Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 4144–4149
Bioorganic & Medicinal Chemistry Letters

Novel selective PPARδ agonists: Optimization of activity by modification of alkynylallylic moiety

Miroslav Havranek,[a,*] Per Sauerberg,[b] John P. Mogensen,[b] Pavel Kratina,[a] Claus B. Jeppesen,[b] Ingrid Pettersson[b] and Pavel Pihera[a]

[a]*RE&D VÚFB, s.r.o., Poděbradská 56/186, 180 66 Praha 9, Czech Republic*
[b]*Novo Nordisk A/S, Novo Nordisk Park, DK-2670 Måløv, Denmark*

Received 29 March 2007; revised 17 May 2007; accepted 17 May 2007
Available online 21 May 2007

Abstract—Y-shaped molecules bearing alkynylallylic moieties were found to be potent and selective PPARδ activators. The alkynylallylic moiety was synthesized from alkyn-1-ols by hydroalumination followed by a cross-coupling reaction. Series of active compounds **6** were obtained by stepwise changing the structure of the known PPARpan agonist **5** into Y-shaped compounds. The most active and selective compound, **6f**, had a PPARδ potency of 0.13 μM, which is 50-fold more potent than compound **5**.
© 2007 Elsevier Ltd. All rights reserved.

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor gene superfamily.[1,2] They play a central role in regulating the storage and catabolism of dietary fat. There are three PPAR subtypes: PPARα, PPARγ, and PPARδ.[3] Synthetic ligands for PPARα and PPARγ have been known for decades and the function of the receptors is well studied.[4–6] The human PPARδ receptor was cloned in the early 1990s[7] and many research groups have been trying to prepare selective ligands to study the biological function and possible application in human therapy.

PPAR agonist can be regarded to consist of three parts: a head group, a linker, and a lipophilic tail group. The head group may consist of a phenyl ring bearing a carboxylate functionality.[9] Examination of the ligand-binding domain in the PPARδ receptor revealed a Y-shaped pocket. One of the first selective and potent PPARδ agonists was GW501516 (**1**).[8] Recently, agonist **2** was found by optimization of hits from a high-throughput screening.[9,10] The structure of compound **3** fitted the cavity of the receptor well, according to docking experiment into a co-crystal structure of the PPARδ ligand-binding domain and GW2433.[11,14] This finding is in an agreement with Epple's recent finding, where Y-shaped 1,3,5-trisubstituted aryls (e.g., **4**) were found to be potent and selective δ agonists (Fig. 1).[12]

We investigated the possibility to obtain selective PPARδ agonists by stepwise changing the structure of the known PPARpan agonist **5**,[13] with first the head group of **1** and then with a Y-shaped tail group consisting of the conformationally restricted phenylalkynylallyl getting compounds of the general structure **6** (Fig. 2).

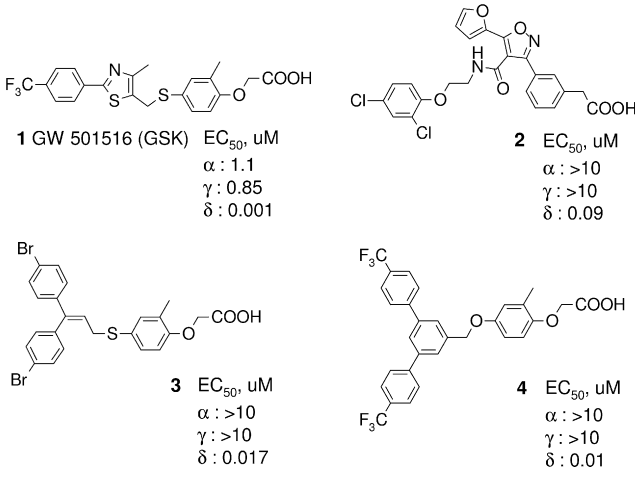


Figure 1. Reported selective PPARδ agonists.[8,10–12]

Keywords: Nuclear receptor; Peroxisome proliferator-activated receptor δ; PPAR agonists; Hydroalumination; Substituted allyl alcohols.
* Corresponding author. Tel.: +420 266 107 827; fax: +420 266 107 852; e-mail: havranek@readvufb.cz

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.05.051

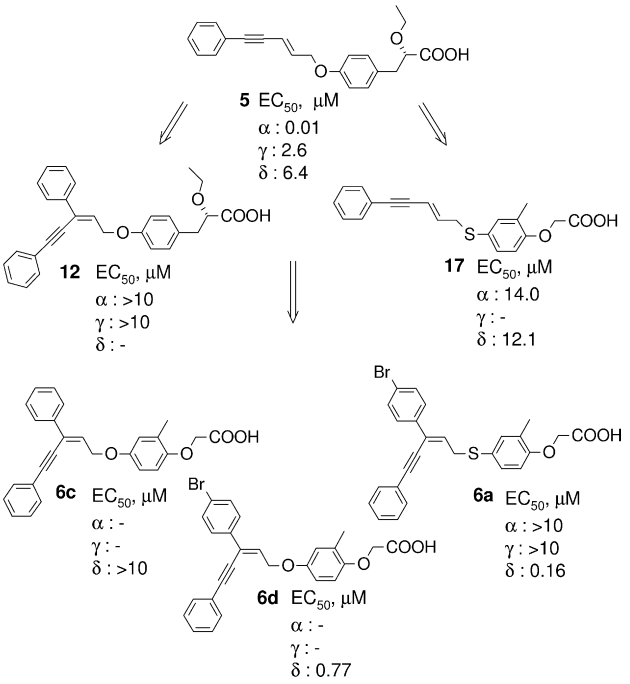
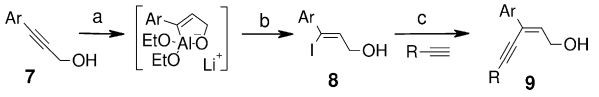


Figure 2. Graphic evolution of the program.

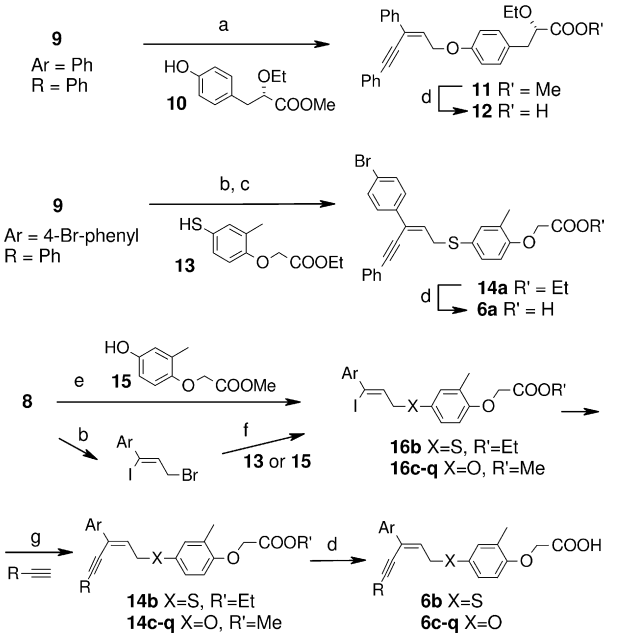
The alkynylallylic tail group was synthesized using a method leading to substituted allylic alcohols with defined stereochemistry. The preparation of the allyliodide intermediate (**8**) was accomplished using hydroalumination[15] followed by a cross-coupling reaction (Scheme 1). The stereochemistry was set-up by formation of the cyclic hydroalumination product. After quench of this product with iodine the (*Z*)-3-iodoallylic alcohol was obtained (**8**). The configuration was retained during the subsequent Sonogashira cross-coupling reactions giving alkynylallylic alcohols (**9**).

Coupling with the phenol head group, **10**, was accomplished under Mitsunobu reaction condition to give the ester **11**, which was hydrolyzed to the desired carboxylic acid **12** (Scheme 2). Thioether **6a** was prepared by conversion of allylic alcohol **9** into bromide and subsequent reaction with thiol **13**. Hydrolysis of the ester afforded the acid **6a**. An alternative method was developed in the preparation of some acids **6**. 3-Iodoallylic alcohol **8** was coupled first with the head group **13** or **15** followed by Sonogashira cross-coupling reaction to give **14**.[16] This methodology allowed the preparation of a wide number of different compounds in the late stage of the synthesis.

It was also found that the coupling with head groups **13** or **15** gave a better yield using a two-step approach, than



Scheme 1. Reagents and conditions: (a) i—$LiAlH_4$, THF, 0 °C, 3 h; ii—$(MeO)_2CO$, 0.5 h; (b) I_2, THF, 0 °C, overnight; (c) $Pd(PPh_3)_2Cl_2$, CuI, diisopropyl amine, THF, 65 °C, overnight.



Scheme 2. Ar and R groups are listed in Table 1. Reagents and conditions: (a) di-2-pyridyl azadicarboxylate, THF, rt, 48 h, 50%; (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, overnight; (c) THF/CH_2Cl_2 5:6, DIPEA, rt, overnight, 65%; (d) LiOH, THF/MeOH/H_2O 3:1:1, rt, 1–2 h; (e) diisopropyl azadicarboxylate, THF, rt, overnight; (f) reaction with **13**: THF/CH_2Cl_2 5:6, DIPEA, rt, overnight; reaction with **15**: Cs_2CO_3, MeCN, rt, overnight; (g) $Pd(PPh_3)_2Cl_2$, CuI, diisopropyl amine, THF, 65 °C.

the one-step Mitsunobu reaction. First the alcohol was converted to the allyllic bromide and then the bromine was substituted with thiophenolate (salt of **13**) or with phenolate (salt of **15**). $Pd(PPh_3)_2Cl_2$ was used as a catalyst for Sonogashira reaction. This catalyst was selective for the reaction with vinylic iodine of **16** over the aromatic bromide (**14d–m**). This selectivity was not obtained using the Fu catalytic conditions (*t*-Bu_3P, $Pd(PhCN)_2Cl_2$).[17]

The aromatic bromine in **14d** was used for the synthesis of **6n**. For this reaction the modified Fu conditions[18,19] using thiophen stannane[20] were used. Preparations of thioether analogs using **13** were only accomplished with a few substituents. The stability of thioethers depended for unknown reason on the substituents. E.g. compounds **6a** and **b** were successively prepared, whereas the preparation of the compounds **6r–t** (Fig. 3) failed, due to decomposition of final compounds.

A few heteroaromatic derivatives were also synthesized. The starting propargylic alcohols (**7**) were prepared

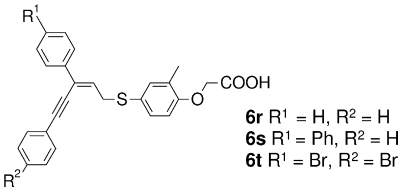
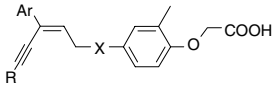
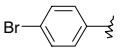
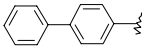
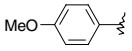
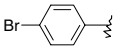
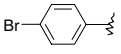
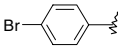
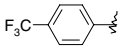
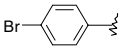
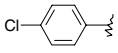
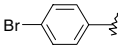
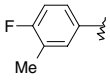
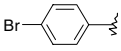
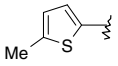
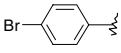
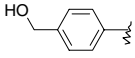
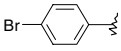
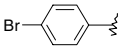
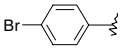
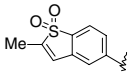
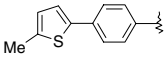
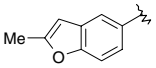
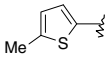
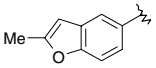
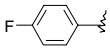
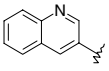


Figure 3. Examples of unstable thioethers.

Table 1. Activity of compounds of the general structure **6** in the hPPAR transactivation assay



Compound	Ar	R	X	hPPARα		hPPARγ		hPPARδ	
				EC_{50} (μM)	% max	EC_{50} (μM)	% max	EC_{50} (μM)	% max
6a			S	>10	>24	>10	>10	0.16	172
6b			S	>10	>58	>10	>33	0.011	176
6c			O	—	<10	—	<10	>10	>121
6d			O	—	<10	—	<10	0.77	174
6e			O	>10	>22	—	<10	0.24	199
6f			**O**	**>10**	**>19**	—	**<10**	**0.13**	**185**
6g			O	>10	>12	—	<10	0.32	184
6h			O	>10	>11	—	<10	2.0	177
6i			O	>10	>15	—	<10	0.22	184
6j			O	>10	>12	>10	>13	0.49	214
6k			O	>10	>34	>10	>28	3.0	23
6l			O	—	<10	—	<10	>10	>131
6m			O	—	<10	—	<10	1.2	159
6n			O	>10	>60	>10	>12	3.9	214
6o			O	5.8	<10	>10	23	0.15	230
6p			O	>10	>41	>10	>11	0.29	188
6q			O	4.1	33	6.6	28	0.29	172
NNC 61-4655 (**5**)				0.01	100	2.6	96	6.4	152
Rosiglitazone				>10	>24	0.3	100	—	<10
GW501516				3.9	68	>10	>22	0.008	272

Compounds were tested in at least three separate experiments in at least five concentrations ranging from 0.001 to 30 μM. EC_{50} is the concentration giving 50% of the maximal activity observed for a given compound. For each compound the efficacy (% max) is given as a relative compared to the maximal activity of NNC 61-4655 (**5**) for PPARα, Rosiglitazone for PPARγ and Carbacyclin for PPARδ. The results are expressed as means and ± SEM was less than 15%. If a plateau was not reached at the highest concentration of compound tested (30 μM), the effect at this concentration was calculated, and the maximal effect is indicted to be grater than this value. In such cases the EC_{50} was assigned as >10 μM. If the maximal effect of a compound was less than 10% no EC_{50} could be calculated.

from the haloaromatics[21] by Sonogashira reaction.[22] Hydroalumination reaction gave again isomerically pure intermediates **8**. The yields of the reactions were however lower than in the previous cases. Next steps were performed by standard procedures, except for the synthesis of the quinoline derivative, where iodoalcohol **8**

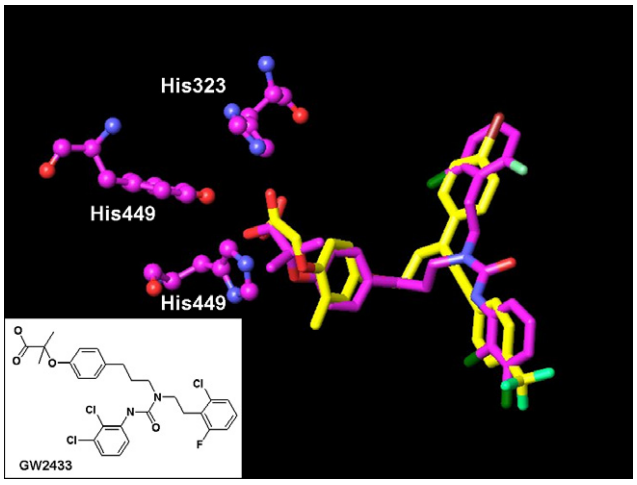


Figure 4. **6f** (yellow) docked into the crystal structure of the ligand binding domain of the PPARδ receptor crystallized with GW2433 (magenta). H323, H449, and Y473 are shown as ball-and-stick.

was converted into allylic chloride by reaction with thionyl chloride in CH_2Cl_2.

The structural starting point was the known compound **5**, which is a PPARpan agonist with high PPARα potency.[13] Replacement of the head group (the moiety bearing the carboxyl) with the one being used in GW501516 (**1**) decreased α and γ activity[25] giving the dual PPARα, δ agonist, **17** (Fig. 2). Modification of the tail group of compound **5** with the Y-shaped alkynylallylic group gave compound **12** which had decreased the PPARα, γ, and δ potency. The combination of both "new" head and tail group, gave a selective PPARδ agonist (**6c**) with low potency. Bromine substitution on the tail group (**6d**) increased the PPARδ potency. The thioether analog **6a** exhibited even higher PPARδ potency.

The synthesis of a series of thioether analogs of compound **6a** was attempted, but many of the thioethers were unstable and decomposed during the work-up. Compound **6b** was one of few stable compounds which exhibited very good PPARδ potency (Table 1).

Because of the instability of thioethers attention was turned back to ether bridged compounds. A large set of alkynylallylic ethers with diverse substituents were synthesized and screened (Table 1). Introduction of a hydrophobic bromine group in the Ar group in **6c** gave compound **6d** with improved PPARδ activity. This reflected that the hydrophobic pocket was better filled up by the bromophenyl group compared with the unsubstituted phenyl ring. In the series of compounds **6d**–**m**, only the acetylenic substituent (R) was altered. Many compounds exhibited higher potency and efficacy on PPARδ activity compared to **6d**, while good selectivity was retained. Generally, aromatic and non-polar substituents exhibited good activity (**6d**–**g**, **i**), while bulky substituents and polar groups decreased the activity (**6k**–**m**). Compound **6h** had a different substitution pattern in the phenyl ring and this resulted in a decreased PPARδ potency. Compound **6j**, having an OH group, exhibited a similar activity profile as **6d**. Replacement of the bromophenyl group (Ar group, Table 1) with a heteroaryl group did not change the activity significantly (**6n** vs. **6d**; **6o** vs. **6i**). The quinoline derivative gained PPARδ activity but lost the selectivity (**6q** vs. **6d**). The benzofuran derivatives **6o** and **p** exhibited good activity and selectivity.

Compound **6f**, which exhibited good PPARδ potency and good selectivity, was docked into the crystal structure of the ligand binding domain of the PPARδ receptor crystallized with GW2433 (1GWX).[14,26] The Y-shaped molecule **6f** adopted similar conformation as the PPAR pan-agonist GW2433 (Fig. 4). The reduced conformational flexibility of **6f** in comparison to GW2433 resulted in higher PPARδ selectivity. Lipophilic Br and CF_3 groups attached on the phenyl rings helped better filling up the hydrophobic cavity. Electronic effects of both the substituents also played the role in the charge distribution in the tail group and thus in interactions between ligand and the cavity of the receptor.

In conclusion, Y-shaped compounds of the general structure **6** were found to be selective and potent PPARδ activators. Good activity and selectivity was obtained by proper combination of both substituents on the allylic tail group. Compound **6f** exhibited good PPARδ potency combined with good selectivity.

Acknowledgments

The technical assistance of D. D. Andersen, P. Kovarova, M. Jelinkova, J. Novak, and V. Balsanek is greatly appreciated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.05.051.

References and notes

1. Issemann, I.; Green, S. *Nature* **1990**, *347*, 645.
2. Mangelsdorf, D.; Evans, R. M. *Cell* **1995**, *83*, 841.
3. A unified nomenclature system for the nuclear receptor superfamily. *Cell* **1999**, *97*, 161.
4. Chilcott, J.; Tappenden, P.; Jones, M. L.; Wright, J. P. *Clin. Therap.* **2001**, *23*, 1792.
5. Boyle, P. J.; King, A. B.; Olansky, L.; Marchetti, A.; Lau, H.; Magar, R.; Martin, J. *Clin. Therap.* **2002**, *24*, 3, 378.
6. Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J.-C. *Circulation* **1998**, *98*, 2088.
7. Schmidt, A.; Endo, N.; Rutledge, S. J.; Vogel, R.; Schinar, D.; Rodan, G. A. *Mol. Endocrinol.* **1992**, *6*, 1634.
8. Sznaiman, M. L.; Haffner, C. D.; Maloney, P. R.; Fivush, A.; Chao, E.; Goreham, D.; Sierra, M. L.; LeGrumelec, C.; Xu, H. E.; Montana, V. G.; Lambert, M. H.; Willsom, T. M.; Oliver, W. R., Jr.; Sternbach, D. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1517.

9. Epple, R.; Russo, R.; Azimioara, M.; Cow, C.; Xie, Y.; Wang, X.; Wityak, J.; Karanewsky, D.; Gerken, A.; Iskandar, M.; Saez, E.; Seidel, H. M.; Tian, S.-S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4376.
10. Epple, R.; Azimioara, M.; Russo, R.; Xie, Y.; Wang, X.; Cow, C.; Wityak, J.; Karanewsky, D.; Barsulaya, B.; Kreusch, A.; Tuntland, T.; Gerken, A.; Iskandar, M.; Saez, E.; Seidel, H. M.; Tian, S.-S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5488.
11. Sauerberg, P.; Olsen, G. S.; Jeppesen, L.; Mogensen, J. P.; Pettersson, I.; Jeppesen, C. B.; Daugaard, J. R.; Galsgaard, E. D.; Ynddal, L.; Fleckner, J.; Panajotova, V.; Polivka, Z.; Pihera, P.; Havranek, M.; Wulff, E. M. *J. Med. Chem.* **2007**, *50*, 1495.
12. Epple, R.; Ayimioara, M.; Russo, R.; Bursulaya, B.; Tian, S.-S.; Gerken, A.; Iskandar, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2969.
13. Deussen, H.-J.; Jeppesen, L.; Schärer, N.; Junager, F.; Betzen, B.; Weber, B.; Weil, V.; Mozer, S. J.; Sauerberg, P. *Org. Process Res. Dev.* **2004**, *8*, 363.
14. Xu, H. E.; Lambert, M. H.; Montana, V. G.; Parks, D. J.; Blanchard, S. G.; Brown, P. J.; Sternbach, D. D.; Lehmann, J. M.; Wisly, G. B.; Willson, T. M.; Kliever, S. A.; Milburn, M. V. *Mol. Cell* **1999**, *3*, 397.
15. Correy, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.
16. General procedure for the preparation of compounds **6**.*Hydroalumination (the preparation of iodide* **8**): NaOMe (0.027 g, 0.5 mmol) was added to a 1 M solution of $LiAlH_4$ in THF (6 mL, 6 mmol). The mixture was cooled to 0 °C and a solution of the appropriate alk-2-yn-1-ol (**7**) [22,23] (5 mmol) in THF (10 mL) was slowly added. The reaction mixture was stirred for 3 h under nitrogen atmosphere at 0 °C and dimethyl carbonate (0.7 mL, 8 mmol) or ethyl acetate (1 mL, 10 mmol) was added. The mixture was stirred for 0.5 h without cooling, then cooled to 0 °C and a solution of iodine (1.52 g, 6 mmol) in THF (10 mL) was added. The mixture was left in a refrigerator (4 °C) overnight. Then MeOH (2 mL) was added, the mixture was stirred for 0.5 h at rt and poured into water, acidified with HCl, and extracted with ethyl acetate (3 × 50 mL). Combined organic layers were washed with aqueous solution of sodium thiosulfate (5%, 100 mL) to remove excess of iodine, dried with sodium sulfate, and concentrated. The residue was purified by column chromatography (silica gel) giving substituted 3-iodoprop-2-en-1-ol. E.g. (*Z*)-3-(4-bromophenyl)-3-iodo-prop-2-en-1-ol was obtained in 84% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.47–7.42 (m, 2H); 7.36–7.31 (m, 2H); 6.25 (t, *J* = 6.0 Hz, 1H); 4.37 (t, *J* = 6.0 Hz, 2H); 1.86 (t, *J* = 6.0 Hz, 1H).
Alkylation of phenol **15** *or thiophenol* **13**: *Method A*. Methyl (4-hydroxy-2-methylphenoxy) acetate (**15**)[8] (1.17 g, 5.96 mmol), triphenylphosphine (1.70 g, 6.48 mmol), and allylic alcohol (**8** or **9**) were dissolved in the mixture of anhydrous toluene (90 mL) and THF (30 mL). Diisopropyl azodicarboxylate (1.2 mL, 6.05 mmol) in THF (10 mL) was added dropwise under nitrogen atmosphere at 0 °C over 20 min. The reaction mixture was stirred overnight at room temperature. The solvents were evaporated in vacuo and the residue was submitted to flash column chromatography (silica gel) giving the desired ether. E.g. Methyl (*Z*)-[4-[3-iodo-3-(2-methylbenzo[b]furan-5-yl)allyloxy]-2-methylphenoxy] acetate (**16o**) was obtained in 59% yield. Mp: 74–77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.59 (bd, *J* = 1.5 Hz, 1H); 7.35 (dd, *J* = 8.6 and 1.8 Hz, 1H); 7.32 (d, *J* = 8.6 Hz, 1H); 6.80 (bd, *J* = 2.1 Hz, 1H); 6.72-6.66 (m, 2H); 6.36 (s, 1H); 6.28 (t, *J* = 5.1 Hz, 1H); 4.71 (d, *J* = 5.1 Hz, 2H); 4.61 (s, 2H); 3.80 (s, 3H); 2.45 (s, 3H); 2.29 (s, 3H).
Method B. Allylic alcohol (**8** or **9**) (2.8 mmol), carbon tetrabromide (0.913 g, 3 mmol), and triphenylphosphine (0.786 g, 3 mmol) were mixed in anhydrous dichloromethane(10 mL) and the mixture was stirred at 0 °C for 3 h and then at 20 °C overnight. Ether (50 mL) and hexanes (30 mL) were added and the mixture was filtered through a pad of silica gel to remove precipitated triphenylphosphine oxide. The mixture was concentrated in vacuo and crude allylic bromide was subsequently used without further purification. Obtained compound (2 mmol), phenol **15**[8] (0.652 g, 2 mmol), and cesium carbonate (0.65 g, 2 mmol) were stirred in acetonitrile (25 mL) at 20 °C overnight. The mixture was filtered and concentrated. The residue was submitted to column chromatography (silica gel). The product was obtained in 60–80% yield. E.g. (*Z*)-[4-[3-(4-bromophenyl)-3-iodoallyloxy]-2-methylphenoxy] acetate (**13d**) was prepared in 71% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.46–7.42 (m, 2H); 7.37–7.32 (m, 2H); 6.78 (s, 1H), 6.68 (d, *J* = 1.5 Hz, 2H); 6.35 (t, *J* = 5.0 Hz, 1H); 4.68 (d, *J* = 5.0 Hz, 2H); 4.61 (s, 2H); 3.80 (s, 3H); 2.29 (s, 3H). The alkylation of thiophenol **13**[24] was performed in CH_2Cl_2/THF mixture (5:6) under exclusion of oxygen with DIPEA as a base.
Method C. (*Z*)-3-Iodo-3-(quinoline-3-yl)prop-2-en-1-ol (**8q**, 1.061 g, 3.41 mmol) was dissolved in anhydrous dichloromethane (15 mL) and thionyl chloride (0.45 mL, 6 mmol) was added. The mixture was stirred for 5 h at ambient temperature. The solvent and excess of thionyl chloride were removed in vacuo and sufficiently pure crude hydrochloride of (*Z*)-3-iodo-3-(quinoline-3-yl)allyl chloride was obtained. This product (0.704 g, 1.9 mmol), phenol **15** (0.392 g, 2.0 mmol), and cesium carbonate (1.304 g, 4 mmol) were mixed in acetonitrile (15 mL) and the resulting mixture was stirred for 3 days. The work-up procedure was as described in *Method B*.
Sonogashira cross-coupling reaction, the preparation of compounds **9** *and* **14a**, **d**–**m**, **o**–**q**: Iododerivative **8** or **16a**, **d**–**m**, **o**–**q** (0.77 mmol), terminal alkyne (R-CCH) (1.54 mmol), and diisopropylamine (0.51 mL, 3.6 mmol) were dissolved in THF (15 mL). The solution was degassed; CuI (15 mg, 0.075 mmol) and $PdCl_2(PPh_3)_2$ (30 mg, 0.042 mmol) were added; the reaction mixture was degassed again and then stirred under inert atmosphere at 65 °C. The reaction was monitored by TLC. When the conversion was completed the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a pad of silica gel. The pad was washed with ethyl acetate and the combined filtrates were concentrated in vacuo. The residue was purified by column chromatography giving desired product in high yield. E.g. Methyl (*Z*)-[4-[3-(4-bromophenyl)-5-(4-trifluoromethylphenyl)pent-2-en-4-ynyloxy]-2-methylphenoxy] acetate (**14f**) was obtained in 96% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.53–7.48 (m, 4H); 7.45 (dm,*J* = 8.6 Hz, 2H); 7.35 (dm, *J* = 8.4 Hz, 2H); 6.82 (d, *J* = 2.8 Hz, 1H); 6.72 (dd, *J* = 8.8 and 2.9 Hz, 1H); 6.68–6.60 (m, 2H); 4.97 (d, *J* = 6.3 Hz, 2H); 4.60 (s, 2H); 3.80 (s, 3H); 2.28 (s, 3H).
Hydrolysis of esters: ester (~0.3 mmol) was dissolved in a mixture of THF (3 mL) and MeOH (1 mL), and aqueous solution of lithium hydroxide monohydrate (22 mg, 0.5 mmol, 1 mL) was added. The mixture was stirred for 2 h and then diluted with saturated aqueous solution of ammonium chloride (20 mL). The resulting mixture was extracted with ethyl acetate (3 × 15 mL); the organic layers were combined and dried with sodium sulfate. The compound was either crystallized or chromatographed on silica gel. E.g. (*Z*)-[4-[3-(4-bromophenyl)-5-(4-trifluoromethylphenyl) pent-2-en-4-ynyloxy]-2-methylphenoxy] acetic acid (**6f**) was obtained in 75% yield. ^{1}H NMR ($CDCl_3$,

300 MHz): 7.82 (m, 4H); 7.73 (d, J = 8.3 Hz, 2H); 7.72 (d, J = 8.3 Hz, 2H); 6.94 (t, J = 5.9 Hz, 1H); 6.86 (m, 1H); 6.79–6.74 (m, 2H); 4.97 (d, J = 6.0 Hz, 2H); 4.54 (s, 2H); 2.15 (s, 3H).

17. Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. lett.* **2000**, *2*, 1729.
18. Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 2411.
19. The preparation of compound **14n**. Compound **14d** (216 mg, 0.440 mmol) and tributyl-(5-methylthiophen-2-yl)tin [20] (223 mg, 0.576 mmol) were dissolved in DMF (10 mL), the solution was degassed and put under nitrogen. $Pd_2dba_3{\cdot}CHCl_3$ (15.4 mg, 0.015 mmol) and t-Bu_3P in cyclohexane (0.15 M, 0.40 mL, 0.060 mmol) were added. The reaction mixture was stirred at 50 °C for 90 min, cooled down, and 10% aqueous solution of potassium fluoride was added. The mixture was stirred for 10 min, filtered through a pad of silica gel and the silica gel was washed with ethyl acetate (50 mL). The filtrate was washed with brine (3 × 15 mL), 10% aqueous solution of potassium fluoride (2 × 10 mL), water (2 × 10 mL), and brine (3 × 15 mL). The organic solution was dried with sodium sulfate, concentrated and purified by flash column chromatography (silica gel, hexanes/ethyl acetate 10:1). The crude product was triturated with hexanes/ethyl acetate mixture (15:1, 16 mL) yielding methyl (*Z*)-[2-methyl-4-[3-[4-(5-methylthiophen-2-yl)phenyl]-5-phenylpent-2- en-4-ynyloxy]phenoxy] acetate (**14n**) as a yellowish amorphous mass in 47% yield.
20. Morimoto, H.; Shimadzu, H.; Kushiyama, E.; Kawanishi, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. *J. Med. Chem.* **2001**, *44*, 3355.
21. 6-Iodo-3-methylbenzofuran was prepared as described in Ref. Hongu, M.; Tanaka, T.; Funami, N.; Saito, K.; Arakawa, K.; Matsumoto, M.; Tsujihara, K. *Chem. Pharm. Bull.* **1998**, *46*, 22.
22. Tretyakov, E.; Tkachev, A. V.; Rybalova, T. V.; Gatilov, Y. V.; Knight, D. V.; Vasilevsky, S. F. *Tetrahedron* **2000**, *56*, 10075.
23. Denis, J.-N.; Greene, A. E.; Serre, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46.
24. Martin, M. T.; Thomas, A. M.; York, D. G. *Tetrahedron Lett.* **2002**, *43*, 2145.
25. PPAR in-vitro transactivation assay was performed as described in Ref. 11.
26. Glide docking. The structure manipulations were performed in Maestro version 7.5 (Maestro 7.0, Schrödinger, LLC, New York, NY, 1999–2005). Glide calculations were performed with Impact version 4.0.[27,28] **6f** was built in Maestro version 7.5, a formal charge of −1 was assigned, and the molecule was minimized with the OPLS_2005 force field. **6f** was docked with Glide version 4.0 using the SP mode and the van der Waals radii of the ligand atoms were scaled by 0.8.
27. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shaw, D. E.; Shelley, M.; Perry, J. K.; Francis, P.; Shenkin, P. S. *J. Med. Chem.* **2004**, *47*, 1739.
28. Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L. *J. Med. Chem.* **2004**, *47*, 1750.