Bioorganic & Medicinal Chemistry 26 (2018) 4382–4389

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis and evaluation of an orally available "Y"-shaped biaryl peroxisome proliferator-activated receptor δ agonist

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ARTICLE INFO

Keywords:
Nuclear receptors
PPARδ
Structure-activity relationship (SAR)
ADMET
PK

ABSTRACT

In this study, we designed and synthesized several novel "Y"-shaped biaryl PPARδ agonists. Structure-activity relationship (SAR) studies demonstrated that compound **3a** was the most active agonist with an EC_{50} of 2.6 nM. We also synthesized and evaluated enantiospecific *R* and *S* isomers of compound **3a** to confirm that *R* isomer (EC_{50} = 0.7 nM) shows much more potent activity than *S* isomer (EC_{50} = 6.1 nM). Molecular docking studies between the PPAR ligand binding domain and enantiospecific *R* and *S* isomers of compound **3a** were performed. *In vitro* absorption, distribution, metabolism, excretion, and toxicity (ADMET) and *in vivo* PK profiles show that compound **3a** possesses superior drug-like properties including good bioavailability. Our overall results clearly demonstrate that this orally administrable PPARδ agonist **3a** is a viable drug candidate for the treatment of various PPARδ-related disorders.

1. Introduction

Peroxisome proliferator-activated receptors (PPARs) have recently received significant attention due to their function as transcription factors that regulate gene expression patterns of biological processes.[1–3] These nuclear receptors comprise three subtypes including PPARα, PPARδ and PPARγ that have tissue-specific expression and functions *in vivo*.[4–10] Among these subtypes, PPARδ has been implicated in various metabolic disorders including diabetes, obesity, atherosclerosis, and cancer.[11] The major functions of PPARδ include reproductive cell expression, regulation of neuronal cell differentiation in the central nervous system (CNS), and anti-inflammatory effects.[12–14] In addition, PPARδ appears to play an important role in adipocyte differentiation and lipid metabolism.[15,16] Recent studies show that PPARδ is also involved in the generation of new mitochondria in muscle and muscle fiber conversion to enhance endurance.[17,18] Thus, diverse strategies for the regulation of lipid metabolism by modulating PPARδ have been considered for the treatment of obesity and various metabolic diseases.

GW501516 and GW610742, discovered and developed by GlaxoSmithKline, are the most well-known PPARδ agonists (Figure 1a).[19,20] They are quite effective and specific PPARδ agonists and may be useful for the treatment of hyperlipidemia and type 2 diabetes.[21,22] However, novel PPARδ agonists are still required. To this extent, a variety of scaffolds for PPARδ agonist have been devised. Recently, we developed a "Y"-shaped GW501516 derivative **1** that shows high potency and selectivity for hPPARδ (Figure 1b).[23] Another "Y"-shaped PPARδ -specific agonist **2** was devised by Evans et al.[24] Based on these works, we developed a new "Y"-shaped PPARδ agonist, compound **3a**, bearing a distinctive biaryl core structure in place of the phenylthiazole (Figure 1c). In this study, we describe the synthesis of

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https://doi.org/10.1016/j.bmc.2018.06.044
Received 10 May 2018; Received in revised form 29 June 2018; Accepted 30 June 2018
Available online 20 July 2018

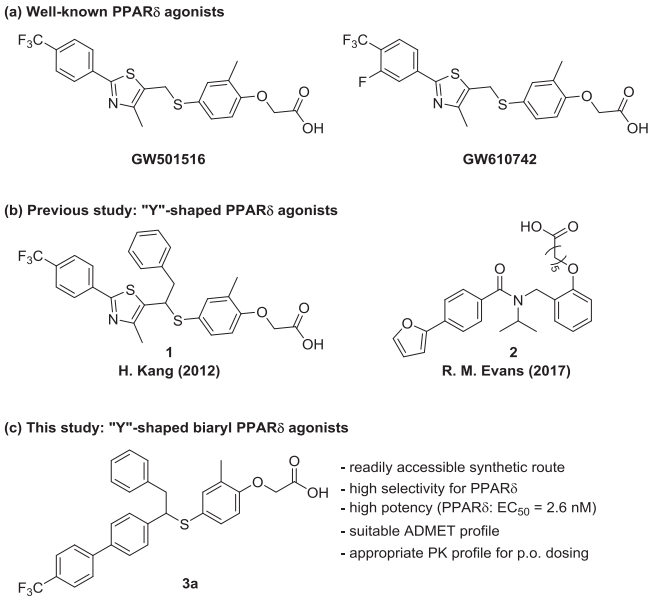


Fig. 1. (a) Well-known PPARδ agonists; (b) previously reported "Y"-shaped PPARδ agonists; (c) devised "Y"-shaped biaryl PPARδ agonists.

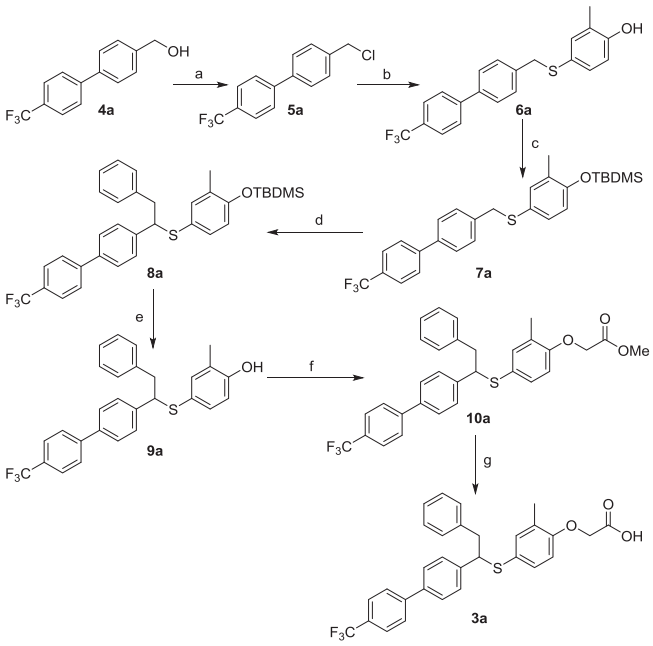
this novel "Y"-shaped biaryl compound that has high potency and selectivity for PPARδ (Figure 1c). Its structure–activity relationship (SAR), *in vitro* ADMET, and *in vivo* PK profiles were also evaluated. Additional molecular docking studies of the best compound in this series, **3a**, were demonstrated to describe the potential binding mode with the target protein.

2. Results and discussion

2.1. Chemistry

The synthesis of compound **3a** is described as the represented scheme for synthesizing the series of "Y"-shaped biaryl PPARδ agonists in this manuscript (Scheme 1).[25] Briefly, the chlorination of **4a** with $SOCl_2$ with a catalytic amount of DMF generates **5a** (93% yield). The S_N2 type reaction of **5a** with 4-mercapto-2-methylphenol affords **6a** which undergoes protection with TBDMSCl to yield **7a**. Benzylation of **7a** was then carried out by treatment with LDA (2 equiv) at −78 °C, followed by slow addition of benzyl bromide into the reaction mixture to provide **8a** (56% yield). Deprotection of **8a** with TBAF gives **9a** which undergoes a S_N2 reaction with methyl 2-bromoacetate to produce **10a**. Finally, hydrolysis of **10a** in the presence of 3 equiv of aqueous 1 M LiOH leads to formation of the target product, **3a** (99% yield).

Based on the above synthetic scheme (Scheme 1), diverse "Y"-shaped biaryl PPARδ agonists **3a-t** were successfully synthesized, and their activities were evaluated (Table 1). SAR analysis, using a transactivation assay, shows that introducing a phenyl group at R^1 and a 4-(trifluoromethyl)-1,1'-biphenyl group at the R^2 position resulted in a potent and selective hPPARδ agonist, **3a** (EC_{50} = 2.6 nM) (Table 1, entry 1). When the R^2 position in compound **3a** was replaced with a 2-(4-(trifluoromethyl)phenyl) pyridyl group, similar activity (compound **3b**, EC_{50} = 3.2 nM) was observed (entry 2). Interestingly, when the R^1 position in compound **3b** was changed to 3,4,5-trifluorophenyl group, it showed less activity (**3c**, EC_{50} = 56.0 nM) than compound **3b** (entry 3). When a 3-(trifluoromethyl)-1,1'-biphenyl group was introduced at the R^2 position, the activities of the corresponding compounds **3d-h** increased in the order phenyl compound **3d** < 3,4,5-trifluorophenyl in **3e** < 2,5-difluorophenyl in **3f** < 2-fluoro-5-(trifluoromethyl)phenyl in **3g** < 2-fluoro-5-chlorophenyl in **3h** (EC_{50} = 18.0, 12.0, 9.1, 5.8, 5.3 nM, respectively) (entries 4–8). A 4-fluoro-1,1'-biphenyl group at the R^2 position with respective substituents such as 3,4,5-trifluorophenyl in **3i**, 2-fluoro-5-(trifluoromethyl)phenyl in **3j**, and 2-fluoro-5-chlorophenyl in **3k** groups at R^1 displayed low activities (EC_{50} = 65.0, 38.0, 25.0 nM) (entries 9–11). However, when the R^1 group was changed to phenyl in **3l** or 2,5-difluorophenyl in **3m** groups, better activities (EC_{50} = 7.0, 4.0 nM) were observed (entries 12–13). As we predicted, compound **3n** functionalized with 3,4,5-trifluorophenyl group at R^1 and biphenyl group at R^2 position showed low activity with an EC_{50} of 86.0 nM (entry 14). Subsequently, changing the R^1 group in **3n** to 2-fluoro-5-chlorophenyl in **3o** or 2-fluoro-5-(trifluoromethyl) phenyl in **3p** lowered the EC_{50} to 26.0 and 10.0 nM, respectively (entries 15–16). Interestingly, replacing the 3,4,5-trifluoro-1,1'-biphenyl group at the R^2 position with various R^1 substituents such as phenyl in **3q**, 2-fluoro-5-chlorophenyl in **3r**, 2,5-difluorophenyl in **3s**, and 2,5-dichlorophenyl in **3t** groups resulted in excellent PPARδ activities overall (EC_{50} = 4.5, 6.9, 6.3, and 9.5 nM, respectively) (entries 17–20). This SAR analysis shows that several of the "Y"-shaped biaryl compounds that we synthesized are excellent PPARδ agonists with compound **3a** being the best among them.



Scheme 1. Synthetic route for "Y"-shaped biaryl PPARδ agonist **3a**. Reagents and conditions: (a) $SOCl_2$, DMF, DCM, rt, 12 h, 93%; (b) 4-mercapto-2-methylphenol, Cs_2CO_3, ACN, rt, 12 h, 72%; (c) TBDMSCl, imidazole, DMF, rt, 12 h, 72%; (d) benzyl bromide, lithium diisopropylamide, THF, −78 °C to rt, 4 h, 56%; (e) TBAF, THF, rt, 1 h, 98%; (f) methyl 2-bromoacetate, Cs_2CO_3, ACN, rt, 12 h, 92%; (g) 1 M LiOH, THF/H_2O, rt, 15 min, 99%

Next, enantiospecific synthesis of compound **3a** was attempted (Scheme 2). Initially, (*R*)- and (*S*)-**9a** were isolated from a racemic mixture of compound **9a** using chiral HPLC (Chiralpak AD-H, Hex:IPA = 90:10). The enantiospecific structures were confirmed by X-ray crystallography of camphanoyl group incorporated (*R*)-**9a** generated by reaction of (*R*)-**9a** with (1*S*)-(-)-camphanic chloride (see SI). Further S_N2 reactions of (*R*)- and (*S*)-**9a** with methyl 2-bromoacetate, followed by hydrolysis were carried out to provide (*R*)- and (*S*)-**3a**, respectively. hPPARδ transactivation assays comparing (*R*)- and (*S*)-**3a** demonstrate that (*R*)-**3a** has a superior EC_{50} of 0.7 nM, whereas that of (*S*)-**3a** was only 6.1 nM. These results demonstrate that the *R*-isomer (*R*)-**3a** shows much better activity than the *S*-isomer (*S*)-**3a** as a PPARδ agonist.