Full Paper

Synthesis, Biological Evaluation and Molecular Modeling of GW 501516 Analogues

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Eleven analogues of GW 501516 (**1**) were prepared and subjected to biological testing in a semi-high throughput human skeletal muscle cell assay. The assay testing indicated that all analogues elicited oxidation of oleic acid. Among the most potent agonists, **2e** (2-{2-ethyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl)methylthio]phenoxy}-2-methylpropanoic acid), was also subjected to a luciferase-based transfection assay, which showed that this compound is a potent agonist against PPARδ and a moderate agonist against PPARα. Docking of compound **2e** into PPARδ revealed that it occupied the agonist binding site and exhibited key hydrogen bonding interactions with His323, His449, and Tyr473.

Keywords: GW 501516 / Agonists / Multi well assay / Molecular modeling / PPARα / PPARδ

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Introduction

Peroxisome proliferator-activated receptors are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily [1]. So far, three isotypes have been identified and characterized: PPARα, PPARδ, and PPARγ. PPARs are involved in expression of genes responsible of the lipid and carbohydrate metabolism by interacting with specific DNA peroxisome proliferator response elements (PPRE) [2]. Agonists acting on the PPARα have been shown to have beneficial effects on lipid metabolism by decreasing both serum triglycerides and free fatty acid metabolism levels, but also increasing high-density lipoprotein level (HDL) [3]. PPARγ agonists have the ability to improve glucose tolerance in type 2 diabetic patients [4]. Dyslipidemia and insulin resistance, two major components of the metabolic syndrome and diabetes, are usually treated with either the fibrate or the thiazolidinedione (TZD) classes of drugs that target PPARα and PPARγ, respectively [4–6]. Several studies have suggested that PPARδ plays an important role in regulating lipid metabolism and energy homeostasis in muscle and adipose tissues [7–11]. Furthermore, the activation of PPARδ increases HDL levels, attenuates weight gain, and improves insulin sensitivity [7, 9]. As of today, no drugs that target the PPARδ receptor have been approved, and only a few selective and potent ligands that target this receptor have been identified [12–15]. In 2003, scientists from GlaxoSmithKline reported the compound GW 501516 (**1**) (Fig. 1) to be both highly potent and selective against the PPARδ receptor [15]. When obese Rhesus monkeys were treated with this agonist, an increase in the plasma HDL level, as well as a decrease in the plasma triglyceride level, was observed [16]. Based on these observations, compound **1** is an interesting lead compound for the development of remedies against type-II diabetes and metabolic syndrome. Moreover, recently dual agonists have received attention as potential remedies against several diseases such as metabolic disorders, type-2 diabetes and cardiovascular diseases [17, 18]. Among such possible dual agonists it may be an advantage to activate simultaneously both PPARα and PPARδ by a single dual compound to effectively reduce the risk of cardiovascular disease [17, 18]. So far only a few dual agonists of this type have been reported [19–22]. Herein we report the synthesis, biological evaluation, and molecular modeling studies of analogues of GW 501516 (**1**) in which structural modifications at the *alpha*-carbon atom next to the carboxylic acid moiety and at the *ortho*-position of the benzene ring **A**

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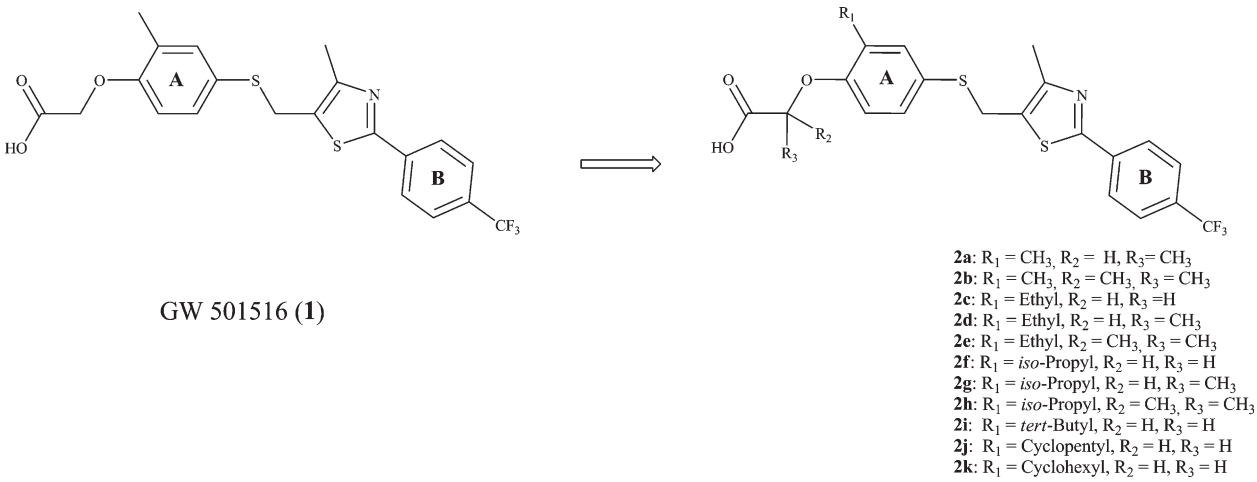


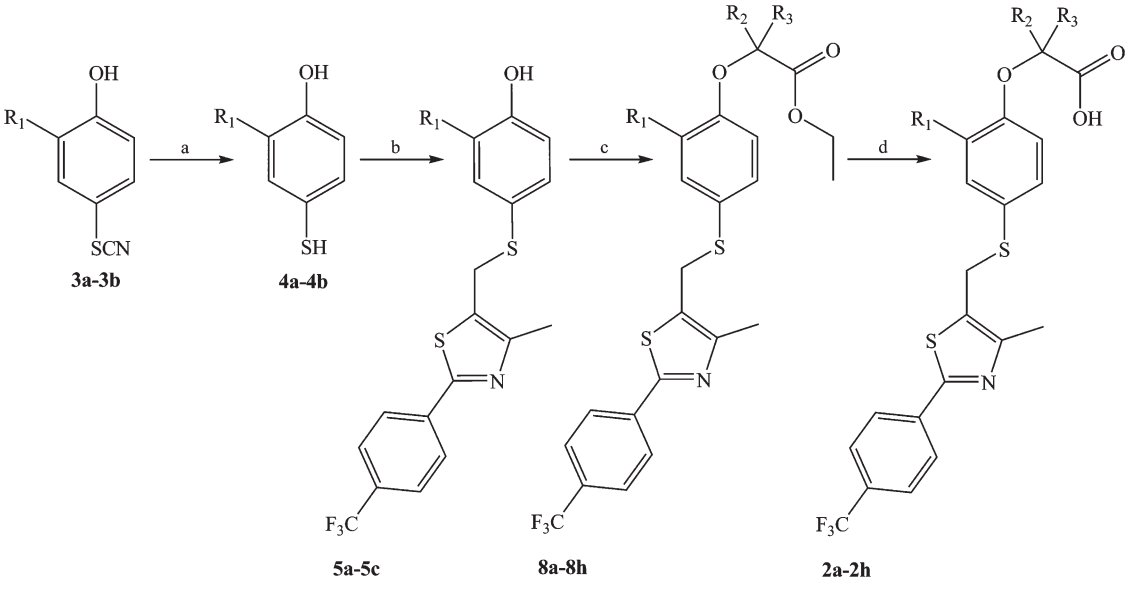
Figure 1. Structure of GW 501516 (**1**) and derivatives **2a–2k**.

have been made (Fig. 1). These efforts led to the identification of a moderate agonist against PPARα while retaining potent agonist effects against PPARδ. Additionally, six other analogues displayed dual agonist effects at 10 μM against both PPARα and PPARδ.

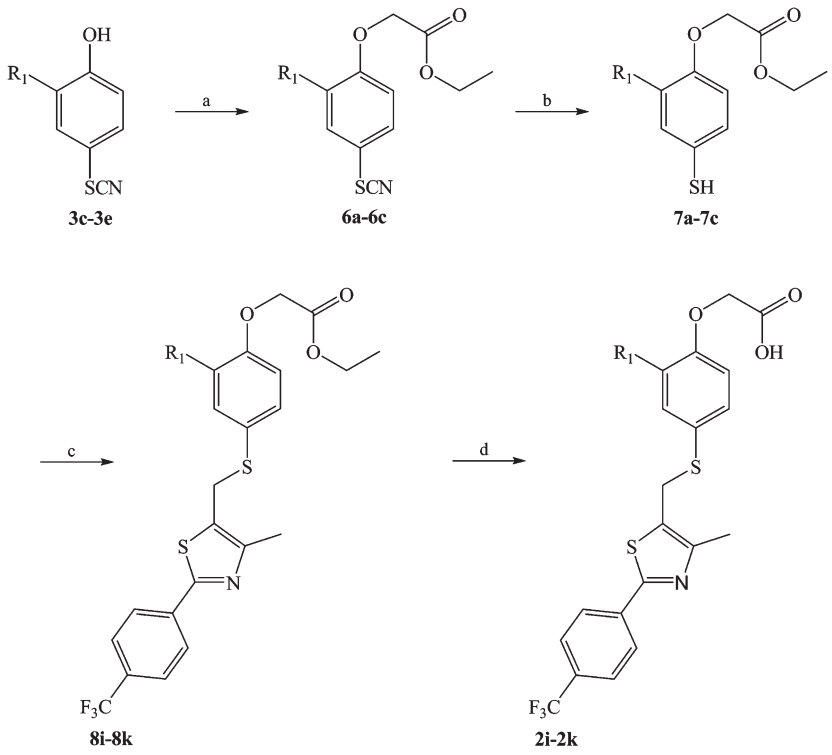
Chemistry

Compounds **3a–3e** were synthesized according to a literature procedure [23]. Thiocyanates **3a** and **3b** were reduced with $LiAlH_4$ to mercaptophenols **4a** and **4b** in 71–88% yield. Reaction between commercially available 4-mercapto-2-methylphenol, **4a** and **4b**, respectively, with commercially available 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl) thiazole in the presence of Cs_2CO_3 at ambient temperature afforded **5a–5c** in 69–84% yield. Sulfur-substituted *para*-mercaptophenols **5a–5c** were then reacted with the corresponding ethyl 2-bromoesters in the presence of Cs_2CO_3 to yield esters **8a–8h** which after basic aqueous hydrolysis afforded acids **2a–2h** in 51–80% yield (Scheme 1).

Treatment of thiocyanates **3c–3e** with $LiAlH_4$ afforded large quantities of the corresponding disulfide dimers.



Scheme 1. Reagents and conditions: (a) $LiAlH_4$, THF; (b) 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole, Cs_2CO_3, CH_3CN; (c) i) ethyl 2-bromoacetate, Cs_2CO_3, CH_3CN or ii) ethyl 2-bromopropionate, Cs_2CO_3, CH_3CN; (d) LiOH, THF, H_2O, 0°C (**8a**, **8c**, **8d**, **8f**, **8g**); $(CH_3)_3COK$, THF, H_2O, reflux (**8b**, **8e**, **8h**).



Scheme 2. Reagents and conditions: (a) ethyl 2-bromoacetate, Cs_2CO_3, CH_3CN; (b) $NaBH_4$, 1,4-dithioerythritol, EtOH; (c) 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole, Cs_2CO_3, CH_3CN; (d) LiOH, THF, H_2O, 0°C.

Hence, compounds **3c–3e** were first reacted with ethyl 2-bromoacetate and then reduced with $NaBH_4$ and 1,4-dithioerythritol to afford **7a–7c** in 61–77% yield [24]. Oxygen-substituted *para*-mercaptophenols **7a–7c** were reacted with 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole to produce the esters **8i–8k** which after basic aqueous hydrolysis afforded acids **2i–2k** in 49–69% yield over the two steps (Scheme 2).

Biological evaluation

GW 501516 (**1**) and compounds **2a–2k** at five different concentrations were exposed for 96 h to fully differentiated human skeletal muscle cells cultured in 96-well plates. After this period of time, the level of oxidation of oleic acid was measured by detection of accumulated ^{14}C-labeled oxidized oleic acid [25]. The EC_{50}-values for compounds **2a–2k** are presented in Table 1. Compounds **2a–2k** were also tested against all three peroxisome proliferator-activated receptors (PPARα, PPARδ, and PPARγ) in a luciferase-based transient transfection assay (Figs. 2–4).

Results and discussion

The results from the oxidation of the oleic acid assay are compiled in Table 1. The lead compound GW 501516 (**1**) was highly potent with EC = 0.10 nM in the human skeletal muscle cell assay (Table 1). Substituting one hydrogen atom from the *alpha*-carbon atom next to the carboxylic acid moiety of GW 501516 (**1**) with a methyl group led to a decrease in potency (**2a**: EC_{50} = 0.65 nM) compared to **1**. Introduction of two methyl groups afforded agonist **2b** that was slightly more potent than **2a** (**2b**: EC_{50} = 0.24 nM), but exhibited slightly lower potency than the lead compound **1**. When the methyl group from the R_1-position of GW 501516

Table 1. Substitution pattern (see Fig. 1) and EC_{50}-values of tested compounds in the oleic acid oxidation assay.

Compound	R_1	R_2	R_3	EC_{50} (nM)[a]
2a	CH_3	H	CH_3	0.65
2b	CH_3	CH_3	CH_3	0.24
2c	Ethyl	H	H	0.31
2d	Ethyl	H	CH_3	0.36
2e	Ethyl	CH_3	CH_3	0.54
2f	*iso*-Propyl	H	H	4.15
2g	*iso*-Propyl	H	CH_3	5.79
2h	*iso*-Propyl	CH_3	CH_3	9.11
2i	*tert*-Butyl	H	H	5.51
2j	Cyclopentyl	H	H	16.60
2k	Cyclohexyl	H	H	17.30
GW 501516	CH_3	H	H	0.10

[a] Results of three experiments

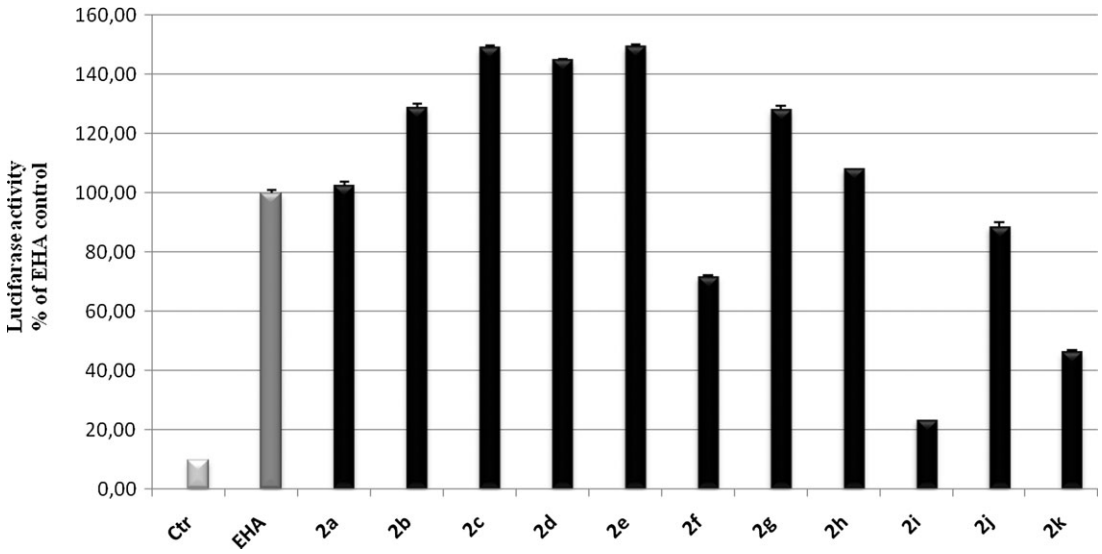


Figure 2. Activation of the ligand-binding domain of PPARα by compounds **2a–2k**. Positive control: EHA ((2*E*,4*E*,8*Z*,11*Z*,14*Z*,17*Z*)-eicosa-2,4,8,11,14,17-hexaenoic acid).

(**1**) was substituted to an ethyl group, a decrease of the potency was noticed (**2c**: EC_{50} = 0.31 nM). Substituting one hydrogen atom in **2c** with a methyl group *alpha*-carbon atom next to the carboxylic acid moiety retained the potency, as observed for **2d** (EC_{50} = 0.36 nM). Increasing the size of the *ortho*-substituent in the benzene ring **A** (R_1), by substitution with an *iso*-propyl, *tert*-butyl, cyclopentyl or cyclohexyl group, led to a reduction in potency (**2f**: EC_{50} = 4.15 nM, **2i**: EC_{50} = 5.51 nM, **2j**: EC_{50} = 16.60 nM, **2k**: EC_{50} = 17.30 nM). These substituents may be too bulky for the ligand-binding domain of PPARδ. Crystallographic studies have shown that a lipophilic pocket in the PPARδ ligand-binding domain can accommodate small substituents at the *ortho*-position of the aromatic ring [15, 26]. Changing the methyl group in **2b** (R_1) to an ethyl group led to agonist **2e** that exhibited an EC_{50}-value of 0.54 nM. Replacing the ethyl group in **2e** with

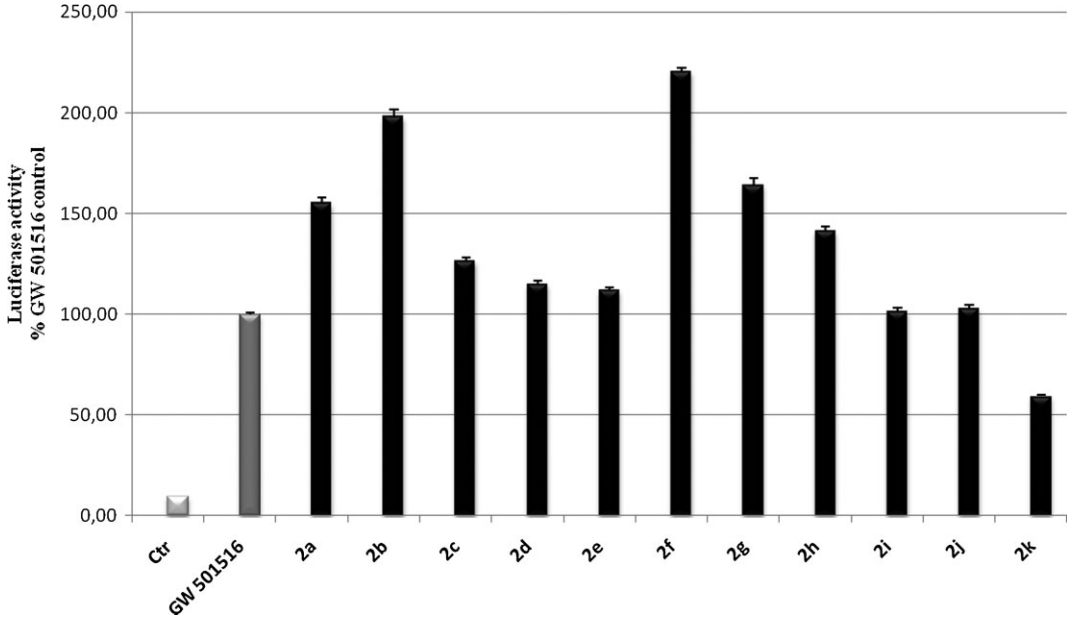


Figure 3. Activation of the ligand-binding domain of PPARδ by compounds **2a–2k**. Positive control: GW 501516 (**1**).

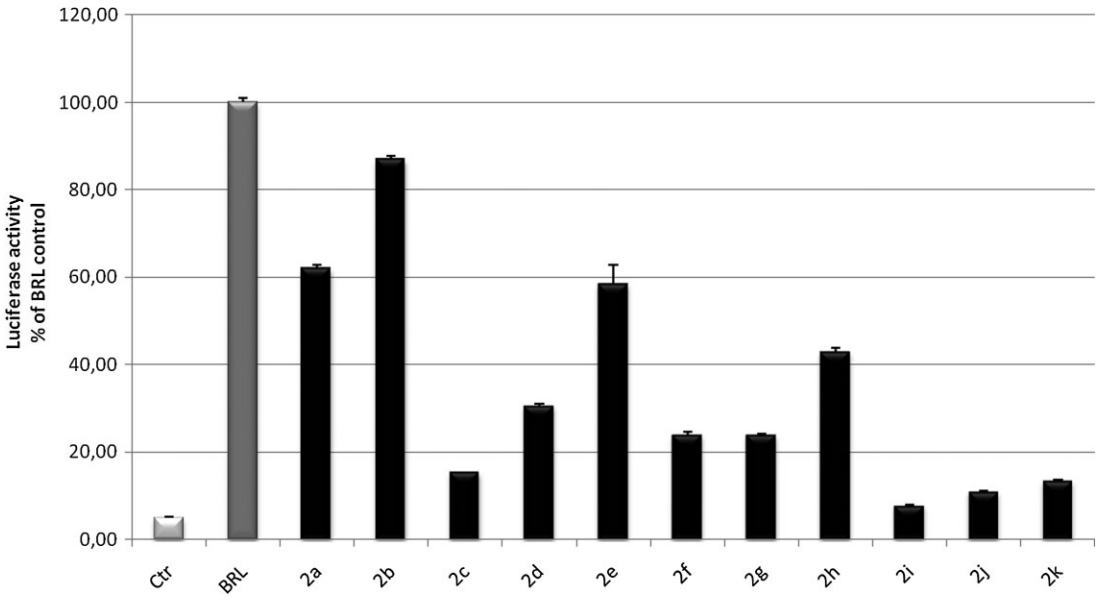


Figure 4. Activation of the ligand-binding domain of PPARγ by compounds **2a–2k**. Positive control: BRL (rosiglitazone).

an *iso*-propyl group afforded agonist **2h** (EC_{50} = 9.11 nM) that was even less potent than **2e**. In the series of compounds **2b**, **2e**, and **2h**, the potency decreased with increasing size of R_1, a trend that was also observed with **2i**, **2j**, and **2k**. Replacement of the hydrogen atoms from the *alpha*-carbon atom to the carboxylic moiety of **2f** with one and two methyl groups diminished the potency compared to **2e**, as noticed for **2g** (EC_{50} = 5.79 nM) and **2h** (EC_{50} = 9.11 nM).

Next, we investigated the effects compounds **2a–2k** exhibited on all of the peroxisome proliferator-activated receptors (PPARα, PPARδ, and PPARγ) in a luciferase-based transient transfection system. Compounds **2a–2e**, **2g**, and **2h** showed a higher activation of both PPARα as well as PPARδ at 10 μM concentrations than the positive controls (Figs. 2 and 3). Compounds **2i** and **2j** activated only the PPARδ receptor with the efficacy comparable to the lead compound **1** at 10 μM (Fig. 3). No notable activation of PPARγ was observed (Fig. 4) at the same concentration of all prepared analogs of **1**. To further investigate the agonist effects of compound **2e**, the EC_{50}-values were determined against all three PPARs using the aforementioned transfection assay. The EC_{50}-value for **2e** against PPARδ was determined to be 5.0 nM, which is slightly lower than the EC_{50}-value of 1.0 nM reported for GW 501516 (**1**) [15]. Interestingly, the EC_{50}-value against the PPARα receptor was determined to be 750 nM, which is a moderate agonist effect. Compound **2e** was found to be inactive against PPARγ (EC_{50} > 5000 nM).

In order to gain information on the binding of **2e** with the ligand-binding domain of the PPARδ receptor, molecular modeling studies were performed. The activation process of PPARs has been extensively studied [27] and X-ray crystallographic structures have been reported for both active and inactive receptor conformations. In the active receptor conformation, the most C-terminal α-helix (helix 12) acts as a lid closing the binding cavity, while in the inactive state the binding site is more accessible from the outside. In the activated receptor conformation of PPARδ, the amino acids His323, His449, and Tyr473 are essential for agonist interactions [28]. In the present study, **2e** was docked into an activated receptor conformation of PPARδ, and the docking showed that **2e** was well accommodated to the activated receptor conformation, with a binding mode very similar to that of the full PPARδ agonist 2-{2,3-dimethyl-4-[2-prop-2-ynyloxy-4-((4-trifluoromethylphenoxy)methyl)phenylthio]phenoxy}acetic acid (PDB entry: 3GZ9) (Fig. 5). The docking of **2e** revealed key interactions with amino acids Arg284, Cys285, His323, His449, and Tyr473 (Fig. 5). As for the full agonist, the acidic group of **2e** interacted with His323, His449, and Tyr473. The trifluoromethyl group had contact with Arg284. The calculated interaction energy of the **2e**—PPARδ complex was −14.9 kcal/mol. The docking mode supports the observation that compound **2e** is a PPARδ agonist.

In the series of tested compounds, the potency decreased with increasing size of the substituent in the R_1-position. In the docked complex of **2e** the ethyl group in R_1 points in the direction of Thr289, Ile326, and Phe327. A larger substituent R_1 will produce severe steric interactions with these residues and this may explain the decrease in potency when the size of the substituent is increased to *iso*-propyl, *tert*-butyl, cyclopentyl or cyclohexyl groups.

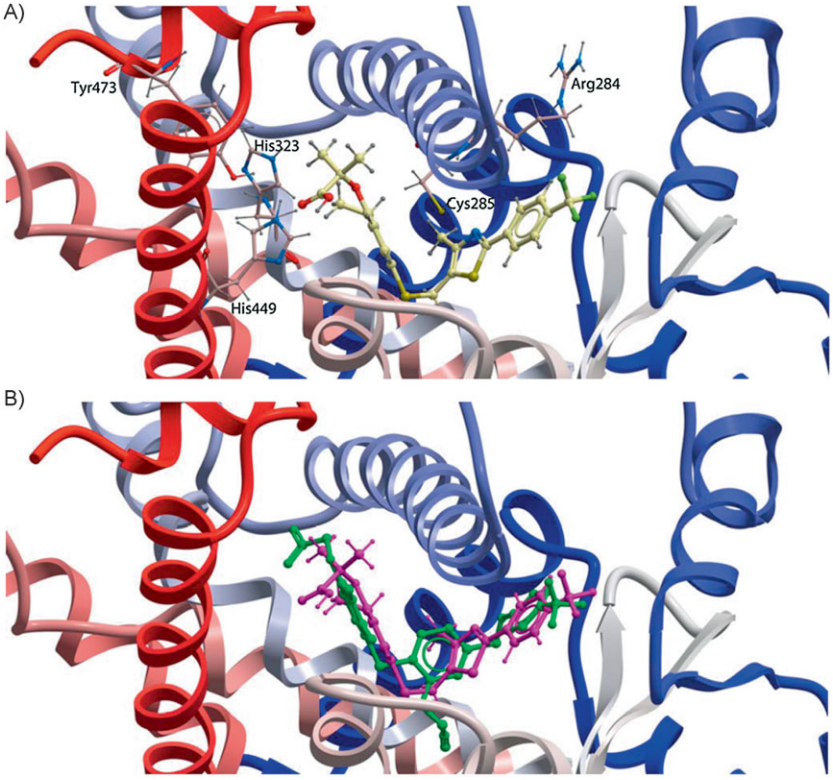


Figure 5. **A**. **2e** docked into PPARδ. Color coding: red O, blue N, grey H, yellow C in **2e**, grey C in PPARδ. Coloring of the Cα traces of PPARδ is blue *via* white to red from N-terminal to C-terminal. **B**. The docked complex of **2e** (purple) superimposed onto the X-ray structure complex of the agonist 2-{2,3-dimethyl-4-[2-prop-2-ynyloxy-4-((4-trifluoromethylphenoxy)methyl)phenylthio]phenoxyacetic acid (green) (PDB entry: 3GZ9).

Conclusions

To the best of our knowledge, very few analogues of GW 501516 (**1**) have been reported in which modifications at the *alpha*-carbon atom next to the carboxylic acid moiety have been made [21, 22, 29–32]. This moiety is a common feature for the chemical structures of most PPARδ agonists reported [12–15]. Herein we report that compounds **2a–2d**, **2g**, and **2h** displayed dual agonist effects at 10 μM against both PPARα and PPARδ. Docking of compound **2e** into the ligand binding domain of PPARδ supported that compound **2e** is a potent PPARδ agonist with EC_{50} = 5 nM. Moderate potency was observed against PPARα for compound **2e** (EC_{50} = 750 nM). Since very few dual PPARα/δ agonists have been reported in the literature [19–22], further studies are underway focusing on the preparation of potent and dual PPARα/δ agonists based on the results reported herein. These efforts will be reported in due course.

Experimental

General methods

All dry solvents were commercially available. NMR spectra were recorded on a Bruker DPX300 spectrometer. Coupling constants (*J*) are reported in hertz, and chemical shifts are reported in parts per million (*δ*) relative to $CDCl_3$ (7.24 ppm for ^{1}H and 77.00 ppm for ^{13}C) or DMSO-d_6 (2.50 ppm for ^{1}H and 39.51 ppm for ^{13}C). Melting points were measured using a Barnstead Electrothermal apparatus. Melting points are uncorrected. Flash column chromatography was performed on silica gel 60 (40–63 μm, Fluka). LC/MS analyses were performed on an Agilent Technologies 1200 Series (Eclipse XDB-C18, 5 μm 4.6 × 150mm), coupled with an Agilent 6310 ion trap. According to LC/MS spectra, all final compounds submitted to the biological testing had a purity >99%.

2-Ethyl-4-thiocyanatophenol ***(3a)***

The title compound was prepared as following: To a stirred solution of 2-ethylphenol (2 mmol, 240 μL), sodium thiocyanate (520 mg, 6.4 mmol) and methanol (40 mL) at 0°C was added a solution of sodium bromide (206 mg, 2 mmol) and bromine (206 μL, 2 mmol) in methanol (60 mL). The mixture was stirred for 3 h under argon at 0°C and then diluted with saturated aqueous solution of $NaHCO_3$. The mixture was extracted (CH_2Cl_2, 3 × 100 mL), the organic phases were combined, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography using hexane/ethyl acetate (3:1) as eluent to give **3a** as a white solid in 70% yield (252 mg, 1.4 mmol). Mp = 61–62°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, J = 2.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.5 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.71 (br s, 1H), 2.64 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.11, 133.40, 133.06, 131.36, 116.79, 112.84, 111.94, 22.75, 13.35.

2-Iso-propyl-4-thiocyanatophenol ***(3b)***

The title compound was prepared in 81% yield (785 mg, 4.07 mmol) as orange oil from 2-*iso*-propylphenol (5 mmol, 685 μL) following the general procedure. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.4, 24 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 5.72 (br s, 1H), 3.19 (hept, J = 6.8 Hz, 1H), 1.21 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.18, 137.34, 131.17, 131.01, 117.07, 113.27, 112.37, 27.17, 22.19.

2-Tert-butyl-4-thiocyanatophenol ***(3c)***

The title compound was prepared in 68% yield (280 mg, 1.35 mmol) as a light yellow solid from 2-*tert*-butylphenol (301 mg, 2 mmol) following the general procedure. Mp = 77–78°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, J = 2.4 Hz, 1H), 7.26 (dd, J = 8.3, 2.4 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.00 (br s, 1H), 1.38 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.89, 138.86, 131.74, 131.55, 118.25, 112.69, 112.40, 34.90, 29.10.

2-Cyclopentyl-4-thiocyanatophenol ***(3d)***

The title compound was prepared in 83% yield (230 mg, 1.05 mmol) as a yellow oil from 2-cyclopentylphenol (353 mg, 2 mmol) following the general procedure. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, J = 2.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.44 (br s, 1H), 3.32–3.18 (m, 1H), 2.19–1.96 (m, 2H), 1.92–1.46 (m, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 156.11, 135.13, 131.50, 131.13, 116.93, 112.76, 112.24, 38.99, 32.51, 25.11.

2-Cyclohexyl-4-thiocyanatophenol ***(3e)***

The title compound was prepared in 61% yield (284 mg, 1.22 mmol) as a yellow oil from 2-cyclohexylphenol (358 mg, 2 mmol) following the general procedure. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 8.4, 2.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.40 (br s, 1H), 3.05–2.87 (m, 1H), 2.10–1.74 (m, 5H), 1.68–1.08 (m, 5H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.41, 136.66, 131.48, 131.06, 117.05, 112.73, 112.59, 37.04, 32.69, 26.68, 26.03.

2-Ethyl-4-mercaptophenol ***(4a)***

The title compound was prepared as following: A solution of 2-ethyl-4-thiocyanatophenol (**3a**) (963 mg, 5.38 mmol) in anhydrous THF (100 mL) was added cautiously to a mixture of $LiAlH_4$ (215 mg, 5.5 mmol) and anhydrous THF (50 mL) at 0°C. The reaction mixture was stirred at ambient temperature for 4 h under argon. Adding moist THF, water, and 1.0 M HCl destroyed the unreacted $LiAlH_4$. The mixture was extracted (ethyl acetate, 3 × 100 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as eluent to give **4a** as a light colorless oil in 71% yield (585 mg, 3.8 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.28 (d, J = 2.1 Hz, 1H), 7.22 (dd, J = 8.2, 2.3 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 4.86 (s, 1H), 2.61 (q, J = 7.5 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.78, 132.46, 130.79, 130.24, 128.62, 115.77, 22.77, 13.64.

2-Iso-propyl-4-mercaptophenol ***(4b)***

Title compound was prepared in 88% yield (578 mg, 3.44 mmol) as a light yellow oil from **3b** (753 mg, 3.9 mmol) following the general procedure. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, J = 2.3 Hz, 1H), 7.03 (dd, J = 8.2, 2.1 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.86 (br s, 1H), 3.36 (s, 1H), 3.15 (hept, J = 6.9 Hz, 1H), 1.22 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 151.60, 135.55, 129.62, 129.58, 119.83, 116.07, 26.97, 22.38.

2-Methyl-4-{[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl]methylthio}phenol ***(5a)***

The title compound was prepared as following: To a solution of 4-mercapto-2-methyl-phenol (280 mg, 2 mmol) in dry CH_3CN (40 mL) was added Cs_2CO_3 (706 mg, 2 mmol). To this mixture was added dropwise a solution of 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole (518 mg, 1.78 mmol) in dry CH_3CN (10 mL). The mixture was stirred for 4 h at ambient temperature under argon, then diluted with water and extracted (ethyl acetate, 3 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (3:1) to give **5a** as a light yellow solid in 96% yield (676 mg, 1.71 mmol). Mp = 126–127°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 1.6 Hz, 1H), 6.91 (dd, J = 8.2, 2.1 Hz, 1H), 6.54 (d, J = 8.2 Hz, 1H), 4.03 (s, 2H), 2.17 (s, 3H), 2.03 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.78, 155.25, 151.11, 137.10, 136.22 (distorted q, J = 1.2 Hz), 133.21, 131.49 (q, J = 32.7 Hz), 131.48, 126.45, 125.96 (q, J = 3.8 Hz), 125.54, 123.81 (q, J = 272.3 Hz), 123.16, 115.13, 32.79, 15.76, 14.21.

2-Ethyl-4-{[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl]methylthio}phenol ***(5b)***

The title compound was prepared in 66% yield (290 mg, 0.71 mmol) as a yellow solid from **4a** (185 mg, 1.2 mmol) and 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole (311 mg, 1.07 mmol) following the general procedure. Mp = 132–133°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 8.2, 2.3 Hz, 1H), 6.54 (d, J = 8.2 Hz, 1H), 4.03 (s, 2H), 2.57 (q, J = 7.5 Hz, 2H), 2.01 (s, 3H), 1.15 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.75, 154.82, 151.16, 136.24 (distorted q, J = 0.9 Hz), 135.72, 133.28, 131.61, 131.48 (q, J = 32.7 Hz), 131.46, 126.44, 125.95 (q, J = 3.8 Hz), 123.81 (q, J = 272.2 Hz), 123.24, 115.38, 32.86, 22.91, 14.16, 13.85.

2-Iso-propyl-4-{[4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl]methylthio}phenol ***(5c)***

The title compound was prepared in 80% yield (576 mg, 1.36 mmol) as a light yellow solid from **4b** (321 mg, 1.9 mmol) and 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole (495 mg, 1.7 mmol) following the general procedure. Mp = 135–136°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 2.1 Hz, 1H), 6.93 (dd, J = 8.2, 2.2 Hz, 1H), 6.53 (d, J = 8.2 Hz, 1H), 4.03 (s, 2H), 3.17 (hept, J = 6.9 Hz, 1H), 1.98 (s, 3H), 1.15 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.75, 154.28, 151.24, 136.28 (distorted q, J = 1.2 Hz), 136.04, 133.28, 133.16, 131.48 (q, J = 32.7 Hz), 131.45, 126.44, 125.95 (q, J = 3.8 Hz), 123.83 (q, J = 272.3 Hz), 123.23, 115.55, 32.91, 26.90, 22.35, 14.10.

Ethyl 2-(2-tert-butyl-4-thiocyanatophenoxy)acetate ***(6a)***

The title compound was prepared as following: to a solution of 2-*tert*-butyl-4-thiocyanatophenol (**3c**) (280 mg, 1.35 mmol) in dry

CH_3CN (30 mL) was added Cs_2CO_3 (483 mg, 1.48 mmol). To this mixture was added dropwise a solution of ethyl 2-bromoacetate (165 μL, 1.48 mmol) in dry CH_3CN (10 mL). The mixture was stirred for 3 h at ambient temperature, then diluted with water and extracted (ethyl acetate, 3 × 100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) to give **6a** as a colorless oil in 79% yield (311 mg, 1.06 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 8.5, 2.5 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 4.63 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.38 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.91, 157.98, 141.04, 131.03, 130.93, 114.50, 113.03, 111.51, 65.04, 61.36, 35.18, 29.26, 14.00.

Ethyl 2-(2-cyclopentyl-4-thiocyanatophenoxy)acetate ***(6b)***

The title compound was prepared in 69% yield (220 mg, 0.72 mmol) as a white solid from **3d** (230 mg, 1.05 mmol) and ethyl-2-bromoacetate (129 μL, 1.16 mmol) following the general procedure. Mp = 45–46°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 8.6, 2.5 Hz, 1H), 6.70 (d, J = 8.6 Hz, 1H), 4.62 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.43–3.25 (m, 1H), 2.11–1.98 (m, 2H), 1.86–1.45 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.11, 157.18, 137.76, 130.72, 130.42, 114.68, 112.42, 111.44, 65.30, 61.31, 39.26, 32.48, 25.20, 13.99.

Ethyl 2-(2-cyclohexyl-4-thiocyanatophenoxy)acetate ***(6c)***

The title compound was prepared in 66% yield (257 mg, 0.8 mmol) as a light yellow oil from **3e** (285 mg, 1.22 mmol) and ethyl 2-bromoacetate (149 μL, 1.34 mmol) following the general procedure. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, J = 2.4 Hz, 1H), 7.30 (dd, J = 8.5, 2.5 Hz, 1H), 6.70 (d, J = 8.6 Hz, 1H), 4.62 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.07–2.91 (m, 1H), 1.93–1.66 (m, 5H), 1.52–1.15 (m, 8H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.13, 156.53, 139.16, 130.58, 130.30, 114.83, 112.45, 111.42, 65.28, 61.30, 37.06, 32.61, 26.71, 26.06, 13.98.

Ethyl 2-(2-tert-butyl-4-mercaptophenoxy)acetate ***(7a)***

The title compound was prepared as following: To a stirred solution of ethyl 2-(2-*tert*-butyl-4-thiocyanatophenoxy)acetate (**6a**) (223 mg, 0.76 mmol) in ethanol (20 mL) at 0°C 1,4-dithioerythritol (154 mg, 1 mmol) and $NaBH_4$ (38 mg, 1 mmol) were added in portions. The reaction was stirred for 20 min. Adding 1 M HCl destroyed the unreacted $NaBH_4$. The mixture was diluted with water and extracted (diethyl ether, 3 × 100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) to give **7a** as a yellow solid in 43% yield (88 mg, 0.33 mmol). Mp = 52–53°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 2.3 Hz, 1H), 7.11 (dd, J = 8.4, 2.3 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 4.58 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.35 (s, 1H), 1.38 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.60, 155.38, 139.56, 129.99, 129.40, 120.61, 112.46, 65.26, 61.21, 34.89, 29.54, 14.08.

Ethyl 2-(2-cyclopentyl-4-mercaptophenoxy)acetate ***(7b)***

The title compound was prepared in 85% yield (166 mg, 0.59 mmol) as a colorless liquid from **6b** (215 mg, 0.70 mmol) following the general procedure. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, J = 2.3 Hz, 1H), 7.06 (dd, J = 8.4, 2.3 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 4.57 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.40–3.26 (m, 2H), 2.13–1.95 (m, 2H), 1.88–1.34 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.71, 154.54, 136.21, 129.86, 128.84, 120.99, 112.03, 65.65, 61.10, 39.04, 32.71, 25.31, 14.01.

Ethyl 2-(2-cyclohexyl-4-mercaptophenoxy)acetate ***(7c)***

The title compound was prepared in 85% yield (200 mg, 0.68 mmol) as a light yellow oil from **6c** (257 mg, 0.80 mmol) following the general procedure. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.16 (d, J = 2.3 Hz, 1H), 7.05 (dd, J = 8.4, 2.3 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.57 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.34 (s, 1H), 3.05–2.89 (m, 1H), 1.91–1.66 (m, 5H), 1.50–1.18 (m, 8H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.73, 153.87, 137.68, 129.75, 128.77, 121.10, 112.01, 65.64, 61.09, 36.89, 32.84, 26.86, 26.21, 14.02.

Ethyl 2-{2-methyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}propanoate ***(8a)***

The title compound was prepared as following: To a solution of 2-methyl-4-{[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl]methylthio}phenol (**5a**) (120 mg, 0.3 mmol) in dry CH_3CN (10 mL) was added Cs_2CO_3 (147 mg, 0.45 mmol). To this mixture was added dropwise a solution of ethyl 2-bromopropanoate (55 μL, 0.39 mmol) in dry CH_3CN (3 mL). The mixture was stirred over night at ambient temperature under argon, then diluted with water and extracted (ethyl acetate, 3 × 100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) to give **8a** as a colorless oil in 97% yield (143 mg, 0.29 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 1.7 Hz, 1H), 7.07 (dd, J = 8.4, 2.1 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 4.68 (q, J = 6.8 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.08 (s, 2H), 2.20 (s, 3H), 2.18 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.90, 163.04, 156.22, 151.24, 136.72 (distorted q, J = 1.2 Hz), 136.08, 132.06, 131.24 (q, J = 32.6 Hz), 130.74, 128.57, 126.37, 125.82 (q, J = 3.8 Hz), 124.94, 123.91 (q, J = 272.2 Hz), 112.21, 72.82, 61.22, 32.44, 18.51, 16.15, 14.76, 14.05.

Ethyl 2-methyl-2-{2-methyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl) methylthio]phenoxy}propanoate ***(8b)***

The title compound was prepared in 83% yield (166 mg, 0.33 mmol) as a yellow oil **5a** (160 mg, 0.4 mmol) and ethyl 2-bromo-2-methylpropanoate (73 μL, 0.52 mmol) following the procedure described for **8a**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 1.8 Hz, 1H), 7.03 (dd, J = 8.3, 2.2 Hz, 1H), 6.53 (d, J = 8.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.08 (s, 2H), 2.18 (s, 3H), 2.15 (s, 3H), 1.56 (s, 6H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 174.18, 163.01, 154.18, 151.34, 136.80 (distorted q, J = 1.3 Hz), 136.02, 131.45, 130.79 (q, J = 32.7 Hz), 130.66, 130.45, 126.34, 125.82 (q, J = 3.9 Hz), 125.44, 123.92 (q, J = 272.2 Hz), 116.68, 79.22, 61.46, 32.38, 25.36, 16.58, 14.80, 14.03.

Ethyl 2-{2-ethyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetate ***(8c)***

The title compound was prepared in 93% yield (406 mg, 0.82 mmol) as a white solid from **5b** (360 mg, 0.88 mmol) and ethyl 2-bromoacetate (128 μL, 1.15 mmol) following the

procedure described for **8a**. Mp = 80–81 C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 8.3, 2.3 Hz, 1H), 6.58 (d, J = 8.3 Hz, 1H), 4.59 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.08 (s, 2H), 2.62 (q, J = 7.5 Hz, 2H), 2.14 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.62, 163.01, 156.02, 151.36, 136.76 (distorted q, J = 1.2 Hz), 134.78, 134.20, 132.26, 131.18 (q, J = 32.6 Hz), 130.68, 126.31, 125.79 (q, J = 3.8 Hz), 125.20, 123.90 (q, J = 272.8 Hz), 111.52, 65.40, 61.26, 32.47, 23.07, 14.70, 14.06, 13.85.

Ethyl 2-{2-ethyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}propanoate ***(8d)***

The title compound was prepared in 93% yield (142 mg, 0.28 mmol) as a yellow oil from **5b** (125 mg, 0.3 mmol) and ethyl 2-bromopropanoate (51 μL, 0.39 mmol) following the procedure described for **8a**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 2.3 Hz, 1H), 7.09 (dd, J = 8.4, 2.3 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.70 (q, J = 6.8 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 2.61 (q, J = 7.5 Hz, 2H), 2.13 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.6 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.82, 162.92, 155.76, 151.34, 136.76 (distorted q, J = 1.3 Hz), 134.81, 134.25, 132.24, 131.12 (q, J = 32.6 Hz), 130.70, 126.28, 125.75 (q, J = 3.7 Hz), 123.89 (q, J = 272.2 Hz), 124.82, 111.97, 72.48, 61.13, 32.46, 23.17, 18.42, 14.66, 13.99, 13.83.

Ethyl 2-{2-ethyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}-2-methylpropanoate ***(8e)***

The title compound was prepared in 83% yield (131 mg, 0.25 mmol) as a yellow oil from **5b** (125 mg, 0.3 mmol) and ethyl 2-bromo-2-methylpropanoate (58 μL, 0.39 mmol) following the procedure described for **8a**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 2.3 Hz, 1H), 7.05 (dd, J = 8.4, 2.4 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 2.55 (q, J = 7.5 Hz, 2H), 2.12 (s, 3H), 1.57 (s, 6H), 1.17 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 174.12, 162.90, 153.79, 151.35, 136.76 (distorted q, J = 1.3 Hz), 135.96, 134.81, 131.65, 131.12 (q, J = 32.6 Hz), 130.68, 126.26, 125.74 (q, J = 3.8 Hz), 125.11, 123.88 (q, J = 272.3 Hz), 116.20, 78.91, 61.36, 32.39, 25.27, 23.40, 14.64, 13.92.

Ethyl 2-{2-iso-propyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetate ***(8f)***

The title compound was prepared in 75% yield (130 mg, 0.26 mmol) as a yellow oil from **5c** (144 mg, 0.34 mmol) and ethyl 2-bromoacetate (49 μL, 0.44 mmol) following the procedure described for **8a**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 2.2 Hz, 1H), 7.13 (d, J = 8.3, 2.3 Hz, 1H), 6.58 (d, J = 8.3 Hz, 1H), 4.59 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 3.31 (hept, J = 6.9 Hz, 1H), 2.09 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.56, 162.97, 155.45, 151.39, 138.43, 136.72 (distorted q, J = 1.2 Hz), 132.42, 132.26, 131.12 (q, J = 32.6 Hz), 130.70, 126.26, 125.74 (q, J = 3.8 Hz), 125.14, 123.87 (q, J = 271.9 Hz), 111.61, 65.38, 61.20, 32.49, 26.73, 22.31, 14.57, 14.01.

Ethyl 2-{2-iso-propyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}propanoate ***(8g)***

The title compound was prepared in 94% yield (170 mg, 0.32 mmol) as a yellow oil from **5c** (144 mg, 0.34 mmol) and ethyl 2-bromopropanoate (57 μL, 0.44 mmol) following the procedure described for **8a**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 2.3 Hz, 1H), 7.10 (dd, J = 8.4, 2.3 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 4.71 (q, J = 6.8 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.05 (s, 2H), 3.31 (hept, J = 6.9 Hz, 1H), 2.09 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H), 1.25–1.07 (m, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.83, 162.97, 155.20, 151.40, 138.43, 136.75 (distorted q, J = 1.3 Hz), 132.45, 132.27, 131.13 (q, J = 32.6 Hz), 130.75, 126.27, 125.75 (q, J = 3.8 Hz), 124.76, 123.88 (q, J = 272.1 Hz), 111.98, 72.44, 61.14, 32.55, 26.78, 22.33, 18.43, 14.59, 14.00.

Ethyl 2-{2-iso-propyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}-2-methylpropanoate ***(8h)***

The title compound was prepared in 53% yield (96 mg, 0.18 mmol) as a yellow oil from **5c** (144 mg, 0.34 mmol) and ethyl 2-bromo-2-methylpropanoate (66 μL, 0.44 mmol) following the procedure described for **8a**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 2.3 Hz, 1H), 7.06 (dd, J = 8.4, 2.4 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 3.25 (hept, J = 6.9 Hz, 1H), 2.09 (s, 3H), 1.57 (s, 6H), 1.17 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 174.19, 163.01, 153.26, 151.41, 140.18, 136.75 (distorted q, J = 1.3 Hz), 132.49, 131.70, 131.20 (q, J = 32.6 Hz), 130.76, 126.31, 125.80 (q, J = 3.8 Hz), 125.06, 123.91 (q, J = 272.0 Hz), 116.24, 78.95, 61.40, 32.52, 26.81, 25.33, 22.44, 14.59, 13.95.

Ethyl 2-{2-tert-butyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetate ***(8i)***

The title compound was prepared as following: To a solution of ethyl 2-(2-*tert*-butyl-4-mercaptophenoxy)acetate (**7a**) (88 mg, 0.33 mmol) in dry CH_3CN (10 mL) was added Cs_2CO_3 (117 mg, 0.33 mmol). To this mixture was added dropwise a solution of 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole (98 mg, 0.34 mmol) in dry CH_3CN (5 mL). The mixture was stirred for 4 h at ambient temperature under argon, then diluted with water and extracted (ethyl acetate, 3 × 100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) to give **8i** as a colorless oil in 94% yield (163 mg, 0.31 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 2.2 Hz, 1H), 7.18 (dd, J = 8.2, 2.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 4.60 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 2.07 (s, 3H), 1.31 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.41, 163.08, 156.98, 151.53, 139.44, 136.77 (distorted q, J = 1.3 Hz), 133.27, 132.80, 130.74, 131.20 (q, J = 32.6 Hz), 126.32, 125.81 (q, J = 3.8 Hz), 124.66, 123.91 (q, J = 272.1 Hz), 112.16, 65.14, 61.28, 34.86, 32.60, 29.42, 14.60, 14.07.

Ethyl 2-{2-cyclopentyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetate ***(8j)***

The title compound was prepared in 58% yield (114 mg, 0.21 mmol) as a yellow oil from **7b** (100 mg, 0.36 mmol) and 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole

(107 mg, 0.37 mmol) following the procedure described for **8i**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.18–7.11 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 4.59 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 3.40–3.22 (m, 1H), 2.11 (s, 3H), 2.06–1.87 (m, 2H), 1.78–1.37 (m, 6H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.62, 163.02, 156.15, 151.45, 136.77 (distorted q, J = 1.3 Hz), 136.23, 133.03, 132.25, 131.18 (q, J = 32.6 Hz), 130.74, 126.30, 125.78 (q, J = 3.6 Hz), 125.04, 123.90 (q, J = 272.3 Hz), 111.67, 65.53, 61.25, 38.91, 32.73, 32.55 25.31, 14.66, 14.07.

Ethyl 2-{2-cyclohexyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetate ***(8k)***

The title compound was prepared in 79% yield (151 mg, 0.27 mmol) as a light yellow oil from **7c** (100 mg, 0.34 mmol) and 5-chloromethyl-4-methyl-2-(4-trifluoromethylphenyl)thiazole (101 mg, 0.35 mmol) following the procedure described for **8i**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 8.3, 2.3 Hz, 1H), 7.11 (d, J = 2.2 Hz, 1H), 6.58 (d, J = 8.3 Hz, 1H), 4.58 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.05 (s, 2H), 3.01–2.85 (m, 1H), 2.08 (s, 3H), 1.87–1.58 (m, 5H), 1.45–0.99 (m, 8H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.62, 162.97, 155.53, 151.50, 137.58, 136.76 (d, J = 1.2 Hz), 133.15, 132.34, 131.14 (q, J = 32.6 Hz), 130.67, 126.28, 125.74 (q, J = 3.7 Hz), 124.99, 123.88 (q, J = 272.3 Hz), 111.65, 65.48, 61.22, 36.79, 32.84, 32.53, 26.83, 26.14, 14.59, 14.05.

2-{2-Methyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}propanoic acid ***(2a)***

The title compound was prepared as following: to a stirred solution of ethyl 2-{2-methyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl)methylthio]phenoxy}propanoate (**8a**) (170 mg, 0.34 mmol) in THF (10 mL) and H_2O (5 mL) at 0°C was added slowly 215 μL of 2.0 M LiOH. The reaction mixture was stirred until TLC indicated completion of the reaction. The mixture was diluted with 50 mL H_2O, acidified with 0.1 M HCl, extracted (diethyl ether, 3 × 50 mL), dried ($MgSO_4$), and concentrated. The residue was recrystallized from ethyl acetate/hexane to give **2a** as a white solid in 50% yield (80 mg, 0.17 mmol). Mp = 78–79°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.97 (br s, 1H), 8.03 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 1.6 Hz, 1H), 7.15 (dd, J = 8.4, 2.1 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 4.80 (q, J = 6.7 Hz, 1H), 4.33 (s, 2H), 2.19 (s, 3H), 2.13 (s, 3H), 1.50 (d, J = 6.7 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 172.92, 161.70, 155.51, 151.08, 136.53 (distorted q, J = 1.0 Hz), 134.36, 131.55, 130.74, 129.61 (q, J = 31.9 Hz), 127.29, 126.34, 126.11 (q, J = 3.8 Hz), 124.38, 124.00 (q, J = 272.3 Hz), 112.46, 71.81, 30.54, 18.28, 15.85, 14.60. MS (ESI) m/z 466.10 [M – H]$^-$, HRMS calcd. for $C_{22}H_{20}F_3NO_3S_2$ [M]$^+$: 467.0837; found: 467.0830.

2-Methyl-2-{2-methyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)- thiazol-5-yl) methylthio]phenoxy}propanoic acid ***(2b)***

The title compound was prepared as following: To a stirred solution of ethyl 2-methyl-2-{2-methyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl)methylthio]phenoxy}propanoate (**8b**) (166 mg, 0.33 mmol) in THF (10 mL) and H_2O (5 mL) was added 1 mL aqueous solution of 2.0 M *t*-BuOK. The reaction mixture was refluxed for 24 h. After the completion, the mixture was diluted with 50 mL H_2O, acidified with 0.1 M HCl, extracted (diethyl ether, 3 × 50 mL), dried ($MgSO_4$), and concentrated. The residue was recrystallized from ethyl acetate/hexane to give **2b** as a white solid in 45% yield (72 mg, 0.15 mmol). Mp = 125–126°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.02 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 1.8 Hz, 1H), 7.02 (dd, J = 8.7, 2.0 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 4.29 (s, 2H), 2.17 (s, 3H), 2.07 (s, 3H), 1.40 (s, 6H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 173.84, 161.64, 156.36, 150.98, 136.53 (distorted q, J = 1.3 Hz), 134.21, 131.61, 130.81, 129.58 (q, J = 32.0 Hz), 126.84, 126.33, 126.07 (q, J = 3.8 Hz), 124.00 (q, J = 272.2 Hz), 123.18, 112.45, 73.66, 30.77, 18.75, 15.96, 14.62. MS (ESI) m/z 480.0 [M – H]$^-$, HRMS calcd. for $C_{23}H_{22}F_3NO_3S_2$ [M]$^+$: 481.0993; found: 481.0988.

2-{2-Ethyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl)methylthio]phenoxy}acetic acid ***(2c)***

The title compound was prepared in 43% yield (86 mg, 0.18 mmol) as a white solid from **8c** (206 mg, 0.42 mmol) following the procedure described for **2a**. Mp = 141–142°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.00 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.15–7.04 (m, 2H), 6.69 (d, J = 9.0 Hz, 1H), 4.28 (s, 2H), 4.26 (s, 2H), 2.51 (q, J = 7.4 Hz, 2H), 2.13 (s, 3H), 1.05 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 172.85, 161.65, 156.65, 151.03, 136.53 (distorted q, J = 1.2 Hz), 132.95, 132.54, 131.74, 131.16, 129.58 (q, J = 32.0 Hz), 126.28, 122.86, 126.09 (q, J = 3.8 Hz), 123.99 (q, J = 272.1 Hz), 112.24, 67.33, 30.95, 22.63, 14.55, 13.90. MS (ESI) m/z 466.1 [M – H]$^-$, HRMS calcd. for $C_{22}H_{20}F_3NO_3S_2$ [M]$^+$: 467.0837; found: 467.0858.

2-{2-Ethyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl)methylthio]phenoxy}propanoic acid ***(2d)***

The title compound was prepared in 50% yield (69 mg, 0.14 mmol) as a white solid from **8d** (142 mg, 0.28 mmol) following the procedure described for **2a**. Mp = 127–128°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.95 (br s, 1H), 8.02 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 8.4, 2.3 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 4.81 (q, J = 6.7 Hz, 1H), 4.30 (s, 2H), 2.52 (q, J = 7.3 Hz, 2H), 2.13 (s, 3H), 1.49 (d, J = 6.7 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 172.97, 161.73, 155.23, 151.18, 136.55 (distorted, J = 1.2 Hz), 133.37, 133.05, 131.52, 131.22, 129.62 (q, J = 32.0 Hz), 126.30, 126.08 (q, J = 3.7 Hz), 124.22, 124.00 (q, J = 272.0 Hz), 112.42, 71.67, 30.77, 22.70, 18.26, 14.50, 13.85. MS (ESI) m/z 480.1 [M – H]$^-$, HRMS calcd. for $C_{23}H_{22}F_3NO_3S_2$ [M]$^+$: 481.0993; found: 481.0980.

2-{2-Ethyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl)methylthio]phenoxy}-2-methylpropanoic acid ***(2e)***

The title compound was prepared in 60% yield (74 mg, 0.15 mmol) as a white solid from **8e** (131 mg, 0.25 mmol) following the procedure described for **2b**. Mp = 132–133°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ = 13.07 (br s, 1H), 8.02 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.15 (dd, J = 8.4, 2.4 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 8.3 Hz, 1H), 4.31 (s, 2H), 2.49 (q, 7.5 Hz, 2H), 2.13 (s, 3H), 1.50 (s, 6H), 1.04 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 175.04, 161.73, 153.12, 151.21, 136.54 (distorted q, J = 1.2 Hz), 134.96, 133.54, 131.39, 130.71, 129.62 (q, J = 32.0 Hz), 126.29, 126.10 (q, J = 3.7 Hz), 124.76, 124.00 (q, J = 272.1 Hz), 116.22, 78.32, 30.65, 24.98, 22.92, 14.49, 13.97. MS (ESI) m/z 494.0 [M – H]$^-$, HRMS calcd. for $C_{24}H_{24}F_3NO_3S_2$ [M]$^+$: 495.1150; found: 495.1173.

2-{2-Iso-propyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetic acid ***(2f)***

The title compound was prepared in 35% yield (43 mg, 0.09 mmol) as a white solid from **8f** (130 mg, 0.26 mmol) following the procedure described for **2a**. Mp = 146–147°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.95 (br s, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.20 (dd, J = 8.4, 1.7 Hz, 1H), 7.07 (d, J = 1.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 4.69 (s, 2H), 4.29 (s, 2H), 3.22 (hept, J = 6.9 Hz, 1H), 2.07 (s, 3H), 1.06 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 170.01, 161.77, 154.98, 151.26, 137.09, 136.57 (distorted q, J = 1.2 Hz), 131.59, 131.48, 130.92, 129.61 (q, J = 32.1 Hz), 126.29, 126.10 (q, J = 3.8 Hz), 124.26, 124.00 (q, J = 272.1 Hz), 112.20, 64.73, 30.91, 26.15, 22.16, 14.43. MS (ESI) m/z 480.1 [M – H]$^-$, HRMS calcd. for $C_{23}H_{22}F_3NO_3S_2$ [M]$^+$: 481.0993; found: 481.0973.

2-{2-Iso-propyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}propanoic acid ***(2g)***

The title compound was prepared in 66% yield (113 mg, 0.23 mmol) as a white solid from **8g** (183 mg, 0.35 mmol) following the procedure described for **2a**. Mp = 170–171°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.97 (br s, 1H), 8.03 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.19 (dd, J = 8.5, 2.3 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 4.83 (q, J = 6.7 Hz, 1H), 4.29 (s, 2H), 3.21 (hept, J = 6.9 Hz, 1H), 2.06 (s, 3H), 1.50 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.90, 161.77, 154.67, 151.29, 137.21, 136.58 (distorted q, J = 1.4 Hz), 131.58, 131.48, 131.04, 129.61 (q, J = 32.0 Hz), 126.30, 126.11 (q, J = 3.7 Hz), 124.13, 124.00 (q, J = 272.2 Hz), 112.51, 71.59, 30.91, 26.23, 22.09, 18.22, 14.40. MS (ESI) m/z 494.1 [M – H]$^-$, HRMS calcd. for $C_{24}H_{24}F_3NO_3S_2$ [M]$^+$: 495.1150; found: 495.1147.

2-{2-Iso-propyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}-2-methylpropanoic acid ***(2h)***

The title compound was prepared in 48% yield (44 mg, 0.09 mmol) as a white solid from **8h** (96 mg, 0.18 mmol) following the procedure described for **2b**. Mp = 122–123°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.03 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 8.5, 2.2 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 4.30 (s, 2H), 3.16 (hept, J = 6.9 Hz, 1H), 2.07 (s, 3H), 1.49 (s, 6H), 1.04 (d, J = 6.9 Hz, 6H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 175.15, 161.79, 152.64, 151.31, 139.06, 136.58 (distorted q, J = 1.3 Hz), 131.49, 131.23, 130.98, 129.61 (q, J = 32.0 Hz), 126.30, 126.15 (q, J = 3.6 Hz), 124.57, 124.02 (q, J = 272.2 Hz), 116.36, 78.41, 30.83, 26.34, 25.02, 22.21, 14.40. MS (ESI) m/z 508.0 [M – H]$^-$, HRMS calcd. for $C_{25}H_{26}F_3NO_3S_2$ [M]$^+$: 509.1306; found: 509.1295.

2-{2-Tert-butyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetic acid ***(2i)***

The title compound was prepared in 44% yield (42 mg, 0.08 mmol) as a white solid from **8i** (94 mg, 0.18 mmol) following the procedure described for **2a**. Mp = 105–106°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.97 (br s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.26 (dd, J = 8.4, 2.2 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 4.69 (s, 2H), 4.26 (s, 2H), 2.01 (s, 3H), 1.23 (s, 9H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 169.82, 161.86, 156.67, 151.45, 138.02, 136.58 (distorted q, J = 1.2 Hz), 132.34, 131.98, 131.55, 129.62 (q, J = 31.9 Hz), 126.30, 126.13 (q, J = 3.8 Hz), 124.01 (q, J = 272.1 Hz), 123.64, 113.01, 64.70, 34.38, 31.12, 29.18, 14.32. MS (ESI) m/z 494.0 [M – H]$^-$, HRMS calcd. for $C_{24}H_{24}F_3NO_3S_2$ [M]$^+$: 495.1150; found: 495.1138.

2-{2-Cyclopentyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetic acid ***(2j)***

The title compound was prepared in 39% yield (37 mg, 0.07 mmol) as a white solid from **8j** (94 mg, 0.18 mmol) following the procedure described for **2a**. Mp = 88–89°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.02 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.14 (dd, J = 8.4, 2.2 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 4.31 (s, 2H), 4.25 (s, 2H), 3.30–3.14 (m, 1H), 2.07 (s, 3H), 1.93–1.77 (m, 2H), 1.63–1.28 (m, 6H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 173.09, 161.70, 156.70, 151.18, 136.55 (distorted q, J = 1.2 Hz), 134.44, 131.84, 131.46, 131.34, 129.58 (q, J = 31.7 Hz), 126.26, 126.09 (q, J = 3.9 Hz), 124.00 (q, J = 272.2 Hz), 122.72, 112.27, 67.27, 38.25, 32.34, 31.07, 24.85, 14.50. MS (ESI) m/z 506.2 [M – H]$^-$, HRMS calcd. for $C_{25}H_{24}F_3NO_3S_2$ [M]$^+$: 507.1150; found 507.1161.

2-{2-Cyclohexyl-4-[(4-methyl-2-(4-trifluoromethylphenyl)-thiazol-5-yl)methylthio]phenoxy}acetic acid ***(2k)***

The title compound was prepared in 48% yield (64 mg, 0.12 mmol) as a white solid from **8k** (135 mg, 0.25 mmol) following the procedure described for **2a**. Mp = 144–145°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.94 (br s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.21 (dd, J = 8.5, 2.2 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 4.68 (s, 2H), 4.27 (s, 2H), 2.91–2.76 (m, 1H), 2.04 (s, 3H), 1.70–1.51 (m, 5H), 1.36–1.04 (m, 5H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 170.06, 161.80, 155.09, 151.42, 136.60 (distorted q, J = 1.0 Hz), 136.13, 131.82, 131.77, 131.51, 129.61 (q, J = 32.1 Hz), 126.30, 126.08 (q, J = 3.6 Hz), 124.02 (d, J = 272.1 Hz), 123.94, 112.14, 64.73, 36.07, 32.26, 30.98, 26.42, 25.58, 14.40. MS (ESI) m/z 520.0 [M – H]$^-$, HRMS calcd. for $C_{26}H_{26}F_3NO_3S_2$ [M]$^+$: 521.1306; found: 521.1310.

Measurement of oleic acid oxidation

Satellite cells were isolated from the *Musculus obliquus internus abdominis* of healthy donors. The biopsies were obtained with informed consent and approval by the Regional Committee for Research Ethics, Oslo, Norway. The cells were cultured in DMEM (5.5 mM glucose) with 2% FCS, 2% Ultroser G, penicillin/streptomycin (P/S) and amphotericin B until 70–80% confluent. Myoblast differentiation to myotubes was then induced by changing medium to DMEM (5.5 mM glucose) with 2% FCS, 25 pM insulin, P/S and amphotericin B. Experiments were performed after 7 days of differentiation, and preincubation with agonists was started after 3 days. The substrate, [1-^{14}C]oleic acid (1 μCi/mL, 100 μM), was given in DPBS with 10 mM HEPES and 1 mM L-carnitine. A 96-well UNIFILTER® microplate was mounted on top of the CellBIND® plate as described before [25], and the cells were incubated at 37°C for 4 h. The CO_2 trapped in the filter was counted by liquid scintillation (MicroBeta®, PerkinElmer) and normalized against protein content. EC_{50}-values were calculated with GraphPad Prism, version 4.

Luciferase-based transient transfection system

COS-1 cells (ATCC no. CRL 1650) were cultured in DMEM supplemented with L-glutamine (2 mM), penicillin (50 U/mL),

streptomycin (50 μG/mL), fungizone (2.5 μg/mL), and 10% inactivated FBS. The cells were incubated at 37°C in a humidified atmosphere of 5%CO_2 and 95% air and used for transient transfections. Cells were plated in six-well plates 1 day before transfection. Transient transfection by lipofectamin 2000 (Invitrogen, Carlsbad, CA) was performed as described. Each well received 990 ng plasmid: 320 ng reporter ((UAS)5-tk-LUC) (UAS = upstream activating sequence and LUC = luciferase), 640 ng pGL3 basic (empty vector) and 30 ng expression plasmid of either pSG5-GAL4-hPPARα, pSG5-GAL4-hPPARδ, and pSG5-GAL4-hPPARγ. 10 μM of the compounds and controls and DMSO (negative control) was added to the media 5 h after transfection. Transfected cells were maintained for 24 h before lysis by reporter lysis buffer. Binding of the ligands to the LBD of PPARs activates GAL4 binding to UAS, which in turn stimulates the tk promoter to drive luciferase expression. Luciferase activity was measured using a luminometer (TD-20/20 luminometer Turner Designs, Sunnyvale, CA) and normalized against protein content. The following compounds were used as positive controls: (2*E*,4*E*,8*Z*,11*Z*,14*Z*,17*Z*)-eicosa-2,4,8,11,14,17-hexaenoic acid (EHA), GW 501516 (**1**) and rosiglitazone (BRL) for PPARα, PPARδ, and PPARγ, respectively. EC_{50} is the concentration of test compounds needed to induce 50% of the maximum luciferase activity. The EC_{50}-value is the average of three separate tests.

*Docking of **2e** into PPAR δ*

The ICM ('Internal Coordinate Mechanics') program (version 3.6-1h) [33] was used for docking and calculation of the interaction energy. The X-ray crystal structure PPARδ (PDB entry: 3GZ9) [28], with an agonist at the binding site, was converted to and ICM object, and receptor maps where calculated based on the agonist position in the crystal structures. **2e** was modeled using the ICM molecule editor and docked into PPARδ using interactive docking, and the interaction energy was calculated using the calcBindingEnergy macro of ICM.

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