Enantioselective Synthesis of a Novel Thiazoline Core as a Potent Peroxisome Proliferator-Activated Receptor δ Agonist

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*Supporting Information

ABSTRACT: The convergent and enantioselective synthesis of a highly potent human peroxisome proliferator-activated receptor delta agonist is presented. More specifically, the thiazoline structure, which constitutes the biosynthetically distinctive core structure of pulicatin (a secondary metabolite of symbiotic bacteria), was synthesized from a commercially available and inexpensive chiral pool of l-threonine.

1. INTRODUCTION

Pulicatin A is a secondary metabolite that was recently isolated from the cone snail-associated symbiotic bacteria, Streptomyces sp. CP32, and possesses a relatively simple but unique stereogenic 5-methyl-arylthiazoline core (see Figure 1).1 Two similar core structures, namely the arylhydrothiazole and the arylthiazole cores, are also present within the pulicatin series and are of particular importance in the discovery of novel bioactive scaffolds, as the symbiotic Streptomyces sp. CP32 isolated from Conus pulicarius biosynthesizes small-molecule allelochemicals as a defensive mechanism in marine bioenviron-
ments.2–4

In addition, a further class of arylthiazole derivatives, namely the anithiactins (Figure 1), was identified from a different marine source, and the total syntheses of anithiactins A–C were investigated as part of the ongoing research into the discovery of novel secondary metabolites from the marine-derived Streptomyces sp.5,6

In the context of drug targets, the nuclear receptor peroxisome proliferator-activated receptor delta (PPARδ) has recently received attention as a re-emerging target for the treatment of diseases, such as metabolic syndromes,7–12 as its activation alters glucose and lipid metabolism through transcriptional regulation and results in beneficial pharmacological effects.13,14 For example, Endurobol (GW501516, 1, Figure 1) is a well-known effective and potent PPARδ agonist, which is currently in late-phase clinical trials.15–18 Because of its highly selective and potent activity compared to other PPARδ agonists, the development of novel synthetic routes toward target 1 and its analogs has received growing attention to allow its use in both structural and biological studies.19–23 Indeed, our group previously reported one of the shortest synthetic routes toward compound 1 and generated a series of different analogs with the aim of discovering novel agonists.20

Figure 1. Structures of pulicatins A, C, D, E, and F, anithiactins A–C, and PPAR δ agonists 1 and 2.

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2. RESULTS AND DISCUSSION

During the course of our studies into the investigation of marine-derived natural products and synthetic agonists toward PPARδ, where we aimed to develop safer and more effective drug leads, we discovered that the bioactive natural products pulicatins C–F and anithiactins A–C (see Figure 1) contain the same phenylthiazole core structure as PPARδ agonist 1.

We also found that pulicatin A contains a biosynthetically distinctive thiazoline structure, which is essentially the enantiospecifically reduced form of the 5′-methylthiazole moiety. Thus, inspired by the fact that these thiazoline and thiazole analogs are produced from the same biological system, we designed a novel scaffold consisting of the stereogenic 4,5-dihydrothiazole core. More specifically, during our investigations into novel anti-obesity drugs, we synthesized 2 based on the structure of 1.

Previously, the synthesis of a series of optically pure 2-aryl-4,5-dihydrothiazole analogs without the 5-methyl substituent was carried out using aryl nitriles and methyl cysteine as the starting materials, and the antibacterial activities of these compounds were examined. However, to date, neither the enantiospecific synthesis of the 2-aryl-5-methyl-4,5-dihydrothiazole core nor the extended scaffold 2 has been explored.

Thus, we herein present the first enantiospecific synthesis of the highly potent PPARδ agonist 2 containing the novel thiazoline scaffold, in addition to the preliminary in vitro pharmacological studies of this compound toward PPAR subtypes.

From a synthetic point of view, the main challenge in the preparation of 2 involves the construction of the two thiazoline stereocenters. We therefore readily available and cheap amino acid.

Thus, one of the two stereocenters in the final product originates from L-threonine, whereas the other is constructed during the formation of the thiazoline ring using either diethylaminosulfur trifluoride (DAST) or methyl N-carbamate (Burgess reagent).

As indicated in Scheme 1, the initial stage of preparation involved acetonide protection of N-(tert-butoxycarbonyl)-L-threonine methyl ester with 2,2-dimethoxypropane (DMP) in the presence of a catalytic amount of boron trifluoride diethyl etherate (BF₃·Et₂O) in CH₂Cl₂ at room temperature to give oxazolidine 3 in 91% yield. The ester group of 3 was then reduced by LiBH₄ in a mixture of tetrahydrofuran (THF)/methanol to afford alcohol 4 in 84% yield. A subsequent Appel reaction of the hydroxy group of 4 with CBr₄ and PPh₃ in CH₂Cl₂ gave brominated product 5 in 41% yield.

The coupling of 5 with 4-mercapto-2-methylphenol was then carried out in the presence of Cs₂CO₃ in acetonitrile at room temperature over 12 h to give 6 in 61% yield. Etherification of the resulting phenol group with ethyl bromoacetate in the presence of Cs₂CO₃ in acetonitrile then afforded 7 in 96% yield. Subsequent deprotection of both acetonide and Boc groups of 7 was achieved in a single step using excess trifluoroacetic acid (TFA) in dimethylformamide (DMF) at 50 °C over 24 h followed by column chromatographic purification, to give alcohol-amine 8 in 64% yield. Subsequently, the introduction of a thioamide group into 8 was carried out using 2-(4-(trifluoromethyl)phenylcarbonothioyl)isoindoline-1,3-dione (11) in the presence of N,N-disopropylethylamine (DIPEA) in CH₂Cl₂ to give the desired thioamide 9 in 43% yield.

To complete the novel synthesis of 2, formation of the thiazoline ring from 9 was performed using DAST in CH₂Cl₂ at −78 °C over 2 h to provide the corresponding thiazoline 10 in 79% yield. Use of Burgess reagent in the place of DAST was also possible in this step to give thiazoline 10 in 64% yield; however, a longer reaction time and a higher temperature were required. Finally, saponification of 10 using 2 M LiOH in a mixture of THF/water provided the desired product 2 as a pale yellow solid in 96% yield. Thus, the first enantiospecific synthesis of the novel scaffold 2 was accomplished over nine steps in an overall yield of 3.6%. Further details regarding the synthetic route and characterization of the final product can be found in the Supporting Information.

We also compared the stereochemistry of some additional products based on that of compound 2 (see Figure 2 below). To synthesize a substance exhibiting the same stereochemical structure, L-threonine methyl ester hydrochloride was treated...
with triethylamine (TEA) and 11 in CH₂Cl₂ at room temperature to give thioamide 12 in 50% yield (Scheme 2). Subsequently, the thiazoline ring was generated using DAST in CH₂Cl₂ to give the cyclized product 13 in 69% yield.

**Scheme 2. Preparation of Pulicatin Derivative 13**

Thus, the absolute configurations of thiazolines 2 and the single isomer of 13 were determined by measuring the specific optical rotations of the two products and carrying out circular dichroism (CD) experiments (Figure 2). The obtained results were compared with the literature value for a similar compound bearing the (4R,5S)-pulicatin A configuration (see Figure 1).¹ The ²H-¹H correlated spectroscopy (COSY), nuclear Overhauser effect spectroscopy (NOESY), and ¹H-¹³C heteronuclear multiple bond correlation (HMBC) nuclear magnetic resonance (NMR) spectra of compound 2 (see the Supporting Information and Figure 3) were also recorded to confirm the stereochemistry of this product.

The biological activities of the two key scaffolds, that is, GW501516 (1) and the synthesized 2, were then examined through screening of their agonist activities toward PPARδ. As shown in the Supporting Information, the novel scaffold 2 displayed highly potent human peroxisome proliferator-activated receptor delta (hPPARδ) activity (EC₅₀ = 6.2 nM) in a cell-based cotransfection assay.

### 3. CONCLUSIONS

We successfully synthesized the novel hPPARδ agonist 2 in a convergent and enantioselective manner using a chiral pool of l-threonine, a naturally occurring amino acid, as the starting material. The developed synthetic protocol for the preparation of the thiazoline structure involved simple and high-yielding chemical transformations. Following preliminary in vitro pharmacological studies, we could also conclude that scaffold 2 displayed highly potent hPPARδ activity. Further investigation into the preparation of synthetic derivatives of 2 and related structure–activity relationship studies are ongoing, and the results will be reported in due course, with the aim of developing a novel hPPARδ agonist for medicinal purposes.

### 4. EXPERIMENTAL SECTION

#### 4.1. General.

All reactions were monitored by thin-layer chromatography (TLC), performed using 0.2 mm silica gel plates (Merck 60 F₂₅₄) and visualized by UV light (254 nm) and stain solutions, such as KMnO₄ and p-anisalddehyde, with heating. Medium pressure liquid chromatography (MPLC) was carried out on a CombiFlash Rf system with RediSep Rf using flash column cartridges packed with silica gel. The purity of the target compounds was determined to be >95% by analytical high-performance liquid chromatography using dual different wavelength UV detector (254 and 280 nm). NMR spectra were recorded on a Bruker spectrometer at 400 MHz for ¹H and 100 MHz for ¹³C. Chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane as an internal standard, and coupling constants were expressed in hertz. Infrared (IR) spectra were obtained using a Shimadzu IRAffinity-1 spectrometer, and mass spectra were measured with a JEOL JMS 700 high-resolution mass spectrometer (HRMS) at the Korean Basic Science Institute (Daegu). Melting points were determined using MP90 Melting Point System with open capillaries, and optical rotations were measured on an AutoPOL I automatic polarimeter. CD spectra were obtained using a Jasco J-810 spectropolarimeter.

#### 4.2. Materials.

Commercially available reagent grade chemicals, such as N-(tert-butoxycarbonyl)-l-threonine methyl ester and l-threonine methyl ester hydrochloride, were used as received without further purification unless noted otherwise.

#### 4.3. Synthetic Procedure: Preparation of 2 (Scheme 1)

**4.3.1. 3-(tert-Butyl) 4-Methyl (4S,5R)-2,2,5-Trimethyloxazolidine-3,4-dicarboxylate (3).** To a solution of N-(tert-butoxycarbonyl)-l-threonine methyl ester (5 g, 21.44 mmol) in CH₂Cl₂ (11 mL) were added DMP (5.3 mL, 42.9 mmol) and boron trifluoride diethyl etherate (0.14 mL, 1.072 mmol), and then the resulting mixture was allowed to stir at room temperature for 3 h. After this time, the reaction mixture was extracted with CH₂Cl₂ (50 mL) and sat. NaHCO₃ (50 mL). The organic layer was then separated, washed with brine (50 mL), and dried over anhydrous MgSO₄. Following filtration and concentration to give crude residue, purification was by MPLC using hexane/ethyl acetate (9:1) as the eluant to give the desired product 3 as a colorless liquid (5.331 g, 91%), which was a mixture of two conformers (major/minor = 65:35); ¹H NMR (400 MHz, CDCl₃): δ 4.19–4.11 (m, 1H), 3.98 and 3.90 (minor: d, J = 7.7 Hz, major: d, J = 7.9 Hz, 1H), 3.76 (s, 3H), 1.64 and 1.56 ppm.

**Figure 2.** Experimental CD spectra of compounds 2 and 13.

**Figure 3.** Key HMBC, COSY, and NOESY correlations for compound 2.
4-methyl (4) added LiBH4 (0.836 g, 38.4 mmol) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. Following complete consumption of the starting material (as determined by TLC), the reaction mixture was quenched using sat. NaHCO3 (10 mL) prior to extracting with ethyl acetate (2×6 mL). The organic layer was dried over MgSO4, filtered, and concentrated to give the crude product. Finally, the obtained residue was purified by MPLC using hexane/ethyl acetate (8:2) as the eluant to give the desired product 4 as a colorless oil (0.731 g, 2.372 mmol) followed by a solution of 3-((2S,3R)-2-Amino-3-hydroxybutyl)thio)-2,2,5-trimethyloxazolidine-3-carboxylate (4) to a solution of 4-mercapto-2-methylphenol (0.366 g, 2.935 mmol) in CH3CN (5 mL). After stirring the reaction mixture at room temperature for 1 h, it was diluted with water (20 mL) and extracted with ethyl acetate (2×30 mL). The organic layers were then combined, washed with brine (50 mL), dried over MgSO4, filtered, and concentrated. The obtained residue was purified by MPLC using hexane/ethyl acetate (6:1) as the eluant to give the desired product 7 as a colorless oil (1.84 g, 96%), which was a mixture of two conformers (major/minor = 52:48). 1H NMR (400 MHz, CDCl3): δ 7.24−7.20 (m, 2H), 6.62 (d, J = 8.0 Hz, 1H), 4.60 (s, 2H), 4.28−4.19 (m, 1H), 3.69 and 3.57 (major: minor; major: s, 1H), 3.39 and 3.22 (minor: major: d, J = 12.7 Hz, 1H), 3.08 and 2.88 (minor: major: d, J = 10.7, 9.5 Hz, major: d, J = 10.9, 10.6 Hz, 1H), 2.25 (s, 3H), 1.60 and 1.56 (major: minor; major: s, 3H), 1.51 (s, 1H), 1.46−1.28 (major: minor; major: 15H), 1.36, 1.35, 1.34, 1.32, 1.30, 1.29, 1.28, 1.27, 1.26, 1.19, 1H; 13C NMR (100 MHz, CDCl3): δ 168.17, 155.7, 151.4, 151.2, 143.8, 143.6, 134.8, 134.5, 128.3, 128.2, 126.3, 111.6, 79.8, 77.3, 65.3, 62.3, 61.2, 38.0, 28.3, 27.5, 26.9, 21.2, 16.0, 14.0, minor conformer: δ 168.8, 155.0, 152.0, 133.0, 128.5, 128.1, 127.0, 111.8, 93.6, 80.0, 74.6, 65.6, 62.6, 61.2, 35.4, 28.5, 28.3, 27.1, 20.4, 16.0, 14.0; FTIR (neat): δ 2980, 2933, 2762, 1696, 1491, 1387, 1366, 1303, 1258, 1186, 1141, 1088, 734 cm−1; HRMS (EI) calcd for [M+Na]+ C23H35NO6SNa+ 455.2185; found, 453.2187.

4.3. tert-Butyl (4S,5R)-4-((Hydroxymethyl)-2,2,5-trimethyloxazolidine-3-carboxylate (4). To a solution of 3-((2S,3R)-2-Amino-3-hydroxybutyl)thio)-2,2,5-trimethyloxazolidine-3-carboxylate (5) as a colorless gum (0.1 g, 64%); 1H NMR (400 MHz, CDCl3) major conformer: δ 4.21−4.15 (major: s, minor: d, J = 6.2 Hz, 3H), 3.16 and 3.11 (major: d, J = 8.4 Hz, 1H), 2.94−2.87 (major: d, J = 12.7 Hz, 1H), 2.38−2.35 (major: s, minor: d, J = 8.4 Hz, 1H), 2.12−2.08 (major: s, minor: d, J = 12.7 Hz, 1H), 1.20−1.16 (major: s, minor: d, J = 8.4 Hz, 1H), 0.85−0.81 (major: s, 3H), 0.56−0.51 (major: s, 3H).
132.5 (q, 2H), 3.68 (dd, J = 7.1, 2H). The reaction mixture was allowed to warm to room temperature, and stirring was continued for 4 h. After this time, the solvent was evaporated from the reaction mixture, and the crude residue was purified by MPLC using hexane/ethyl acetate (4:1) as the eluant to give the desired product 9 as a yellow oil (0.070 g, 43%); 1H NMR (400 MHz, CDCl3): δ 8.01 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 1.7 Hz, 1H), 7.24 (dd, J = 8.4, 2.2 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 4.78–4.73 (m, 4H), 4.56 (s, 2H), 4.47–4.39 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.36–3.24 (m, 2H), 2.55 (s, 1H), 2.22 (s, 3H), 2.19 (t, J = 7.1 Hz, 1H), 1.25 (d, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 197.7, 168.7, 155.6, 144.6, 133.8, 132.5 (q, JCF = 32.6 Hz), 129.7, 128.6, 126.9, 125.7, 125.3 (q, JCF = 38.5 Hz), 123.6 (q, JCF = 270.7 Hz), 111.7, 67.2, 65.4, 61.3, 59.6, 35.7, 20.9, 16.0, 14.0; FTIR (neat): 3443, 3366, 2977, 2930, 1740, 1492, 1413, 1325, 1189, 1311, 1068, 1015, 911, 849, 733 cm⁻¹; HRMS (EI): calcd for [M⁺] C23H24F3NO3S2 455.0837; found, 455.0836.

4.3.10. 2-(4-(Trifluoromethyl)phenylcarboxanilidyl)-isoindoline-1,3-dione (11). To a stirred solution of 4-(trifluoromethyl)benzothioamide (3.0 g, 14.6 mmol) in THF (30 mL) at 0–5 °C were added K₂CO₃ (3.1 g, 21.9 mmol) and phthaloyl dichloride (2.53 mL, 17.5 mmol, dropwise). The resulting reaction mixture was stirred at 0–5 °C for 3 h, then diluted with water (20 mL) and ethyl acetate (30 mL). The organic layer was separated, washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated. The resulting crude compound was purified by MPLC using hexane/ethyl acetate (8:2) as the eluant to give the desired product 11 as a purple solid (3.8 g, 78%); mp 125–126 °C; 1H NMR (400 MHz, CDCl₃): δ 8.01 (dd, J = 5.5, 3.0 Hz, 2H), 7.90–7.85 (m, 4H), 7.64 (d, J = 8.2 Hz, 2H); 13C NMR (100 MHz, CDCl₃): δ 200.1, 164.6, 145.0, 135.5, 134.0 (q, JCF = 32.5 Hz), 130.9, 128.5, 125.4 (q, JCF = 36.4 Hz), 127.4, 123.5 (q, JCF = 271.1 Hz); FTIR (neat): 2917, 1790, 1228, 1120, 1070, 1017, 871, 847, 789, 717 cm⁻¹; HRMS (EI): calcd for [M⁺] C₂₇H₂₂F₅NO₅S₂ 535.0228; found, 535.0228.

4.3. Synthetic Procedure: Preparation of Pulicatin Derivative 13 (Scheme 2). 4.4.1. Methyl (4-(Trifluoromethyl)phenylcarboxanilidyl)-L-threonine (12). To a stirred solution of L-threonine methyl ester hydrochloride (0.170 g, 1 mmol) in anhydrous CH₂Cl₂ (5 mL) was added TEA (0.31 mL, 2.2 mmol) followed by a solution of 2-(4-(trifluoromethyl)phenylcarboxanilidyl)isoindolene-1,3-dione 11 (0.369 g, 1.1 mmol) in CH₂Cl₂ (5 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature, and stirring was continued at this temperature for 3 h. After this time, the solvent was evaporated from the reaction mixture, and the obtained crude residue was purified by MPLC using hexane/ethyl acetate (3:1) as the eluant to give the desired product 12 as a yellow oil (0.166 g, 50%); 1H NMR (400 MHz, CDCl₃): δ 8.21 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 5.45 (dd, J = 8.6, 2.2 Hz, 1H), 4.61–4.55 (m, 1H), 3.83 (s, 3H), 2.08 (d, J = 4.2 Hz, 1H), 1.35 (d, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl₃): δ 199.3, 170.3, 144.3, 132.8 (q, JCF = 32.4 Hz), 127.2, 125.5 (q, JCF = 3.6 Hz), 123.6 (q, JCF = 271.0 Hz), 68.0, 63.1, 52.9, 20.3; FTIR (neat): 3385, 3317, 2956, 1739, 1734, 1521, 1413, 1325, 1130, 1017, 871, 847, 789, 717 cm⁻¹; HRMS (EI): calcd for [M⁺] C₂₇H₂₂F₅NO₅S₂ 535.0228; found, 535.0228.

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The luciferase activity was normalized with β-galactosidase addition using a Microlumat Plus Luminometer (Berthold). After incubation, cell lysates were obtained using cell lysis DMEM and incubated with freshly delipidated 5% FBS DMEM. The 24 h post-transfected cells were washed with serum-free medium and then transfected with a plasmid mixture containing human PPAR expression vector, β-galactosidase, and TK-PPRE-Luc vector by SuperFect reagent (QIAGEN). The 24 h post-transfected cells were washed with serum-free DMEM and incubated with freshly delipidated 5% FBS DMEM supplemented with either compounds or DMSO vehicle for 24 h. After incubation, cell lysates were obtained using cell lysis buffer, and a luciferase activity was determined upon substrate addition using a Microlumat Plus Luminometer (Berthold). The luciferase activity was normalized with β-galactosidase activity using an ONPG buffer. All of the assays were performed in triplicate.

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