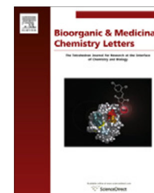
Bioorganic & Medicinal Chemistry Letters 21 (2011) 2345–2350

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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



Phenoxyacetic acids as PPARδ partial agonists: Synthesis, optimization, and in vivo efficacy

Karen A. Evans [a,*], Barry G. Shearer [b], David D. Wisnoski [a], Dongchuan Shi [a], Steven M. Sparks [b], Daniel D. Sternbach [b], Deborah A. Winegar [b], Andrew N. Billin [b], Christy Britt [b], James M. Way [b], Andrea H. Epperly [b], Lisa M. Leesnitzer [c], Raymond V. Merrihew [c], Robert X. Xu [c], Millard H. Lambert [c], Jian Jin [a]

[a] Discovery Medicinal Chemistry, Discovery Research, GlaxoSmithKline Pharmaceuticals, 1250 South Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989, United States
[b] Metabolic Diseases Center of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709-3398, United States
[c] Discovery Research, GlaxoSmithKline Pharmaceuticals, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709-3398, United States

ARTICLE INFO

Article history:
Received 29 November 2010
Revised 18 February 2011
Accepted 22 February 2011
Available online 15 March 2011

Keywords:
PPARd
Partial agonist

ABSTRACT

A series of phenoxyacetic acids as subtype selective and potent hPPARδ partial agonists is described. Many analogues were readily accessible via a single solution-phase synthetic route which resulted in the rapid identification of key structure–activity relationships (SAR), and the discovery of two potent exemplars which were further evaluated in vivo. Details of the SAR, optimization, and in vivo efficacy of this series are presented herein.

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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] PPARδ remains the least understood PPAR subtype and currently no marketed PPARδ agonists exist. However, evidence implicating PPARδ as a key regulator of lipid homeostasis and glucose disposal is growing.[2] For example, the full PPARδ agonist GW501516[3] (**1**) has been shown to reduce serum triglycerides and prevent the decrease of HDL-c and apoA-1 levels observed in sedentary human volunteers.[2c] These positive results suggest that PPARδ is a promising target for the novel treatment of metabolic diseases.

While the number of PPARδ selective agonists described in the literature has grown in recent years, additional chemical tool compounds with a range of functional activity profiles are still needed to further elucidate the biologic roles of PPARδ and provide additional insights into potential therapeutic utilities of modulating this receptor.

As part of our effort to identify PPARδ partial agonists,[4] we searched our internal database of PPAR program compounds for potential templates to exploit. The goal of this effort was to identify potent and selective partial PPARδ agonists for testing across a panel of in vivo models. Standard PPAR binding and cell-based reporter assays were used as primary screens to profile compounds. Phenoxyacetic acid **2** (hPPARδ binding $pIC_{50} = 5.9$, hPPARδ $pEC_{50} = 6.8$, 75%max) was identified as a compound with modest potency and submaximal efficacy that could serve as a promising starting point for SAR exploration.[5]

A number of structural modifications of agonist **2** were initially designed and implemented. This ultimately resulted in the preparation of compound **3** (Fig. 1) which was in fact a potent and selective partial agonist of PPARδ (hPPARδ binding $pIC_{50}\ \delta = 7.3$; hPPARδ functional $pEC_{50} = 7.6$, 56%max). Compound **3** also demonstrated promising pharmacokinetic properties in the mouse via oral administration ($DNAUC_{0-24\ h} = 575$ ng h/mL/mg/kg).[6] This compound became our new partial agonist lead compound in order to more fully explore the structure–activity relationships of this new series, as well as to further optimize for potency, oral exposure, and in vivo efficacy.

Systematic structural modifications of this template at five positions of diversity were primarily achieved through a solution-phase synthesis as described in Scheme 1. The appropriate phenol **4** was treated with substituted bromoacetate **5** and potassium carbonate in *N*,*N*-dimethylformamide (DMF) under microwave conditions to afford the phenoxyacetic acid ester **6**. Immediately following treatment of **6** with chlorosulfonic acid,

* Corresponding author. Tel.: +1 610 917 7764; fax: +1 610 917 6151.
E-mail address: karen.a.evans@gsk.com (K.A. Evans).

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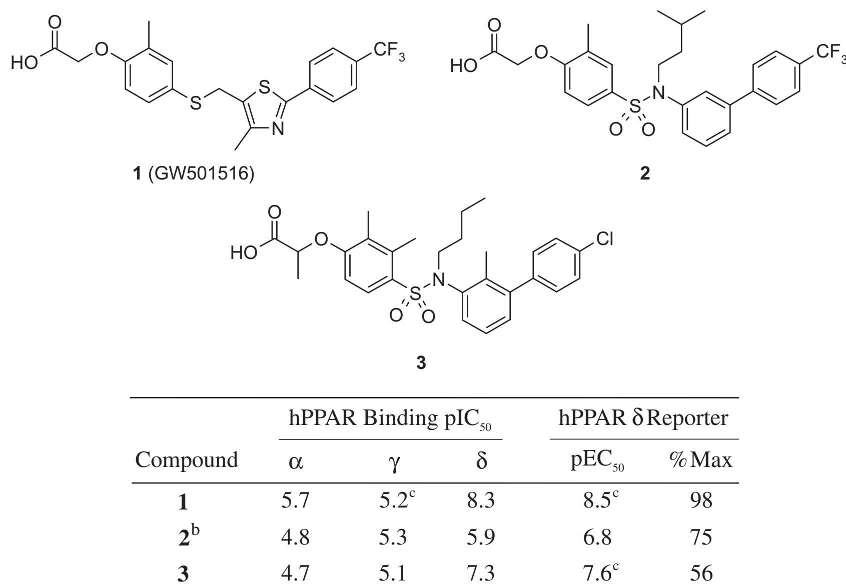
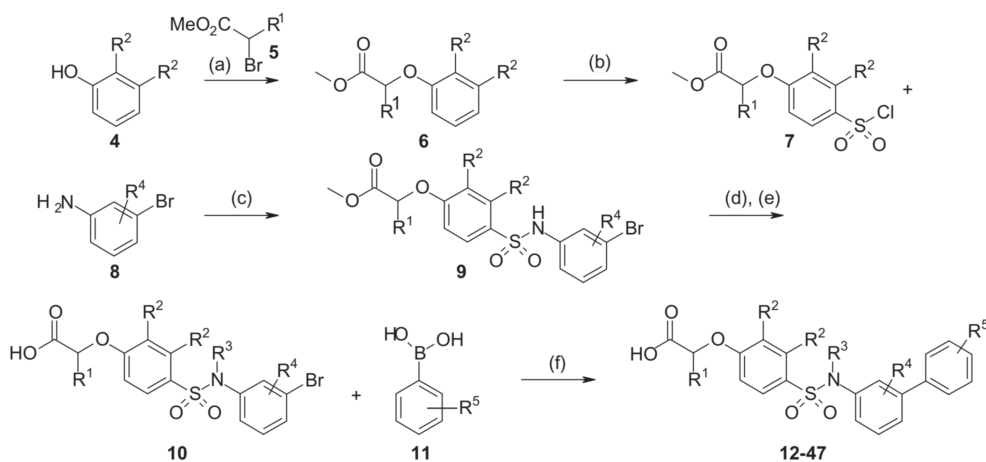
doi:10.1016/j.bmcl.2011.02.077



Compound	hPPAR Binding pIC_{50}			hPPAR δ Reporter	
	α	γ	δ	pEC_{50}	%Max
1	5.7	5.2[c]	8.3	8.5[c]	98
2[b]	4.8	5.3	5.9	6.8	75
3	4.7	5.1	7.3	7.6[c]	56

Figure 1. Structures and assay results for lead phenoxyacetic acids. Values are means of at least two experiments, standard deviation (SD) <0.2 unless otherwise noted. [b]Values are n = 1. [c]SD = 0.3.



Scheme 1. Reagents and conditions: (a) K_2CO_3, DMF, microwave 170 °C, 10 min; (b) chlorosulfonic acid, 0 °C to rt, 4 h; (c) pyridine, 16 h; (d) R^3Br, K_2CO_3, DMF, microwave 170 °C, 7 min; (e) LiOH, THF/H_2O; (f) $Pd(dppf)_2Cl_2$, Cs_2CO_3, THF:H_2O (1:1), microwave 160 °C, 10 min.

the resulting sulfonyl chloride **7** was combined with the appropriate aniline **8** in pyridine to afford sulfonamide **9**. Alkylation of the sulfonamide nitrogen with an alkyl halide in DMF under microwave conditions, followed by hydrolysis of the methyl ester afforded the phenoxyacetic acid intermediate **10** which was then coupled with a variety of boronic acids **11** in parallel to produce the final products **12–47**. This synthetic strategy proved to be a highly efficient and robust method for rapid SAR identification for this series, using one synthetic sequence to explore four points of diversity simultaneously. All final compounds were purified by reversed-phase HPLC to purities of >95% (LC–MS, UV 214 nm detection). PPARδ binding affinity and subtype selectivity were then determined in an in vitro ligand displacement assay[7] and functional PPARδ activity was evaluated in a standard Gal4 chimera cell-based reporter assay.[8] The results are summarized below.

Initially the SAR at the alpha position of the phenoxyacetic acid (R^1) was investigated (Table 1). Ligand bound crystal structures have shown that PPARδ possesses a narrow lipophilic pocket adjacent to the AF-2 helix where the phenoxyacetic acid headgroup binds and participates in a key hydrogen bonding network.[9] Therefore, incorporating alkyl substituents adjacent to the carboxylic acid to disrupt stabilization of the AF-2 helix could lead to partial efficacy. A similar strategy was reported by researchers at Novo Nordisk.[10] We discovered that potency and efficacy could be modulated by changing the substituents at this position. The desmethyl analogue **12** was the most potent, but displayed the highest level of PPARδ agonist activity (85%). Lengthening the R^1 alkyl group resulted in further erosion of binding affinity and functional activity (**13–15**). Chiral separation of compound **3** generated compounds ***(S)*-3a** and ***(R)*-3b**.[11] Data from the cell-based reporter assay demonstrated a distinct difference in functional potency but similar efficacy for these two compounds, with the *R*-enantiomer (**3b**) displaying superior potency.

Efforts to crystallize PPARδ in complex with partial agonists such as **3** were unsuccessful. However, crystals were obtained with more agonistic compounds such as **48** (hPPARδ binding pIC_{50} = 7.5, n = 3, hPPARδ pEC_{50} = 8.1, 90%max).[12]

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