			hPPARδ reporter	
					α	γ	δ	pEC_{50}	% Max
GW1516	—	—	—	—	5.7	5.2	8.3	8.5	98
GW9371	H	H	H	H	<5	5.1	6.9	5.9	61
2	Me	H	H	H	<5	<5	<5	<5	—
3	H	Me	H	H	5.0	5.3	7.9	6.7	51
4	H	Cl	H	H	5.3	5.4	8.1	6.9	53
5	H	Br	H	H	5.4	5.6	8.1	6.7	48
6	H	F	H	H	5.2	5.2	7.6	6.3	50
7	H	CF_3	H	H	5.8	5.5	8.3	6.8	55
8	H	H	Br	H	5.3	5.4	8.3	6.8	51
9	H	H	H	Me	<5	<5	<5	<5	—

[a] Values had a standard deviation of ⩽10% ($n \geqslant 3$).

acid and twist the phenyl rings away from the shape that fits within the binding pocket.

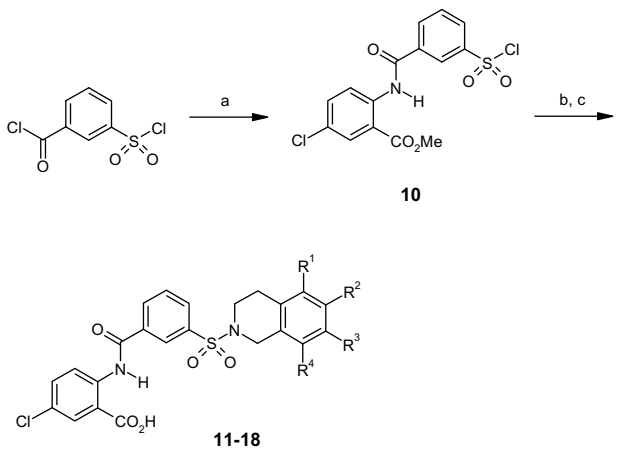
Substitution of the anthranilic acid with small substituents meta or para to the carboxylic acid led to a significant increase in PPARδ binding affinity as predicted by the ligand bound crystal structure of **GW9371**. All of these compounds were at least 10-fold more potent than **GW9371**, with compounds **7** and **8** exhibiting binding affinities equipotent to the full agonist **GW501516** (pIC_{50} = 8.3). All of the compounds in this series are functional partial agonists in the reporter assay with measured efficacies less than 55% versus G**W501516** at saturation. The functional potencies of these compounds are approximately 10-fold weaker than their corresponding binding affinities. This trend is similar to the result observed with **GW9371**. The potency differences observed between the binding and cell-based functional assay may be due to various factors. For example, the cell penetration properties of a compound can influence cell-based assay results. In addition, PPAR activity is known to be influenced by a number of factors other than ligand binding including the presence of coactivator and corepressor proteins, which are absent in the binding assay.[14]

We next investigated the tetrahydroisoquinoline region of the series. Based upon the crystal structure of **GW3971** bound to the PPARδ ligand binding domain, this region of the molecule binds in the vicinity of the AF-2 helix and the incorporation of additional substituents could potentially enhance binding and induce conformational changes that influence functional activity. A limited number of compounds were synthesized according to Scheme 2. Intermediate **10** was prepared in modest yield (58%) by heating 3-(chlorosulfonyl)benzoyl chloride and methyl 5-chloro anthranilate in toluene. Reaction of intermediate **10** with various substituted tetrahydroisoquinolines followed by saponification readily provided the desired final targets.

The binding potency and PPARδ functional activity of these substituted tetrahydroisoquinoline analogues is summarized in Table 2. Substitution of the aromatic tetrahydroisoquinoline ring produced analogues with binding affinities and functional activity profiles similar to the unsubstituted analogue **4**. The placement of a hydroxy or carboxylic acid group at R^1 in an attempt to interact with the AF-2 helix maintained binding affinity, but failed to improve functional potency as evidenced by compounds **12** and **13**. The alkoxyacetic acid analogue **14** extends the carboxylic acid group further from the tetrahydroisoquinoline ring. This modification resulted in little effect on binding potency. However, no functional activity was observed with this analogue. The lack of cell-based activity may be due to poor cell penetration stemming from the physical properties of a diacid compound. Alternatively, this modification may have shifted the analogues efficacy below the sensitivity of the functional assay (~20%).

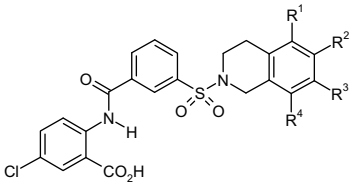
The failure to improve functional activity through structural modifications of the tetrahydroisoquinoline group may be influenced by the conformational flexibility of the tetrahydroisoquinoline ring system. Adding rigidity to this region of the molecule could provide conformations that lead to increased ligand-receptor interactions and enhance functional potency. In an effort to explore this hypothesis, we replaced the tetrahydroisoquinoline ring with substituted indoles to reduce conformational flexibility.

Our indole sulfonamide analogues were prepared according to the synthetic route described in Scheme 3. An appropriately substituted anthranilic ester was converted to sulfonyl chloride intermediate **19** as described for intermediate **10** in Scheme 2. Reaction of sulfonyl chloride **19** with substituted indoles using cesium carbonate in refluxing THF provided the desired sulfonamide intermediates. Alternatively, using BEMP in CH_3CN at room temperature provided milder and more efficient reaction conditions for the synthesis of the sulfonamide intermediates.[15] Finally, saponification with aqueous LiOH in THF at 50 °C provided the final targets **20**–**36**. Yields for the saponification reaction varied and were often low due to cleavage of the sulfonamide. We found that the methyl



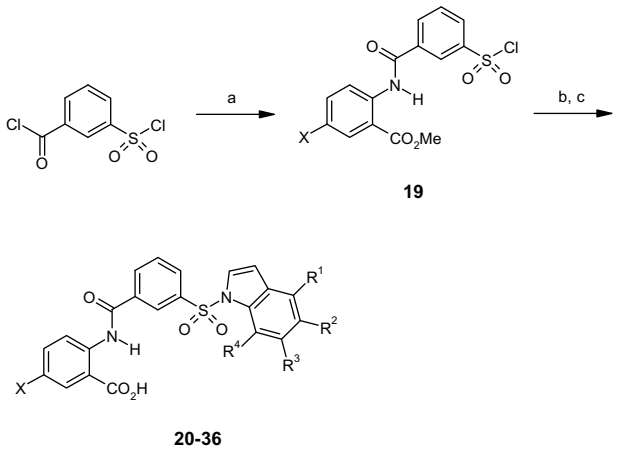
Scheme 2. Reagents and conditions: (a) methyl 5-chloro anthranilate, toluene, 100 °C; (b) substituted 1,2,3,4-tetrahydroisoquinoline, DIEA, $CHCl_3$, rt; (c) NaOH, THF/H_2O.

Table 2
Human PPAR binding and functional potency of substituted tetrahydroisoquinoline analogues[a]



Compound	R^1	R^2	R^3	R^4	hPPAR binding pIC_{50}[a]			hPPARδ reporter	
					α	γ	δ	pEC_{50}	% Max
GW1516	—	—	—	—	5.7	5.2	8.3	8.5	98
4	H	H	H	H	5.3	5.4	8.1	6.9	53
11	OMe	H	H	H	5.1	5.3	7.9	5.9	63
12	OH	H	H	H	<5	5.3	7.7	5.7	45
13	CO_2H	H	H	H	5.4	5.1	8.4	5.9	37
14	OCH_2CO_2H	H	H	H	5.3	5.1	8.0	<5	—
15	H	OMe	H	H	5.0	5.2	8.0	6.1	48
16	H	H	F	H	5.2	5.5	7.8	6.0	50
17	H	H	Cl	H	5.1	5.4	7.6	6.1	42
18	H	H	Cl	Me	5.0	5.3	7.8	6.5	54

[a] Values had a standard deviation of ⩽10% ($n \geqslant 3$).



Scheme 3. Reagents and conditions: (a) substituted 5-chloro anthranilate, toluene, 100 °C; (b) substituted indole, Cs_2CO_3, THF, 80 °C or BEMP, CH_3CN, rt; (c) NaOH, THF/H_2O, 50 °C or LiI, pyridine, 120 °C, microwave, 10 min.

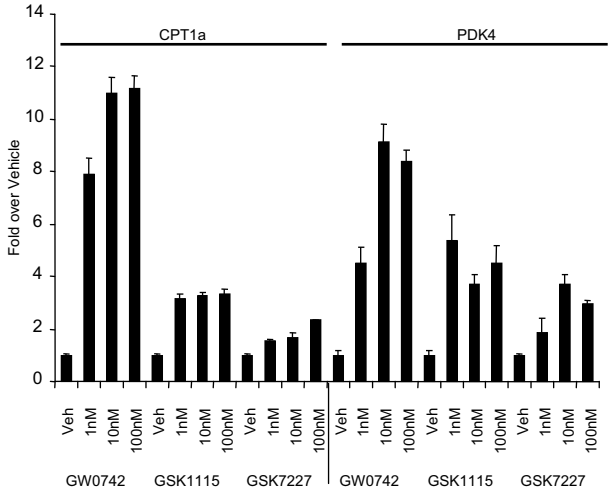
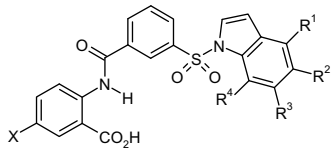


Figure 3. Expression of PPARδ target genes CPT1a and PDK4.

ester compounds could be readily converted to the desired carboxylic acid analogues in excellent yields using LiI in pyridine[16] with heating in a microwave at 120 °C for 10 min.

The ability of the indole sulfonamide analogues to bind and functionally activate hPPARδ in cells is summarized in Table 3. All compounds exhibited potent and selective affinity for PPARδ with the significant majority exhibiting pIC_{50} values $\geqslant$7.3. Unlike the tetrahydroisoquinoline analogues, these compounds generally possess functional potencies in the cell-based assay consistent with their binding affinities. Substitution of the indole ring had small effects on the PPARδ binding affinity but did influence functional potency and efficacy. For example, monosubstitution of the indole ring at the C4 position (R^1) gave analogues with slightly higher efficacies in the cell-based assay as evidenced by compounds **20**–**22** and **33**. Substitution at the C5 position (R^2) is also well tolerated with functional efficacies slightly lower than the C4 substituted analogues. The placement of substituents at either C6 or C7 of the indole ring as exemplified by analogues **26**–**31** did not significantly affect binding potency. However, the placement of substituents at C7 (R^4) produced compounds with appreciably lower functional potencies relative to binding affinity. This may be the result of reduced interactions of the indole ring with the AF-2 helix arising from conformational changes of the ligand induced by unfavorable steric interactions between the R^4 substituents and the sulfonamide group. For the indole series, the C7 substituted analogues possess the greatest potency differential between binding and cell-based receptor activation. The disubstituted analogues **32 (GSK7227)** and **36 (GSK1115)** represent the most potent and selective compounds in this series with pEC_{50} values of 7.9 (% max = 33) and 7.8 (% max = 35), respectively.

Table 3
Human PPAR binding and functional potency of substituted indole sulfonamide analogues[a]



Compound	X	R^1	R^2	R^3	R^4	hPPAR binding pIC_{50}[a]			hPPARδ reporter	
						α	γ	δ	pEC_{50}	% Max
20	Me	Me	H	H	H	6.0	5.7	8.2	7.7	42
21	Me	Br	H	H	H	5.9	5.9	8.0	7.9	45
22	Me	OMe	H	H	H	5.9	5.8	8.0	7.4	44
23	Me	H	Me	H	H	6.0	5.6	8.0	7.5	34
24	Me	H	Cl	H	H	5.7	5.8	7.7	7.3	27
25	Me	H	OMe	H	H	5.1	5.0	6.8	6.3	31
26	Me	H	H	Me	H	5.6	5.6	8.0	7.3	37
27	Me	H	H	Cl	H	5.5	5.7	7.2	6.7	33
28	Me	H	H	OMe	H	5.4	5.1	7.5	7.0	35
29	Me	H	H	H	Me	5.8	6.0	8.4	7.1	47
30	Me	H	H	H	Cl	5.5	6.1	7.8	6.8	45
31	Me	H	H	H	OMe	<5	5.3	7.3	6.2	37
32	Me	Me	OMe	H	H	5.5	5.5	7.7	7.9	33
33	Cl	OMe	H	H	H	6.1	5.7	8.2	6.8	49
34	Cl	H	OMe	H	H	5.5	5.4	7.9	6.8	29
35	Cl	H	H	OMe	H	5.8	5.6	7.9	7.0	32
36	Cl	Me	OMe	H	H	5.5	5.5	7.8	7.8	35

[a] Values had a standard deviation of $\leqslant$10% ($n \geqslant 3$).

GSK7227 and **GSK1115** were studied for their effects on the expression of two important PPARδ-regulated genes in human skeletal muscle cells as previously described.[8] The target gene CPT1a is a key regulator of fatty acid β-oxidation in skeletal muscle cells.[17] PDK4 plays a key role in skeletal muscle metabolism by contributing to the regulation of glucose metabolism.[18] **GW0742** is a full PPARδ agonist that robustly induces the target genes CPT1a and PDK4 (Fig 3). Both anthranilic acid analogues **GSK7227** and **GSK1115** induce these same target genes, but with reduced efficacy compared to the full agonist. All of the compounds were exceptionally potent, yielding maximal activity at the 10 nM dose. Thus, these two new PPARδ ligands act as potent partial agonists on endogenous PPARδ target gene expression consistent with their profiles in the cell-based reporter assay.

In this disclosure, we have described the identification of a novel class of PPARδ ligand. Compounds with potent and selective partial PPARδ transcriptional activity in a cell-based reporter assay have been detailed. Two compounds, **GSK1115** and **GSK7227**, have been shown to affect partial induction of key PPARδ-regulated target genes in skeletal muscle cells and represent useful tool compounds for the further elucidation of PPARδ biology.

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