European Journal of Medicinal Chemistry 45 (2010) 3047–3055

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and dual PPARα/δ agonist effects of 1,4-disubstituted 1,2,3-triazole analogues of GW 501516

Calin C. Ciocoiu [a], Nataša Nikolić [b], Huyen Hoa Nguyen [b], G. Hege Thoresen [b], Arne J. Aasen [a], Trond Vidar Hansen [a,*]

[a] School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, PO BOX 1068, Blindern, N-0316 Oslo, Norway
[b] School of Pharmacy, Department of Pharmaceutical Biosciences, University of Oslo, PO BOX 1068, Blindern, N-0316 Oslo, Norway

ARTICLE INFO

Article history:
Received 2 November 2009
Received in revised form
23 March 2010
Accepted 23 March 2010
Available online 27 March 2010

Keywords:
Triazoles
GW 501516
Agonists
PPARα
PPARδ
Multiwell assay

ABSTRACT

Ten 1,4-disubstituted 1,2,3-triazoles **2a**–**2j** were prepared and tested for their ability to increase oleic acid oxidation in human myotubes using a high-throughput multiwell assay. Compounds **2e** (2-{4-[(1-(3-fluoro-4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetic acid) and **2i** (2-{4-[(1-(3-chloro-4-(trifluoromethoxy)phenyl)-1*H*-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetic acid) exhibited potent agonist activities. Compounds **2e** and **2i** also exhibited powerful agonist effects for both PPARα and PPARδ in a luciferase-based assay. Consequently, these triazoles can be categorized as dual PPAR agonists.

1. Introduction

The peroxisome proliferator-activated receptors (PPARα, PPARδ and PPARγ) belong to the nuclear receptor family of proteins and function as ligand-activated transcription factors [1]. These receptors play a key role in various tissues by controlling the expression of genes involved in lipid and carbohydrate metabolism. Agonists acting on the PPARs have been shown to have beneficial effects on lipid and glucose metabolism by decreasing triglyceride levels and increasing high density cholesterol level (HDL). Furthermore, PPAR agonists have the ability to improve glucose tolerance in type 2 diabetic patients [2]. Dyslipidemia and insulin resistance, two major components of the metabolic syndrome, have usually been treated with either the fibrate or the TZD classes of drugs that target PPARα and PPARγ receptors, respectively [3,4]. In contrast, no drugs have been developed that target the PPARδ and only a few selective and potent ligands that target this receptor have been identified [5]. The thiazole based compound GW 501516 (**1**) (Fig. 1) has been reported to be both highly potent and selective against the PPARδ receptor [5a].

Interestingly, when obese rhesus monkeys were treated with GW 501516 (**1**) [5b], an increased level in the plasma HDL cholesterol as well as a decrease in the plasma triglyceride level was observed. Based on these observations, compound **1** is an interesting lead compound for the development of remedies against diabetes and the metabolic syndrome. Shen and coworkers reported several PPARα/δ dual agonists when the methyl-thiazole heterocycle in **1** was replaced with a 1,2,4-thiadiazole moiety [6]. Recently, a regioselective copper(I) catalyzed cycloaddition reaction between terminal alkynes and azides affording 1,4-disubstituted 1,2,3-triazoles in high yields [7] was reported independently by the Sharpless and the Meldal groups. This reaction has found many applications [8]. For example, 1,4-disubstituted 1,2,3-triazoles have recently been employed as mimics for amides [9] in combinatorial chemistry library syntheses [10], in modifications of natural products [11] and *in situ* library screening [12]. Grimm's bioisosteric rule [13] suggests bioisosteric substitution with triazoles should be five-membered heterocyclic rings such as the thiazole heterocyclic ring in GW 501516 (**1**) [14]. Furthermore, using our recently reported *in vitro* high-throughput multiwell assay method [15], fast access to measuring agonist effects in a whole cell-based system has become available to us. Since development of new agonists that target the PPARs is still of great interest within medicinal chemistry and drug discovery [16], we

* Corresponding author. Tel.: +47 22857450; fax: +47 22855947.
E-mail address: t.v.hansen@farmasi.uio.no (T.V. Hansen).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.03.035

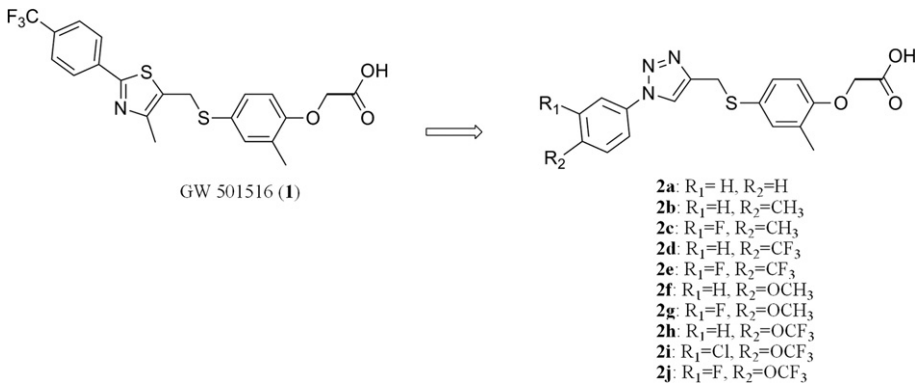


Fig. 1. Structures of GW 501516 (**1**) and triazoles **2a**–**2j**.

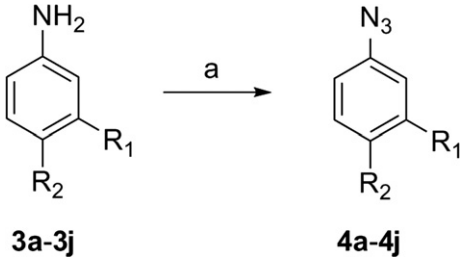
decided to prepare triazole analogues of GW 501516 (**1**). Herein, our synthetic efforts and the biological evaluation of *in vitro* agonist effects of ten 1,4-disubstituted 1,2,3-triazole analogues of **1** are reported.

2. Chemistry

1,2,3-Triazoles can be prepared from the thermally induced Huisgen dipolar cycloaddition reaction between azides and alkynes [17]. This cycloaddition reaction usually affords mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles [18]. Recently, the groups of Sharpless and Meldal independently reported that 1,4-disubstituted 1,2,3-triazoles are specifically prepared from azides and terminal alkynes under copper(I) catalysis [7]. Our synthetic efforts towards the target 1,4-disubstituted 1,2,3-triazoles **2a**–**2j** started with the synthesis of alkyne **7** and azides **4a**–**4j**. The azides **4a**–**4j** were obtained from the anilines **5a**–**5j** using standard diazotization conditions (Scheme 1) [19]. Terminal alkyne **7** was obtained in 54% isolated yield over a two step sequence from the known *p*-mercaptophenol **5** via **6** [20]. Reaction of the alkyne **7** with the azides **4a**–**4j** under copper(I) catalysis using Sharpless and coworkers' conditions [7a] yielded triazole esters **8a**–**8j**. Basic aqueous hydrolysis of esters **8a**–**8j** afforded the target compounds **2a**–**2j** (Scheme 2). The 1,2,3-triazoles **2a**–**2j** were obtained in 20–48% overall yields in a four step sequence from *p*-mercaptophenol **5**. The spectral data of all new products were in accord with their assigned structures.

3. Biological evaluation

GW 501516 (**1**) as well as all ten 1,4-disubstituted 1,2,3-triazoles **2a**–**2j**, at five different concentrations, was 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 the accumulation of ^{14}C-labeled oxidized oleic acid [15]. The results from the oxidation of



Scheme 1. (a) Reagents and conditions: $NaNO_2$, NaN_3, H_2O:HCl (1:1), 0 °C, r.t.

^{14}C-labeled oleic acid at different concentrations of triazoles **2a**–**2j** are compiled in Fig. 2. The EC_{50}-values for the five triazoles **2d**, **2e**, **2i**, **2j** and **2h** were obtained from Fig. 3 (Table 1). Compounds **2e** and **2i** were also tested against the three peroxisome proliferator-activated receptors (PPARα, PPARδ and PPARγ) in a luciferase-based transient transfection assay (Fig. 4).

4. Results and discussion

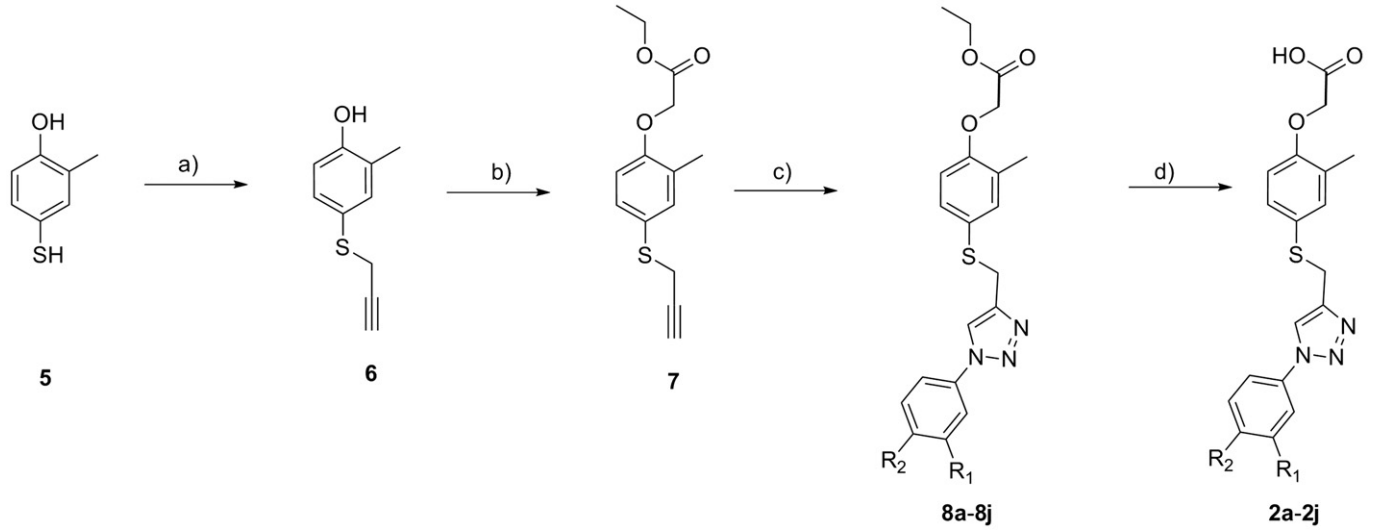
All ten triazoles showed the ability to induce oxidation of oleic acid (Table 1, Fig. 2); however, all were less potent than GW 501516 (**1**). The most potent triazoles were **2d**, **2e** and **2j** which exhibited a 10-fold lower potency than the lead compound GW 501516 (**1**) (Table 1, Figs. 2A–C, Fig. 3A). The EC_{50}-values for these three triazoles from these experiments were calculated to be 1.8 nM, 0.85 nM, and 1.4 nM, respectively. Triazoles **2h** and **2i** exhibited a 100-fold lower potency compared to lead GW 501516 (**1**) (Table 1, Figs. 2D,E, Fig. 3B).

We next investigated the effects of triazoles **2e** and **2i** exercised on the three different peroxisome proliferator-activated receptors (PPARα, PPARδ and PPARγ) in a luciferase-based transient transfection system. Interestingly, **2e** and **2i** both activated PPARα as well as PPARδ at 10 μM concentration. Triazole **2i** was as efficient as the known PPARα agonist ((2*E*,4*E*,8*Z*,11*Z*,14*Z*,17*Z*)-eicosa-2,4,8,11,14,17-hexaenoic acid) at this concentration, while **2e** was slightly less efficient (Fig. 4A). Triazole **2e** was as efficient at 10 μM as GW 501516 (**1**) towards PPARδ (Fig. 4B). No activity towards PPARγ was observed for compounds **2e** and **2i**.

Dual activation of PPARs is currently of interest as remedies against several diseases such as metabolic disorders, type II diabetes and cardiovascular diseases [21]. Activation of PPARα has been reported to reduce the levels of triglycerides in blood while activation of PPARδ has been reported to enhance both the fatty acid metabolism and the HDL cholesterol level. So far very few potent PPARα/δ dual agonists have been reported in the literature [6,22]. Our results reported herein augment the limited structural information available for activation of both PPARα and PPARδ. These results merit further investigations.

5. Conclusions

We have prepared ten new triazole analogues of the known PPARδ agonist GW 501516 (**1**). Five of these analogues proved to be potent, activating the fatty acid oxidation in human myotubes in concentrations below 10 μM. Interestingly, dual PPARα/δ agonist effects were observed for both compounds **2e** and **2i**. Further studies towards preparing more potent dual agonists are underway. These efforts will be reported in due course.



Scheme 2. Reagents and conditions: (a) propargyl bromide, Cs_2CO_3, CH_3CN; (b) ethyl bromoacetate, Cs_2CO_3, CH_3CN; (c) sodium ascorbate, $CuSO_4 \cdot 5H_2O$, *t*-BuOH, H_2O, azides **4a**–**4j**; (d) LiOH, THF, H_2O.

6. Experimental

6.1. General methods

All dry solvents were commercially available. NMR spectra were recorded on a Bruker DP × 300 spectrometer. 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 × 150 mm), coupled with an Agilent 6310 ion Trap. The purities of the final products **2a**–**2j** were >98% as judged from the HPLC analyses. The purities of all intermediates were >95% as judged by NMR and HPLC analyses.

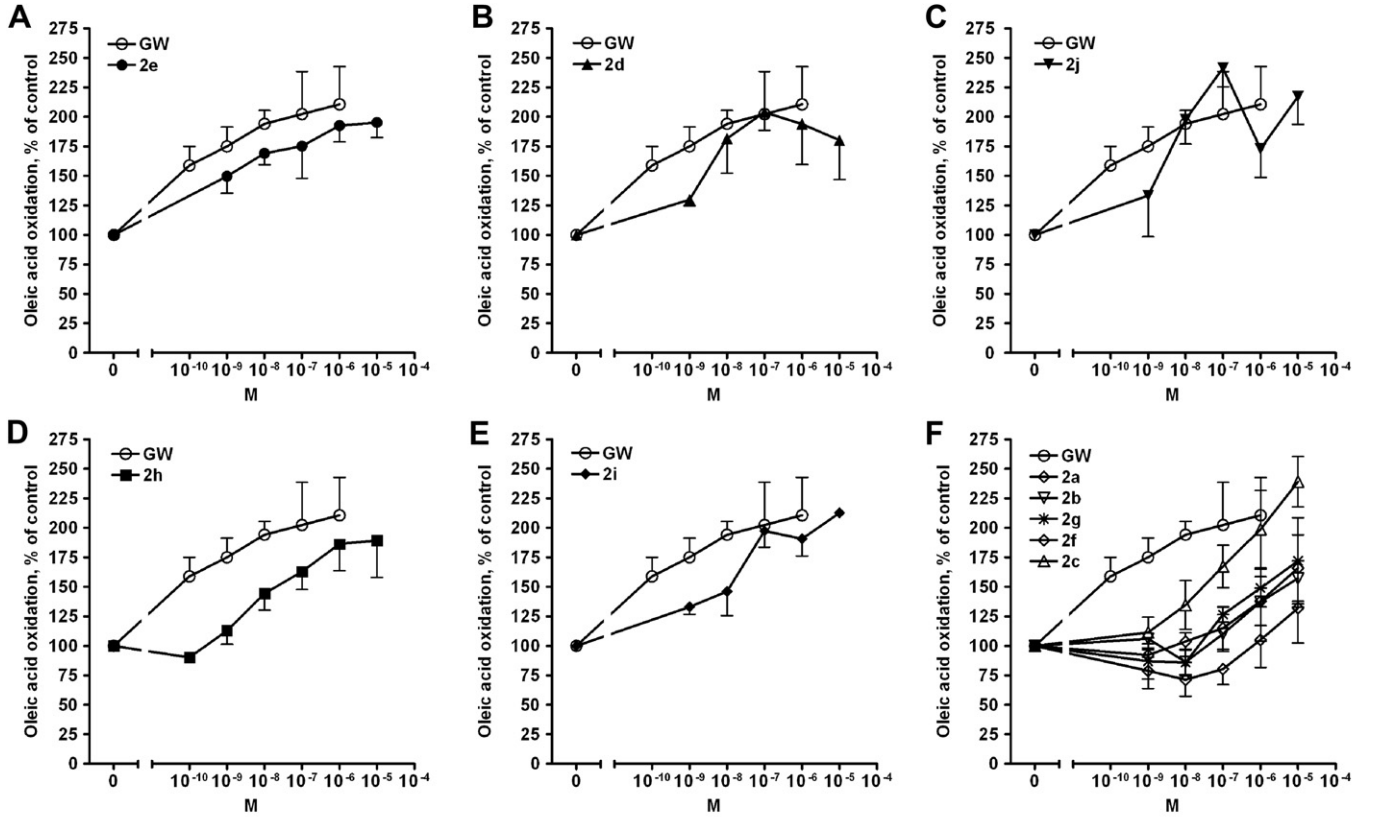


Fig. 2. Oxidation of oleic acid in human myotubes in the presence of the triazoles **2a**–**2j** at different concentrations. Myotubes were cultured and oleic acid oxidation assessed as described in Section 6.34. GW 501516 (**1**) was used as positive control.

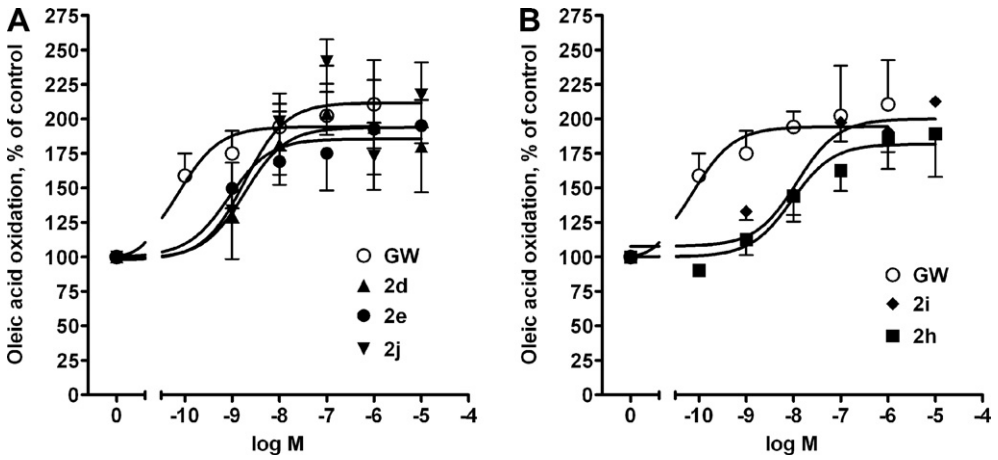


Fig. 3. Non-linear fit curves of oleic acid oxidation in human myotubes in the presence of different concentrations of the triazoles **2d**, **2e**, **2j** (A), **2i** and **2h** (B). Myotubes were cultured and oleic acid oxidation assessed as described in Section 6.34. GW 501516 (**1**) was used as positive control.

6.2. Azidobenzene (*4a*)

General procedure: the amine (1 mmol) was suspended in HCl/H_2O (1:1) (10 mL) and cooled to 0 °C. An aqueous solution of sodium nitrite (82.8 mg, 1.2 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h. An aqueous solution of sodium azide (1.2 mmol) was added dropwise. The reaction mixture was stirred at room temperature for another 3 h, and extracted with hexane (3 × 50 mL). The organic layers were washed with brine (2 × 100 mL), dried over $MgSO_4$ and concentrated. The title compound was prepared in 36% yield (434 mg, 3.64 mmol) as a brown oil from aniline (**3a**) (10 mmol) according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.04–7.07$ (m, 2H), 7.14–7.19 (m, 1H), 7.35–7.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 118.97, 124.81, 129.69, 139.95$.

6.3. 1-Azido-4-methylbenzene (*4b*)

The title compound was prepared in 41% yield (274 mg, 2.06 mmol) as a yellow oil from *p*-toluidine (**3b**) (536 mg, 5 mmol) according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.34$ (s, 3H), 6.93 (d, $J = 8.39$ Hz, 2H), 7.16 (d, $J = 8.07$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.78, 118.80, 130.2, 134.56, 137.12$.

6.4. 4-Azido-2-fluoro-1-methylbenzene (*4c*)

The title compound was prepared in 70% yield (533 mg, 3.53 mmol) as an orange oil from 3-fluoro-4-methylaniline (**3c**) (625 mg, 5 mmol) according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.25$ (d, $J = 1.95$ Hz, 3H), 6.76–6.75 (m, 2H), 7.15 (t, $J = 8.21$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.98$ (d, $J = 3.34$ Hz), 106.27 (d, $J = 26.03$ Hz), 114.31 (d, $J = 3.40$ Hz), 121.40 (d, $J = 17.51$ Hz), 132.12 (d, $J = 6.31$ Hz), 139.02 (d, $J = 9.91$ Hz), 161.61 (d, $J = 246.30$ Hz).

Table 1
Substitution pattern (see Fig. 1) and EC_{50}-values for the prepared triazoles.

Compound	R_1	R_2	EC_{50}[a] (nM)
2a	H	H	n.d.[b]
2b	H	CH_3	n.d.
2c	F	CH_3	n.d.
2d	H	CF_3	1.8
2e	F	CF_3	0.85
2f	H	OCH_3	n.d.
2g	F	OCH_3	n.d.
2h	H	OCF_3	10
2i	Cl	OCF_3	12
2j	F	OCF_3	1.4
1	–	–	0.07

[a] Results of three experiments.
[b] n.d. = not determined.

6.5. 1-Azido-4-trifluoromethylbenzene (*4d*)

The title compound was prepared in 55% yield (1028 mg, 5.5 mmol) as a light yellow oil from 4-trifluoromethylaniline (**3d**) (10 mmol) according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.10$ (d, $J = 8.27$ Hz, 2H), 7.60 (d, $J = 8.35$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 119.39, 123.94$ (q, $J = 269.8$ Hz), 126.95 (q, $J = 3.75$ Hz), 127.04 (q, $J = 32.7$ Hz), 143.6 (distorted q, $J = 1.2$ Hz).

6.6. 4-Azido-2-fluoro-1-trifluoromethylbenzene (*4e*)

The title compound was prepared in 46% yield (187 mg, 0.91 mmol) as a yellow oil from 3-fluoro-4-trifluoromethylaniline (**3e**) (358 mg, 2 mmol) according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.82–6.91$ (m, 2H), 7.57 (t, $J = 8.1$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 107.79$ (d, $J = 24.14$ Hz), 114.47 (d, $J = 3.51$ Hz), 114.81 (qd, $J = 33.60, 12.78$ Hz), 122.40 (qd, $J = 271.61, 1.27$ Hz), 128.46 (qd, $J = 4.61, 3.05$ Hz), 146.05 (distorted dq, $J = 10.07, 0.78$ Hz), 160.60 (dq, $J = 257.70, 2.06$ Hz).

6.7. 1-Azido-4-methoxybenzene (*4f*)

The title compound was prepared in 11% yield (67 mg, 0.45 mmol) as a light yellow oil from 4-methoxyaniline (**3f**) (492 mg, 4 mmol) according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.79$ (s, 3H), 6.68–6.91 (m, 2H), 6.93–6.97 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.52, 115.08, 119.94, 132.30, 156.95$.

6.8. 4-Azido-2-fluoro-1-methoxybenzene (*4g*)

The title compound was prepared in 49% yield (330 mg, 1.97 mmol) as a brown solid from 3-fluoro-4-methoxyaniline (**3g**) (564 mg, 4 mmol) according to the general procedure. Mp = 56–57 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.87$ (s, 3H), 6.71–6.83 (m, 2H), 6.93 (t, $J = 9.0$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.57, 107.74$ (d, $J = 21.81$ Hz), 114.33–114.49 (m, 2 × C), 132.90 (d, $J = 8.57$ Hz), 145.03 (d, $J = 10.82$ Hz), 152.75 (d, $J = 248.11$ Hz).

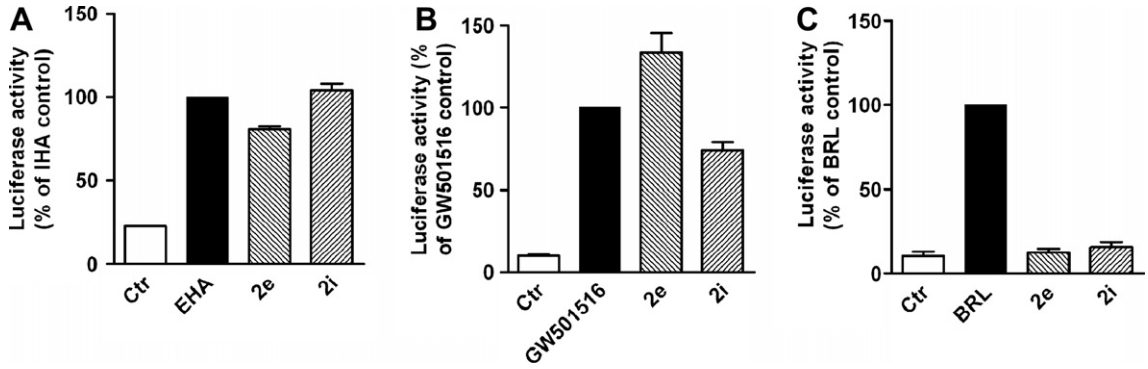


Fig. 4. Activation of the ligand-binding domain of PPARα (A), PPARδ (B), PPARγ (C) of triazoles **2e** and **2i** in comparison with known agonists in a luciferase-based transfection assay. Positive controls: PPARα: EHA ((2*E*,4*E*,8*Z*,11*Z*,14*Z*,17*Z*)-eicosa-2,4,8,11,14,17-hexaenoic acid); PPARδ: GW 501516 (**1**); PPARγ: BRL (rosiglitazone).

6.9. 1-Azido-4-trifluoromethoxybenzene (*4h*)

The title compound was prepared in 57% yield (215 mg, 1.06 mmol) as a light yellow oil from 4-trifluoromethoxyaniline (**3h**) (1.86 mmol) according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.01–7.06$ (m, 2H), 7.19–7.22 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 120.13$, 120.45 (q, $J = 257.16$ Hz), 122.61 (distorted q, $J = 0.66$ Hz), 138.82, 146.02 (q, $J = 1.96$ Hz).

6.10. 4-Azido-2-chloro-1-trifluoromethoxybenzene (*4i*)

The title compound was prepared in 77% yield (460 mg, 1.93 mmol) as an orange oil from 3-chloro-4-trifluoromethoxyaniline (**3i**) (528 mg, 2,5 mmol) according to the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.94$ (dd, $J = 8.82$, 2.70 Hz, 1H), 7.13 (d, $J = 2.68$ Hz, 1H), 7.30 (dd, $J = 8.82$, 1.26 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 118.27$, 120.46 (q, $J = 259.23$ Hz), 121.179, 123.88 (distorted q, $J = 1.08$ Hz), 128.95, 139.84, 142.04 (q, $J = 1.89$ Hz).

6.11. 4-Azido-2-fluoro-1-trifluoromethoxybenzene (*4j*)

The title compound was prepared in 49% yield (243 mg, 1.1 mmol) as an orange oil from 3-fluoro-4-trifluoromethoxyaniline (**3j**) (2.25 mmol) according to the general procedure. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.75–6.90$ (m, 2H), 7.20–7.33 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 108.32$ (d, $J = 22.15$ Hz), 114.86 (d, $J = 3.73$ Hz), 120.49 (qd, $J = 259.0$, 0.46 Hz), 124.92, 133.26 (dq, $J = 12.72$, 2.15 Hz), 140.49 (d, $J = 8.73$ Hz), 155.20 (d, $J = 254.50$ Hz).

6.12. 2-Methyl-4-(prop-2-ynylthio)phenol (*6*)

To a solution of *p*-mercapto-2-methylphenol (**5**) (140 mg, 1 mmol) in dry CH_3CN (20 mL) was added Cs_2CO_3 (326 mg, 1 mmol). To this mixture was added dropwise a solution of propargyl bromide (0.85 mmol) in dry CH_3CN (5 mL). The mixture was stirred for 2 h at r.t., then diluted with water and extracted with 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) affording 2-methyl-4-(prop-2-ynylthio)phenol in 67% yield (119 mg, 0.67 mmol) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.23–2.45$ (m, 4H), 3.50 (d, $J = 2.6$ Hz, 2H), 4.89 (s, 1H), 6.74 (d, $J = 8.2$ Hz, 1H), 7.26–7.33 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.64$, 24.60, 71.52, 80.28, 115.54, 124.71, 124.82, 131.94, 135.71, 154.03.

6.13. Ethyl 2-[2-methyl-4-(prop-2-ynylthio)phenoxy]acetate (*7*)

To a solution of 2-methyl-4-(prop-2-ynylthio)phenol (**6**) (178 mg, 1 mmol) in dry CH_3CN (20 mL) was added Cs_2CO_3 (489 mg, 1.5 mmol). To the mixture was added dropwise a solution of ethyl bromoacetate (1.4 mmol) in dry CH_3CN (5 mL). The mixture was stirred for 4 h under Ar at r.t., then diluted with water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) to obtain the title compound as a light yellow oil in 74% yield (196 mg, 0.74 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 7.14$ Hz, 3H), 2.22 (t, $J = 2.61$, 1H), 2.27 (s, 3H), 3.49 (d, $J = 2.60$ Hz, 2H), 4.26 (q, $J = 7.14$ Hz, 2H), 4.62 (s, 2H), 6.65 (d, $J = 8.12$ Hz, 1H), 7.27–7.33 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.09$, 16.09, 24.23, 61.27, 65.59, 71.47, 80.17, 111.55, 125.81, 128.19, 130.99, 135.10, 156.10, 168.74.

6.14. Ethyl 2-{2-methyl-4-[(1-phenyl-1H-1,2,3-triazol-4-yl) methylthio]phenoxy}acetate (*8a*)

General procedure: the alkyne **7** (1 mmol) and the azide (1 mmol) were solved in *t*-BuOH/H_2O (1:1, 10 mL). Sodium ascorbate (40 mg, 20 mol %) and copper sulfate (10 mg, 5 mol %) were added. The mixture was stirred at ambient temperature over night. A precipitate was formed. Water/ice (50 mL) was added, the precipitate was filtered off, washed with aqueous NH_3 (3.5% × 100 mL) and cold water. The precipitate was purified by column chromatography using hexane/ethyl acetate (4:1) as eluent. The title compound was prepared in 80% yield (234 mg, 0.61 mmol) as a white solid from **7** (200 mg, 0.76 mmol) and azidobenzene (**4a**) (90 mg, 0.76 mmol) according to the general procedure. Mp = 49–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.14$ Hz, 3H), 2.21 (s, 3H), 4.17–4.24 (m, 4H), 4.58 (s, 2H), 6.58 (d, $J = 8.42$ Hz, 1H), 7.14 (dd, $J = 2.15$, 8.41 Hz, 1H), 7.19 (d, $J = 1.65$ Hz, 1H), 7.35–7.49 (m, 3H), 7.60–7.64 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.05$, 16.05, 30.46, 61.23, 65.53, 111.63, 120.10, 120.35, 126.17, 128.28, 128.60, 129.63, 130.38, 134.59, 136.90, 145.74, 155.75, 168.71.

6.15. Ethyl 2-{2-methyl-4-[(1-p-tolyl-1H-1,2,3-triazol-4-yl) methylthio]phenoxy}acetate (*8b*)

The title compound was prepared in 92% yield (99 mg, 0.24 mmol) as a white solid from **7** (70 mg, 0.26 mmol) and 1-azido-4-methylbenzene (**4b**) (35 mg, 0.26 mmol) according to the general procedure. Mp = 99–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.14$ Hz, 3H), 2.21 (s, 3H), 2.37 (s, 3H), 4.16 (s, 2H), 4.21

(q, J = 7.14 Hz, 2H), 4.58 (s, 2H), 6.59 (d, J = 8.40 Hz, 1H), 7.14 (dd, J = 8.40, 2.17 Hz, 1H), 7.19 (d, J = 1.64 Hz, 1H), 7.25 (d, J = 8.22 Hz, 2H), 7.49–7.52 (m, 2H), 7.61 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.08, 16.07, 21.01, 30.54, 61.25, 65.57, 111.65, 120.07, 120.29, 126.31, 128.27, 130.12, 130.34, 134.57, 134.68, 138.68, 145.63, 155.74, 168.74.

6.16. Ethyl 2-{4-[(1-(3-fluoro-4-methylphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetate (**8c**)

The title compound was prepared in 59% yield (192 mg, 0.46 mmol) as a white solid from **7** (207 mg, 0.78 mmol) and 4-azido-2-fluoro-1-methylbenzene (**4c**) (118 mg, 0.78 mmol) according to the general procedure. Mp = 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.12 Hz, 3H), 2.19–2.27 (m, 6H), 4.13–4.23 (m, 4H), 4.57 (s, 2H), 6.57 (d, J = 8.38 Hz, 1H), 7.11–7.37 (m, 5H), 7.60 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.03, 14.19 (d, J = 3.26 Hz), 16.01, 30.41, 61.20, 65.48, 107.66 (d, J = 27.20 Hz), 111.60, 115.32 (d, J = 3.66 Hz), 119.95, 125.42 (d, J = 17.29 Hz), 126.09, 128.24, 130.34, 132.19 (d, J = 6.04 Hz), 134.55, 135.74 (d, J = 10.05 Hz), 145.83, 155.73, 161.14 (d, J = 247.07 Hz), 168.67.

6.17. Ethyl 2-{2-methyl-4-[(1-(4-trifluoromethylphenyl)-1H-1,2,3-triazol-4-yl)methylthio]phenoxy}acetate (**8d**)

The title compound was prepared in 96% yield (112 mg, 0.25 mmol) as a white solid from **7** (70 mg, 0.26 mmol) and 1-azido-4-(trifluoromethyl)benzene (**4d**) (48 mg, 0.26 mmol) according to the general procedure. Mp = 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.14 Hz, 3H), 2.21 (s, 3H), 4.17 (s, 2H), 4.22 (q, J = 7.14 Hz, 2H), 4.60 (s, 2H), 6.58 (d, J = 8.44 Hz, 1H), 7.13 (dd, J = 8.42, 2.17 Hz, 1H), 7.19 (d, J = 1.71 Hz, 1H), 7.63 (s, 1H), 7.75 (d, J = 8.88 Hz, 2H), 7.80 (d, J = 8.84 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.10, 16.12, 30.52, 61.32, 65.48, 111.59, 119.88, 120.29, 123.52 (q, J = 271.94 Hz), 125.94, 127.04 (q, J = 3.77 Hz), 128.42, 130.55 (q, J = 30.21 Hz), 130.69, 134.86, 139.33 (distorted q, J = 1 Hz), 146.39, 155.91, 168.76.

6.18. Ethyl 2-{4-[(1-(3-fluoro-4-trifluoromethylphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetate (**8e**)

The title compound was prepared in 77% yield (94 mg, 0.2 mmol) as a white solid from **7** (70 mg, 0.26 mmol) and 4-azido-2-fluoro-1-(trifluoromethyl)benzene (**4e**) (54 mg, 0.26 mmol) according to the general procedure. Mp = 84–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.14 Hz, 3H), 2.21 (s, 3H), 4.15 (s, 2H,), 4.21 (q, J = 7.14 Hz, 2H), 4.60 (s, 2H), 6.58 (d, J = 8.43 Hz, 1H), 7.12 (dd, J = 8.42, 2.1 Hz, 1H), 7.18 (d, J = 1.57 Hz, 1H), 7.53–7.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.07, 16.09, 30.45, 61.31, 65.42, 108.93 (d, J = 25.54 Hz), 111.58, 115.00 (d, J = 3.90 Hz), 118.15 (qd, J = 33.70, 12.65 Hz), 119.80, 122.01 (qd, J = 272.45, 1.15 Hz), 125.76, 128.44, 128.75 (qd, J = 4.58, 2.53 Hz), 130.70, 134.89, 140.76 (d, J = 10.30 Hz), 146.69, 155.93, 160.22 (dq, J = 258.74, 1.94 Hz), 168.72.

6.19. Ethyl 2-{4-[(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetate (**8f**)

The title compound was prepared in 72% yield (446 mg, 1.08 mmol) as a white solid from **7** (400 mg, 1.51 mmol) and 1-azido-4-methoxybenzene (**4f**) (225 mg, 1.51 mmol) according to the general procedure. Mp = 63–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.14 Hz, 3H), 2.22 (s, 3H), 3.83 (s, 3H), 4.17 (s, 2H), 4.22 (q, J = 7.14 Hz, 2H), 4.59 (s, 2H), 6.59 (d, J = 8.41 Hz, 1H), 6.94–7.00 (m, 2H), 7.15 (dd, J = 8.40, 2.10 Hz, 1H), 7.19 (d, J = 1.64 Hz, 1H), 7.52–7.56 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.12, 16.12, 30.58, 55.59, 61.30, 65.62, 111.68, 114.71, 120.28, 122.08, 126.37, 128.33, 130.37, 130.49, 134.61, 145.61, 155.78, 159.73, 168.79.

6.20. Ethyl 2-{4-[(1-(3-fluoro-4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetate (**8g**)

The title compound was prepared in 78% yield (255 mg, 0.59 mmol) as a white solid from **7** (200 mg, 0.76 mmol) and 4-azido-2-fluoro-1-methoxybenzene (**4g**) (127 mg, 0.76 mmol) according to the general procedure. Mp = 111–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.14 Hz, 3H), 2.20 (s, 3H), 3.90 (s, 3H), 4.15 (s, 2H), 4.21 (q, J = 7.14 Hz, 2H), 4.58 (s, 2H), 6.58 (d, J = 8.41 Hz, 1H), 7.02 (t, J = 8.78 Hz, 1H), 7.11–7.18 (m, 2H), 7.33 (ddd, J = 8.81, 2.53, 1.59 Hz, 1H), 7.42 (dd, J = 11.34, 2.58 Hz, 1H), 7.55 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.08, 16.08, 30.44, 56.46, 61.26, 65.53, 109.46 (d, J = 22.79 Hz), 111.64, 113.66 (d, J = 2.68 Hz), 116.19 (d, J = 3.87 Hz), 120.14, 126.13, 128.31, 130.07 (d, J = 8.79 Hz), 130.38, 134.60, 145.82, 147.95 (d, J = 10.53 Hz), 152.18 (d, J = 248.98 Hz), 155.78, 168.72.

6.21. Ethyl 2-{2-methyl-4-[(1-(4-trifluoromethoxyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]phenoxy}acetate (**8h**)

The title compound was prepared in 61% yield (214 mg, 0.46 mmol) as a white solid from **7** (200 mg, 0.76 mmol) and 1-azido-4-(trifluoromethoxy)benzene (**4h**) (154 mg, 0.76 mmol) according to the general procedure. Mp = 103–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.14 Hz, 3H), 2.20 (s, 3H), 4.15 (s, 2H), 4.21 (q, J = 7.14 Hz, 2H), 4.59 (s, 2H), 6.58 (d, J = 8.42 Hz, 1H), 7.12 (dd, J = 8.42, 2.03 Hz, 1H), 7.18 (d, J = 1.47 Hz, 1H), 7.33 (d, J = 8.30 Hz, 2H), 7.59 (bs, 1H), 7.65–7.70 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06, 16.08, 30.46, 61.27, 65.47, 111.57, 120.06, 120.28 (q, J = 258.25 Hz), 121.77, 122.18 (distorted q, J = 0.66 Hz), 125.99, 128.34, 130.58, 134.74, 135.31, 148.79 (q, J = 1.83 Hz), 155.83, 168.73.

6.22. Ethyl 2-{4-[(1-(3-chloro-4-trifluoromethoxyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetate (**8i**)

The title compound was prepared in 95% yield (360 mg, 0.72 mmol) as a white solid from **7** (200 mg, 0.76 mmol) and 4-azido-2-chloro-1-(trifluoromethoxy)benzene (**4i**) (180 mg, 0.76 mmol) according to the general procedure. Mp = 112–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.14 Hz, 3H), 2.21 (s, 3H), 4.15 (s, 2H), 4.21 (q, J = 7.14 Hz, 2H), 4.59 (s, 2H), 6.58 (d, J = 8.44 Hz, 1H), 7.12 (dd, J = 8.42, 2.08 Hz, 1H), 7.18 (d, J = 1.67 Hz, 1H), 7.44 (dd, J = 8.90, 1.28 Hz, 1H), 7.56–7.60 (m, 2H), 7.85 (d, J = 2.57 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.08, 16.10, 30.44, 61.30, 65.47, 111.60, 119.45, 119.47, 120.33 (q, J = 259.65 Hz), 121.69, 123.54 (distorted q, J = 1.22 Hz), 125.87, 128.40, 128.91, 130.60, 134.78, 135.73, 148.89 (q, J = 1.51 Hz), 146.46, 155.89, 168.72.

6.23. Ethyl 2-{4-[(1-(3-fluoro-4-trifluoromethoxyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetate (**8j**)

The title compound was prepared in 53% yield (82 mg, 0.17 mmol) as a yellow solid from **7** (85 mg, 0.32 mmol) and 4-azido-2-fluoro-1-(trifluoromethoxy)benzene (**4j**) (71 mg, 0.32 mmol) according to the general procedure. Mp = 80–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.14 Hz, 3H), 2.21 (s, 3H), 4.16 (s, 2H), 4.22 (q, J = 7.14 Hz, 2H), 4.60 (s, 2H), 6.58 (d, J = 8.44 Hz, 1H), 7.12 (dd, J = 8.40, 2.17 Hz, 1H), 7.19 (d, J = 1.62 Hz, 1H), 7.37–7.50 (m, 2H), 7.57 (s, 1H), 7.59–7.67 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.09, 16.12, 30.46, 61.32, 65.47, 109.96 (d, J = 23.34 Hz), 111.60, 115.96 (d, J = 4.05 Hz), 119.94, 120.33 (q, J = 260.02 Hz), 124.82,

125.86, 128.44, 130.66, 134.83, 135.60–136.80 (m, 2 × C), 146.51, 154.81 (d, $J = 255.53$ Hz), 155.92, 168.76.

6.24. 2-{2-Methyl-4-[(1-phenyl-1H-1,2,3-triazol-4-yl)methylthio] phenoxy}acetic acid (**2a**)

General procedure: to a stirred solution of ester (1 mmol) in THF (10 mL) and H_2O (5 mL) at 0 °C was added slowly 625 μL of 2.0 M LiOH. The reaction mixture was stirred until TLC indicated completion of the reaction and then diluted with 50 mL H_2O. The reaction mixture was washed with hexane (3 × 50 mL). The organic layers were then washed with H_2O (3 × 50 mL). The combined water phases were acidified with 0.1 M HCl and extracted with diethyl ether, dried over $MgSO_4$, concentrated and recrystallized from CH_2Cl_2. The title compound was prepared in 37% yield (77 mg, 0.22 mmol) as a white solid from **8a** (231 mg, 0.60 mmol) according to the general procedure. Mp = 138–139 °C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.15$ (s, 3H), 4.23 (s, 2H), 4.67 (s, 2H), 6.79 (d, $J = 8.46$ Hz, 1H), 7.18–7.24 (m, 2H), 7.45–7.50 (m, 1H), 7.56–7.61 (m, 2H), 7.83–7.86 (m, 2H), 8.57 (s, 1H), 12.97 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.81$, 29.15, 64.47, 111.91, 119.85, 121.21, 125.47, 126.89, 128.49, 129.37, 129.79, 130.06, 136.47, 144.92, 155.19, 170.03. MS (ESI) m/z 354.1 $[M-H]^-$, HRMS calcd for $C_{18}H_{17}N_3O_3S$ $[M]^+$: 355.0991; found 355.0989.

6.25. 2-{2-Methyl-4-[(1-p-tolyl-1H-1,2,3-triazol-4-yl)methylthio] phenoxy}acetic acid (**2b**)

The title compound was prepared in 58% yield (76 mg, 0.21 mmol) as a white solid from **8b** (142 mg, 0.36 mmol) according to the general procedure. Mp = 127–128 °C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.15$ (s, 3H), 2.37 (s, 3H), 4.22 (s, 2H), 4.67 (s, 2H), 6.78 (d, $J = 8.44$ Hz, 1H), 7.18–7.23 (m, 2H), 7.36 (d, $J = 8.17$ Hz, 2H), 7.72 (d, $J = 8.48$ Hz, 2H), 8.51 (s, 1H), 12.88 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.83$, 20.47, 29.20, 64.79, 111.92, 119.74, 121.10, 125.48, 126.90, 129.38, 130.12, 133.07, 134.25, 138.11, 144.78, 155.24, 170.11. MS (ESI) m/z 368.1 $[M-H]^-$, HRMS calcd for $C_{19}H_{19}N_3O_3S$ $[M]^+$: 369.1147; found 369.1141.

6.26. 2-{4-[(1-(3-Fluoro-4-methylphenyl)-1H-1,2,3-triazol-4-yl) methylthio]-2-methylphenoxy}acetic acid (**2c**)

The title compound was prepared in 48% yield (84 mg, 0.22 mmol) as a white solid from **8c** (190 mg, 0.46 mmol) according to the general procedure. Mp = 133–134 °C. ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.15$ (s, 3H), 2.29 (s, 3H), 4.22 (s, 2H), 4.67 (s, 2H), 6.78 (d, $J = 8.26$ Hz, 1H), 7.21 (d, $J = 10.02$ Hz, 2H), 7.49 (t, $J = 8.14$ Hz, 1H), 7.62–7.76 (m, 2H), 8.61 (s, 1H), 12.98 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.74$ (d, $J = 2.95$ Hz), 15.80, 29.13, 64.68, 106.97 (d, $J = 27.42$ Hz), 111.91, 115.36 (d, $J = 3.47$ Hz), 121.27, 124.58 (d, $J = 17.16$ Hz), 125.44, 126.90, 129.35, 132.59 (d, $J = 6.04$ Hz), 133.04, 135.49 (d, $J = 10.39$ Hz), 145.03, 155.20, 160.51 (d, $J = 244.34$ Hz), 170.04. MS (ESI) m/z 386.1, $[M-H]^-$, HRMS calcd for $C_{19}H_{18}FN_3O_3S$ $[M]^+$: 387.1053; found 387.1062.

6.27. 2-{2-Methyl-4-[(1-(4-trifluoromethylphenyl)-1H-1,2,3-triazol-4-yl)methylthio]phenoxy}acetic acid (**2d**)

The title compound was prepared in 66% yield (91 mg, 0.21 mmol) as a white solid from **8d** (144 mg, 0.32 mmol) according to the general procedure. Mp = 235–236 °C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.11$ (s, 3H), 4.18–4.20 (m, 4H), 6.67 (d, $J = 8.43$ Hz, 1H), 7.12–7.17 (m, 2H), 7.97 (d, $J = 8.59$ Hz, 2H), 8.12 (d, $J = 8.58$ Hz, 2H), 8.67 (s, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): $\delta = 16.00$, 29.56, 67.42, 112.04, 120.25, 121.41, 123.71 (q, $J = 272.05$ Hz), 123.59, 126.49, 127.08 (q, $J = 3.72$ Hz), 128.43 (q, $J = 32.42$ Hz), 129.77, 133.24, 139.18 (distorted q, $J = 1.12$ Hz), 145.50, 156.57, 172.38. MS (ESI) m/z 422.1, $[M-H]^-$, HRMS calcd for $C_{19}H_{16}F_3N_3O_3S$ $[M]^+$: 423.0864; found 423.0875.

6.28. 2-{4-[(1-(3-Fluoro-4-trifluoromethyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetic acid (**2e**)

The title compound was prepared in 42% yield (102 mg, 0.23 mmol) as a white solid from **8e** (258 mg, 0.55 mmol) according to the general procedure. Mp = 134–135 °C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.14$ (s, 3H), 4.24 (s, 2H), 4.67 (s, 2H), 6.77 (d, $J = 8.46$ Hz, 1H), 7.17–7.23 (m, 2H), 7.96 (d, $J = 3.69$ Hz, 2H), 8.12 (d, $J = 12.10$ Hz, 1H), 8.77 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.82$, 29.16, 64.80, 108.62 (d, $J = 25.83$ Hz), 111.93, 115.61 (d, $J = 3.50$ Hz), 115.89 (qd, $J = 32.97$, 12.30 Hz), 121.66, 122.23 (q, $J = 272.45$ Hz), 125.36, 126.99, 129.00–129.06 (m), 129.50, 133.17, 140.90 (d, $J = 10.76$ Hz), 145.74, 155.35, 159.35 (dq, $J = 254.53$, 2.07 Hz), 170.14. MS (ESI) m/z 440.0, $[M-H]^-$, HRMS calcd for $C_{19}H_{15}F_4N_3O_3S$ $[M]^+$: 441.0770; found 441.0776.

6.29. 2-{4-[(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl) methylthio]-2-methylphenoxy}acetic acid (**2f**)

The title compound was prepared in 40% yield (33 mg, 0.08 mmol) as a white solid from **8f** (80 mg, 0.2 mmol) according to the general procedure. Mp = 84–85 °C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.15$ (s, 3H), 3.82 (s, 3H), 4.21 (s, 2H), 4.66 (s, 2H), 6.78 (d, $J = 8.44$ Hz, 1H), 7.09–7.13 (m, 2H), 7.18–7.23 (m, 2H), 7.74 (d, $J = 9.04$ Hz, 2H), 8.45 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.82$, 29.20, 55.45, 64.84, 111.90, 114.76, 121.18, 121.51, 125.43, 126.85, 129.35, 129.91, 133.03, 144.61, 155.25, 159.09, 170.11. MS (ESI) m/z 384.1, $[M-H]^-$, HRMS calcd for $C_{19}H_{19}N_3O_4S$ $[M]^+$: 385.1096; found 385.1098.

6.30. 2-{4-[(1-(3-Fluoro-4-methoxyphenyl)-1H-1,2,3-triazol-4-yl) methylthio]-2-methylphenoxy}acetic acid (**2g**)

The title compound was prepared in 44% yield (103 mg, 0.26 mmol) as a white solid from **8g** (255 mg, 0.59 mmol) according to the general procedure. Mp = 128–129 °C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.15$ (s, 3H), 3.91 (s, 3H), 4.22 (s, 2H), 4.68 (s, 2H), 6.78 (d, $J = 8.46$ Hz, 1H), 7.18–7.24 (m, 2H), 7.33–7.39 (m, 1H), 7.64–7.68 (m, 1H), 7.81 (dd, $J = 12.09$, 2.59 Hz, 1H), 8.55 (s, 1H), 12.98 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.82$, 29.18, 56.26, 64.70, 108.62 (d, $J = 22.92$ Hz), 111.92, 114.36 (d, $J = 2.50$ Hz), 116.18 (d, $J = 3.63$ Hz), 121.30, 125.52, 126.93, 129.34, 129.50 (d, $J = 9.07$ Hz), 133.04, 144.90, 147.10 (d, $J = 10.38$ Hz), 151.19 (d, $J = 245.72$ Hz), 155.21, 170.07. MS (ESI) m/z 402.1, $[M-H]^-$, HRMS calcd for $C_{19}H_{18}FN_3O_4S$ $[M]^+$: 403.1002; found 403.0999.

6.31. 2-{2-Methyl-4-[(1-(4-trifluoromethoxyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]phenoxy}acetic acid (**2h**)

The title compound was prepared in 53% yield (80 mg, 0.18 mmol) as a white solid from **8h** (160 mg, 0.34 mmol) according to the general procedure. Mp = 149–150 °C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.15$ (s, 3H), 4.24 (s, 2H), 4.68 (s, 2H), 6.78 (d, $J = 8.37$ Hz, 1H), 7.17–7.24 (m, 2H), 7.59 (d, $J = 8.61$ Hz, 2H), 7.97–8.02 (m, 2H), 8.64 (s, 1H), 12.96 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.80$, 29.14, 64.69, 111.89, 119.92 (q, $J = 256.98$ Hz), 121.50, 121.83, 122.47, 125.39, 126.92, 129.45, 133.12, 135.33, 145.19, 147.69 (q, $J = 1.72$ Hz), 155.24, 170.06. MS (ESI) m/z 438.1, $[M-H]^-$, HRMS calcd for $C_{19}H_{16}F_3N_3O_4S$ $[M]^+$: 439.0814; found 439.0823.

6.32. 2-{4-[(1-(3-Chloro-4-trifluoromethoxyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetic acid (**2i**)

The title compound was prepared in 47% yield (160 mg, 0.34 mmol) as a white solid from **8i** (360 mg, 0.72 mmol) according to the general procedure. Mp = 157–158 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.15 (s, 3H), 4.24 (s, 2H), 4.68 (s, 2H), 6.78 (d, J = 8.50 Hz, 1H), 7.18–7.25 (m, 2H), 7.81 (dd, J = 8.98, 1.28 Hz, 1H), 8.02 (dd, J = 8.97, 2.64 Hz, 1H), 8.29 (d, J = 2.60 Hz, 1H), 8.74 (s, 1H), 12.98 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.80, 29.11, 64.68, 111.91, 119.91 (q, J = 259.06 Hz), 120.19, 121.69, 122.15, 124.34 (distorted q, J = 1.06 Hz), 125.34, 126.91, 127.34, 129.41, 133.08, 135.95, 143.38 (q, J = 1.76 Hz), 145.43, 155.23, 170.03. MS (ESI) m/z 472.3 $[M-H]^-$, HRMS calcd for $C_{19}H_{15}ClF_3N_3O_4S$ $[M]^+$: 473.0424; found 473.0429.

6.33. 2-{4-[(1-(3-Fluoro-4-trifluoromethoxyphenyl)-1H-1,2,3-triazol-4-yl)methylthio]-2-methylphenoxy}acetic acid (**2j**)

The title compound was prepared in 63% yield (76 mg, 0.17 mmol) as a white solid from **8j** (130 mg, 0.27 mmol) according to the general procedure. Mp = 140–141 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.15 (s, 3H), 4.24 (s, 2H), 4.67 (s, 2H), 6.78 (d, J = 8.42 Hz, 1H), 7.17–7.24 (m, 2H), 7.71–7.95 (m, 2H), 8.06–8.24 (m, 1H), 8.71 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.77, 30.05, 65.81, 110.64 (d, J = 23.67 Hz), 112.87, 117.63 (d, J = 3.83 Hz), 122.62, 124.24 (q, J = 273.55 Hz), 126.14, 126.34, 127.85, 130.39, 134.04, 135.54 (distorted dq, J = 12.33, 1.95 Hz), 137.23 (d, J = 9.54 Hz), 146.43, 154.79 (d, J = 251.38 Hz), 156.28, 171.10. MS (ESI) m/z 456.1 $[M-H]^-$, HRMS calcd for $C_{19}H_{15}F_4N_3O_4S$ $[M]^+$: 457.0719; found 457.0718.

6.34. 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 [15], 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. Non-linear regression curves and EC_{50}-values were calculated with GraphPad Prism, version 4.

6.35. 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.

Acknowledgment

Fruitful discussions with professor Arild Chr. Rustan are gratefully acknowledged.

References and notes

[1] D.J. Mangelsdorf, R.M. Evans, The RXR heterodimers and orphan receptors. Cell 83 (1995) 841–850.
[2] B. Goke, I. Gause-Nilsson, A. Persson, The effects of tesaglitazar as add-on treatment to metformin in patients with poorly controlled type 2 diabetes. Diab. Vasc. Dis. Res. 4 (2007) 204–213.
[3] P.T.W. Cheng, R. Mukherjee, PPARs as targets for metabolic and cardiovascular diseases. Mini-Rev. Med. Chem. 5 (2005) 741–753.
[4] A.Z. Fernandez, PPARs as targets for the modulation of cardiovascular risk factors associated with the metabolic syndrome. Curr. Opin. Invest. Drugs 5 (2004) 936–940.
[5] (a) M.L. Sznaidman, C.D. Haffner, P.R. Maloney, A. Fivush, E. Chao, D. Goreham, M.L. Sierra, C. LeGrumelec, H.E. Xu, V.G. Montana, M.H. Lambert, T.M. Willson, W.R. Oliver Jr., D.D. Sternbach, Novel selective small molecule agonists for peroxisome proliferator-activated receptor δ (PPARδ) – synthesis and biological activity. Bioorg. Med. Chem. Lett. 13 (2003) 1517–1521;
(b) W.R. Oliver Jr., J.L. Shenk, M.R. Snaith, C.S. Russell, K.D. Plunket, N.L. Bodkin, M.C. Lewis, D.A. Winegar, M.L. Sznaidman, M.H. Lambert, H.E. Xu, D. D. Sternbach, S.A. Kliewer, B.C. Hansen, T.M. Willson, A selective peroxisome proliferator-activated receptor δ agonist promotes reverse cholesterol transport. Proc. Natl. Acad. Sci. U.S.A. 98 (2001) 5306–5311.
[6] (a) L. Shen, Y. Zhang, A. Wang, E. Sieber-McMaster, X. Chen, P. Pelton, J.Z. Xu, M. Yang, P. Zhu, L. Zhou, M. Reuman, Z. Hu, R. Russell, A.C. Gibbs, H. Ross, K. Demarest, W.V. Murray, G.-H. Kuo, Synthesis and structure–activity relationships of thiadiazole-derivatives as potent and orally active peroxisome proliferator-activated receptors α/δ dual agonists. Bioorg. Med. Chem. 16 (2008) 3321–3341;
(b) L. Shen, Y. Zhang, A. Wang, E. Sieber-McMaster, X. Chen, P. Pelton, J.Z. Xu, M. Yang, P. Zhu, L. Zhou, M. Reuman, Z. Hu, R. Russell, A.C. Gibbs, H. Ross, K. Demarest, W.V. Murray, G.-H. Kuo, Synthesis and identification of [1,2,4] thiadiazole derivatives as a new series of potent and orally active dual agonists of peroxisome proliferator-activated receptors α and δ. J. Med. Chem. 50 (2007) 3954–3963.
[7] (a) V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. Angew. Chem., Int. Ed. 41 (2002) 2596–2599;
(b) C.W. Tornøe, C. Christensen, M. Meldal, Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. J. Org. Chem. 67 (2002) 3057–3064.
[8] H.C. Kolb, K.B. Sharpless, The growing impact of click chemistry on drug discovery. Drug Discov. Today 8 (2003) 1128–1137.
[9] S. Kim, M. Cho, T. Lee, S. Lee, H.-Y. Min, S.K. Lee, Design, synthesis, and preliminary biological evaluation of a novel triazole analogue of ceramide. Bioorg. Med. Chem. Lett. 17 (2007) 4584–4587.
[10] J. Li, M. Zheng, W. Tang, P.-L. He, W. Zhu, T. Li, J.-P. Zuo, H. Liu, H. Jiang, Syntheses of triazole-modified zanamivir analogues via click chemistry and anti-AIV activities. Bioorg. Med. Chem. Lett. 16 (2006) 5009–5013.
[11] P.L. Suarez, Z. Gándara, G. Gómez, Y. Fall, Vitamin D and click chemistry. Part 1: a stereoselective route to vitamin D analogues with triazole rings in their side chains. Tetrahedron Lett. 45 (2004) 4619–4625.
[12] W.G. Lewis, L.G. Green, F. Grynszpan, Z. Radic, P.R. Carlier, P. Taylor, M.G. Finn, K.B. Sharpless, Click chemistry in situ: acetylcholinesterase as a reaction vessel for the selective assembly of a femtomolar inhibitor from an array of building blocks. Angew. Chem., Int. Ed. 41 (2002) 1053–1057.
[13] (a) H.G. Grimm, On the systematic arrangement of chemical compounds from the perspective of research on atomic composition and on some challenges in experimental chemistry. Naturwissenschaften 17 (1929) 535–540;
(b) L.B. Kier, L.H. Hall, Bioisosterism: quantitation of structure and property effects. Chem. Biodivers. 1 (2004) 138–151.

[14] G.C. Tron, T. Pirali, R.A. Billington, P.L. Canonico, G. Sorba, A.A. Genazzani, Click chemistry reactions in medicinal chemistry: applications of the 1,3-dipolar cycloaddition between azides and alkynes. Med. Res. Rev. 28 (2008) 278–308.
[15] A.J. Wensaas, A.C. Rustan, K. Lovstedt, B. Kull, S. Wikstrom, C.A. Drevon, S. Hallen, Cell-based multiwell assays for the detection of substrate accumulation and oxidation. J. Lipid Res. 48 (2007) 961–967.
[16] P. Balakumar, M. Rose, M. Singh, PPAR ligands: are they potential agents for cardiovascular disorders? Pharmacology 80 (2007) 1–10.
[17] R. Huisgen, G. Szeimies, L. Moebius, 1,3-Dipolar cycloadditions. XXXII. Kinetics of the addition of organic azides to carbon–carbon multiple bonds. Chem. Ber. 100 (1967) 2494–2507.
[18] C.-K. Sha, A.K. Mohanakrishnan, Azides. in: A. Padwa, W.H. Pearson (Eds.), Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products. John Wiley & Sons Inc., New Jersey, 2003, pp. 623–679.
[19] K. Odlo, J. Hentzen, J. Fournier, S. Ducki, O.A.B.S.M. Gani, I. Sylte, M. Skrede, V. A. Florenes, T.V. Hansen, 1,5-Disubstituted 1,2,3-triazoles as cis-restricted analogues of combretastatin A-4: synthesis, molecular modeling and evaluation as cytotoxic agents and inhibitors of tubulin. Bioorg. Med. Chem. 16 (2008) 4829–4838.
[20] Z.-L. Wei, A.P. Kozikowski, A short and efficient synthesis of the pharmacological research tool GW 501516 for the peroxisome proliferator-activated receptor δ. J. Org. Chem. 68 (2003) 9116–9118.
[21] J.-i. Kasuga, D. Yamasaki, Y. Araya, A. Nakagawa, M. Makishima, T. Doi, Y. Hashimoto, H. Miyachi, Design, synthesis, and evaluation of a novel series of α-substituted phenylpropanoic acid derivatives as human peroxisome proliferator-activated receptor (PPAR) α/δ dual agonists for the treatment of metabolic syndrome. Bioorg. Med. Chem. 14 (2006) 8405–8414.
[22] P. Balakumar, M. Rose, S.S. Ganti, P. Krishan, M. Singh, PPAR dual agonists: are they opening Pandora's Box? Pharmacol. Res. 56 (2007) 91–98.