Bioorganic & Medicinal Chemistry Letters 22 (2012) 4122–4126

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Total synthesis and dual PPARα/γ agonist effects of Amorphastilbol and its synthetic derivatives

Taejung Kim [a,†], Woojung Lee [a,†], Kyu Hyuk Jeong [a], Jung Ho Song [a], Soon-Hye Park [a], Pilju Choi [a], Su-Nam Kim [a], Seokjoon Lee [b], Jungyeob Ham [a,*]

[a] Natural Medicine Center, Korea Institute of Science and Technology, Gangneung 210-340, Republic of Korea
[b] Department of Basic Science, Kwandong University College of Medicine, Gangneung 210-701, Republic of Korea

ARTICLE INFO

Article history:
Received 30 December 2011
Revised 10 April 2012
Accepted 11 April 2012
Available online 19 April 2012

Keywords:
Natural product
Amorphastilbol
Type 2 diabetes
Dual PPARα/γ agonists
Suzuki–Miyaura cross-coupling

ABSTRACT

Amorphastilbol (APH-1), isolated from a *Robinia pseudoacacia* var. *umbraculifer* seed extract, is a biologically interesting natural *trans*-stilbene compound with dual peroxisome proliferator-activated receptor (PPAR) α/γ agonist activity. After total synthesis of APH-1 and its derivatives by Pd-catalyzed Suzuki–Miyaura cross-coupling of a common (*E*)-styryl bromide intermediate and various aromatic trifluoroborate compounds, we biologically evaluated APH-2–APH-12 for PPAR agonist activity. APH-4 and APH-11 were effective PPARα/γ transcriptional activators, compared with APH-1. Therefore, we suggest that APH-4 and APH-11 are novel dual PPARα/γ agonists and are potentially useful for treating type 2 diabetes by enhancing glucose and lipid metabolism.

© 2012 Elsevier Ltd. All rights reserved.

Type 2 diabetes (T2DM) is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency and is usually associated with dyslipidemia, hypertension, atherosclerosis, and obesity.[1] Although its pathophysiology remains incompletely understood, metabolic defects in the liver, pancreatic β-cells, adipose tissue, and skeletal muscle contribute to the development of T2DM. Recently, the members of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors have emerged as key pharmacological targets in the management of T2DM, because their activation can normalize metabolic dysfunctions and reduce some cardiovascular risk factors associated with this disease.

PPARs occur as 3 isoforms: PPARα, PPARγ, and PPARδ.[2] PPARα is expressed predominantly in the liver and regulates genes involved in fatty acid uptake and oxidation. PPARα agonists such as fibrates have been used for treating hyperlipidemia and ameliorating cardiovascular disease. PPARγ is expressed mainly in adipose tissue and regulates genes involved in fatty acid uptake and storage and in glucose homeostasis. PPARγ agonists such as thiazolidinediones or glitazones have been used for treating insulin resistance and hyperglycemia. PPARδ is expressed in most tissues and regulates genes involved in fatty acid catabolism and macrophage lipid homeostasis. PPARδ agonists such as GW501516 may have a beneficial effect on lipid and lipoprotein metabolism.[3]

PPAR agonists are effective drugs for improving the metabolic abnormalities linking hyperlipidemia to diabetes, hyperglycemia, insulin resistance, and atherosclerosis. Especially, dual PPARα/γ agonists, such as muraglitazar[4] and tesaglitazar,[5] combine the plasma triglyceride- and very low-density lipoprotein-lowering and high-density lipoprotein cholesterol-raising effects of a PPARα activator with the insulin resistance- and blood glucose level-reducing and insulin-sensitizing properties of a PPARγ activator. Therefore, dual PPARα/γ agonists are expected to be effective hypoglycemic and hypolipidemic agents.[6]

There is growing interest in the therapeutic use of natural products for metabolic syndrome, because such products are considered to be less toxic and cause fewer side effects. In the field of drug discovery, natural products and their analogs can be developed into useful lead compounds by highly efficient bioactivity-guided fractionation, followed by synthesis of natural product-based libraries.[7] Among the dual PPARα/γ activators, however, natural ligands are generally less potent than biochemically optimized synthetic ligands.[8]

We previously discovered amorphastilbol (APH-1), having a C-geranylated 4′-dehydroxyresveratrol structure (Fig. 1), as the most active compound of the *Robinia pseudoacacia* var. *umbraculifer* (RPU) extract, and explored its effects on the transcriptional activities of PPARα and PPARγ, adipogenesis in 3T3-L1 cells, insulin resistance-associated disorders in *db/db* mice (mouse model of T2DM), and hypolipidemia in a high-fat diet model.[9] Especially, APH-1 stimulates PPARα/γ transcriptional activity at the lower

* Corresponding author. Tel.: +82 33 650 3502; fax: +82 33 650 3629.
E-mail address: ham0606@kist.re.kr (J. Ham).
† These authors are equally contributed on this work.

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.04.062

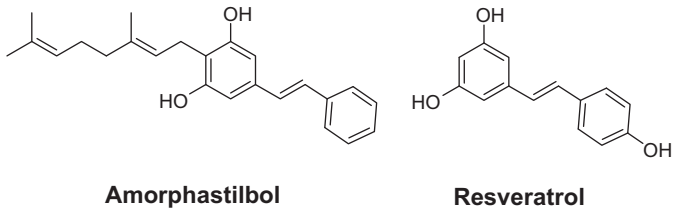
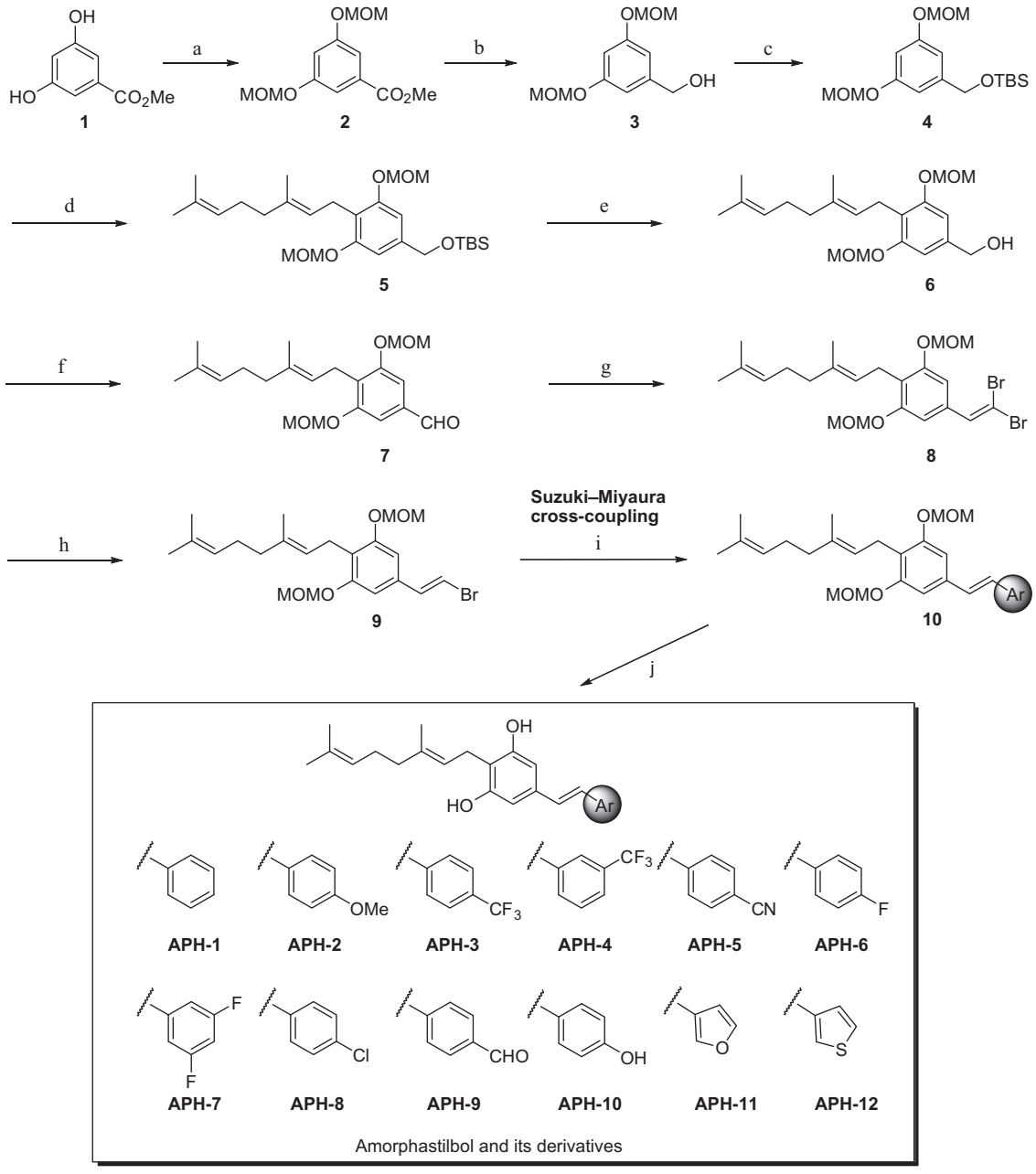


Figure 1. Structure of amorphastilbol and resveratrol

concentration than previously reported natural PPARs ligands.[8] Therefore, we focused on the total synthesis of APH-1 from RPU seed extract (0.04% yield). Here, we describe the total synthesis of APH-1 and its derivatives and their biological evaluation as PPAR transcriptional activators.

The synthesis of APH-1 and its derivatives (APH-2–APH-12) is described in Scheme 1. Initially, conversion to the known benzyl alcohol (**6**) was readily accomplished starting from methyl 3, 5-dihydroxybenzoate (**1**) using the literature methods.[10a,b] After protection of phenolic alcohols by using MOMCl, general reduction of the MOM-protected ester (**2**) produced benzyl alcohol (**3**). TBS-mediated protection of benzyl alcohol completed the silyl ether synthesis. Geranylation of the silyl ether (**4**) was investigated under several well-known conditions in the presence of copper catalysts such as CuI, CuCN, and CuBr-DMS. However, the best result was obtained only by using geranyl bromide and *n*-BuLi, without a copper catalyst.[10] TBAF-mediated deprotection of the TBS ether yielded the corresponding alcohol (**6**) in 2 steps (83% yield). To construct the *trans*-stilbene skeleton, (*E*)-styryl bromide (**9**), a common precursor of APH derivatives, was also obtained from



Scheme 1. Reagents and conditions: (a) MOMCl, NaH, DMF, rt, 12 h, 97%; (b) LAH, THF, rt, 2 h, 94%; (c) TBSCl, imidazole, DMAP, rt, 5 h, 99%; (d) *n*-BuLi, THF, 0 °C, 0.5 h, then geranylbromide, rt, 6 h, 83%; (e) TBAF, THF, rt, 1 h, 99%; (f) PCC, MS 4 Å, CH_2Cl_2, rt, 3 h, 98%; (g) CBr_4, PPh_3, Zn dust, CH_2Cl_2, rt, 1.5 h, 78%; (h) diethyl phosphite, Et_3N, DMF, rt, 2 h, 98%; (i) potassium aryltrifluoroborate, 5 mol % of $Pd(PPh_3)_4$, K_2CO_3, EtOH, 60 °C, 6 h; (j) CSA, MeOH, rt, 10 h, 45–75% (2 steps).

Table 1
In vitro PPAR binding and transactivation activity of APH derivatives

Entry	Compound	TA EC_{50} [a] (μM)						Binding IC_{50} [b] (μM)	
		h-PPARα[c] (%max)		h-PPARγ[c] (%max)		h-PPAR[c] (%max)		h-PPARα	h-PPARγ
1	Amorphastilbol (**APH 1**)	12	(66)	5	(83)	NA	(21)	1.52	0.85
2	**APH 2**	19	(63)	14	(66)	NA	(20)	2.50	0.63
3	**APH 3**	ND	(ND)	ND	(ND)	NA	(ND)	3.33	8.10
4	**APH 4**	4	(ND)	5	(ND)	NA	(ND)	1.21	0.53
5	**APH 5**	20	(54)	ND	(41)	NA	(15)	3.47	1.20
6	**APH 6**	6	(88)	11	(68)	NA	(17)	2.48	2.32
7	**APH 7**	ND	(ND)	7	(ND)	NA	(ND)	2.08	0.90
8	**APH 8**	ND	(ND)	ND	(ND)	NA	(ND)	7.47	0.54
9	**APH 9**	ND	(35)	ND	(27)	NA	(7)	2.82	0.89
10	**APH 10**	8	(ND)	8	(ND)	NA	(ND)	1.21	0.11
11	**APH 11**	6	(87)	5	(98)	NA	(34)	2.03	0.65
12	**APH 12**	14	(56)	6	(68)	NA	(24)	5.41	1.01
Wy14643		0.13	(100)					10.11	ND
Troglitazone				0.40	(100)			ND	0.30
GW501516						0.0012	(100)	ND	ND

[a] TA (PPARα/γ/δ transactivation assay) measuring the ligand-mediated luminescence resulting from PPARα/γ/δ-induced transcription of a luciferase reporter. PPARα/γ/δ and the luciferase reporter genes are transfected into CV-1 cells, then treated with test compound. The EC_{50} values are the mean of two independent experiments in triplicate. NA denotes inactive where compounds did not shows any fold induction above the basal level shown by vehicle and ND denotes not determined.
[b] Binding affinity for PPARα and PPARγ using TR-FRET (time-resolved fluorescence resonance energy transfer).
[c] The maximum percent efficacy (%max) of all compound 30 μM compared to reference compounds (Wy14643 for PPARα, Troglitazone for PPARγ and GW501516 for PPARδ) normalized to 100%.

the alcohol (**6**). After oxidation with a PCC suspension and by using molecular sieves (4 Å), geranylated benzaldehyde (**7**) was converted to dibromoolefine (78% yield) by the Ramirez olefination reaction. Subsequent treatment with diethyl phosphite followed by quenching with water produced (*E*)-styryl bromide (**9**) with excellent yield (98%).

Finally, (*E*)-styryl bromide (**9**) was cross-coupled with potassium phenyltrifluoroborate under the standard Suzuki–Miyaura reaction conditions to produce a *trans*-stilbene. Deprotection of the MOM ether by treatment with 10-camphorsulfonic acid (CSA) yielded APH-1. The derivatives, i.e., APH-2 to APH-12, were similarly synthesized. Their synthesis required only 2 steps from the common (*E*)-styryl bromide (**9**) intermediate: Pd-catalyzed Suzuki–Miyaura cross-coupling reaction with various aromatic trifluoroborate compounds for fixation of the *trans*-stilbene moiety and removal of the MOM-protected groups.

The PPAR agonist activity of the APH derivatives was evaluated by both cell-based and cell-free assays. Wy14643 (a potent PPARα ligand), troglitazone (a PPARγ ligand), and GW501516 (a PPARδ ligand) were used as positive controls, strongly and dose-dependently activated reporter gene. However, these synthetic ligands are generally more potent than natural product-derived ligands.[8] We therefore attempted the PPAR-agonist activity test of APH derivatives compared with APH-1 which has reported natural product-derived dual PPAR α/γ agonists.[9] The results are summarized in Table 1. All the compounds seemed to have little effect on

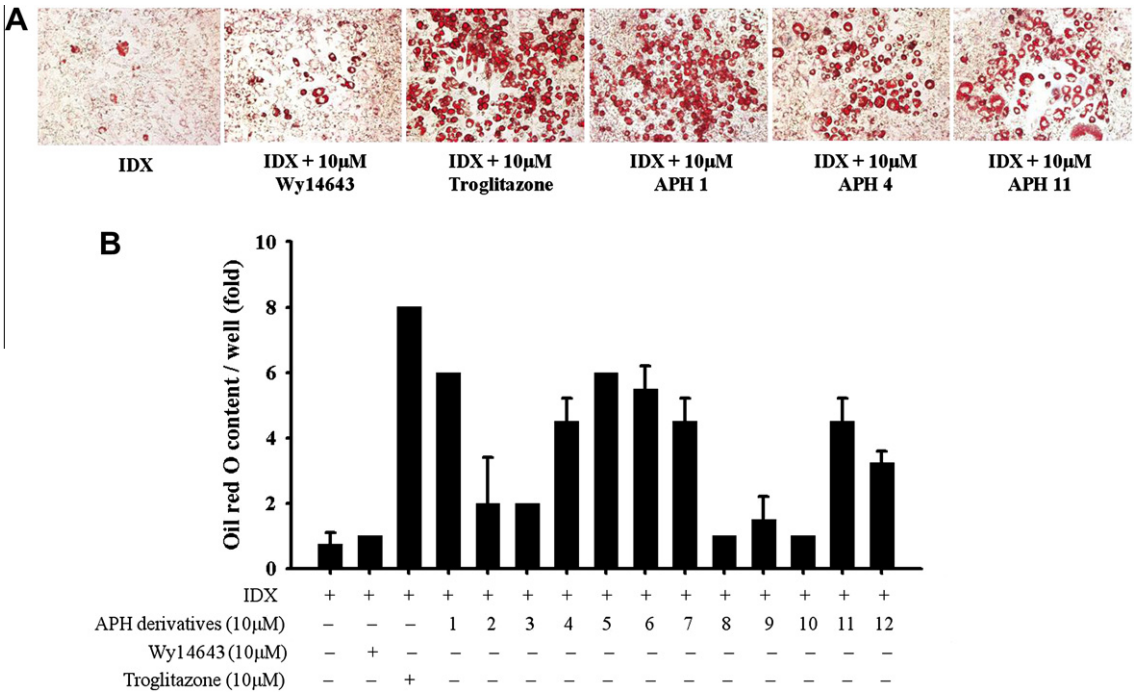
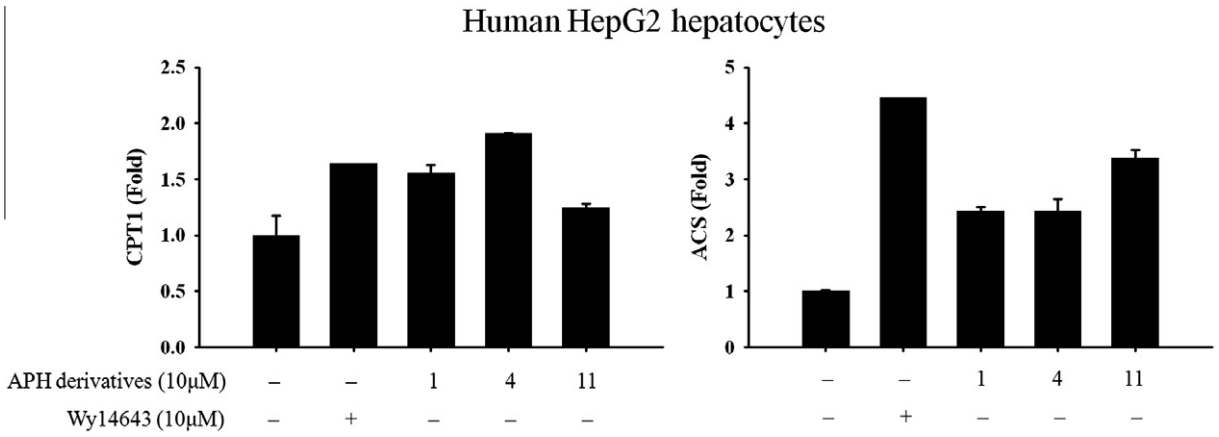


Figure 2. The effects of APH derivatives on adipocyte differentiation. 3T3-L1 cells were grown in the IDX condition and treated with Wy14643 (10 μM), troglitazone (10 μM) and APH derivatives (10 μM). (A) Morphological changes associated with adipogenesis were assessed by staining the cellular triglyceride deposition with Oil Red O. (B) The stained oil droplets were dissolved in isopropanol and were quantified by measuring the absorbance 520 nm. Relative Oil red O levels were expressed as the fold increase relative to the control. Data were expressed as mean ± SD.



PPARδ. However, APH-4 (PPARα, EC_{50} = 4 μM; PPARγ, EC_{50} = 5 μM) and APH-11 (PPARα, EC_{50} = 6 μM; PPARγ, EC_{50} = 5 μM) were effective transcriptional activators of both PPARα and PPARγ; they exhibited similar PPARγ agonist activity to but better PPARα agonist activity than APH-1 (PPARα, EC_{50} = 4 μM; PPARγ, EC_{50} = 5 μM). At 30 μM, APH-11 had higher agonist efficacy (PPARα, 87%; PPARγ, 98%) than APH-1 (PPARα, 66%; PPARγ, 83%), but APH-4 induced cytotoxicity. We then examined whether the APH derivatives could directly bind to PPARα or PPARγ by using LanthaScreen™ technology (Invitrogen) in a TR-FRET PPARα/γ competitive binding assay (Invitrogen).[11] APH-4 exhibited increased binding affinity (IC_{50} = 1.21 μM and 0.53 μM, respectively) for PPARα and PPARγ compared with APH-1 (IC_{50} = 1.52 μM and 0.85 μM, respectively); APH-11 exhibited increased binding affinity only for PPARγ (IC_{50} = 0.65 μM).

To explore the potential effects of the APH derivatives on adipogenesis, 3T3-L1 preadipocytes were differentiated with the derivatives for 8 days in combination with the adipogenic IDX cocktail (insulin, dexamethasone, and IBMX).[12] When preadipocytes differentiated into adipocytes, morphological changes were observed because of the cytoplasmic accumulation of lipid droplets. Adipocyte differentiation was confirmed by Oil Red O staining to observe lipid droplet accumulation. Lipid droplet accumulation in adipocytes was significantly greater with the APH-1 treatment than without the APH-1 treatment (Fig. 2). However, the APH-4 and APH-11 treatments decreased lipid droplet accumulation to a greater extent than the APH-1 treatment. APH-4 and APH-11 had better PPARα agonist activity but not PPARγ agonist activity than APH-1, leading to the relative reduction in lipid droplet accumulation in 3T3-L1 cells.[13]

In conclusion, we synthesized APH-1 and its derivatives by Pd-catalyzed Suzuki–Miyaura cross-coupling of a common (*E*)-styryl bromide intermediate and various aromatic trifluoroborate compounds. Synthetic APH-1 stimulated PPARα/γ transcriptional activity at a lower concentration than natural APH-1. Further, the APH-1 derivatives APH-4 and APH-11 were effective PPARα/γ transcriptional activators.[14,15] Therefore, we suggest that APH-4 and APH-11 are novel dual PPARα/γ agonists and are potentially useful for treating T2DM and obesity by enhancing glucose and lipid metabolism.

Acknowledgment

This research was supported by the KIST Institutional Program (2Z03550), Republic of Korea.

References and notes

1. (a) Ohtsubo, K.; Chen, M. Z.; Olefsky, J. M.; Marth, J. D. *Nat. Med.* **2011**, *17*, 1067; (b) Donath, M. Y.; Shoelson, S. E. *Nat. Rev. Immunol.* **2011**, *11*, 98; (c) Reaven, G. M. *Med. Clin. North Am.* **2011**, *95*, 875; (d) Ehsesa, J. A.; Lacrazb, G.; Giroixb, M.-H.; Schmidlinc, F.; Coulaudb, J.; Kassisb, N.; Irmingerd, J.-C.; Kergoatc, M.; Porthab, B.; Homo-Delarcheb, F.; Donath, M. Y. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 13998; (e) Ogawa, W.; Kasuga, M. *Science* **2008**, *322*, 1483; (f) Andreozzi, F.; Laratta, E.; Cardellini, M.; Marini, M. A.; Lauro, R.; Hribal, M. L.; Perticone, F.; Sesti, G. *Diabetes* **2006**, *55*, 2021; (g) Henke, B. R. *J. Med. Chem.* **2004**, *47*, 4118.
2. (a) Gross, B.; Staels, B. *Best Pract. Res. Clin. Endocrinol.* **2007**, *21*, 687; (b) Akiyama, T. E.; Meinke, P. T.; Berger, J. P. *Curr. Diab. Rep.* **2005**, *5*, 45; (c) Ferré, P. *Diabetes* **2004**, *53*, 43; (d) Berger, J.; Moller, D. E. *Annu. Rev. Med.* **2002**, *3*, 409; (e) Kersten, S.; Desvergne, B.; Wahli, W. *Nature* **2000**, *405*, 421.
3. (a) Barroso, E.; Eyre, E.; Palomer, X.; Vázquez-Carrera, M. *Biochem. Pharmacol.* **2011**, *81*, 534; (b) Wagner, K. D.; Wagner, N. *Pharmacol. Ther.* **2010**, *125*, 423; (c) Grimaldi, P. A. *Curr. Opin. Lipidol.* **2010**, *21*, 186; (d) Coll, T.; Rodrïguez-Calvo, R.; Barroso, E.; Serrano, L.; Eyre, E.; Palomer, X.; Vázquez-Carrera, M. *Curr. Mol. Pharmacol.* **2009**, *2*, 46; (e) Rosen, E. D.; Spiegelman, B. M. *Nature* **2006**, *444*, 847; (f) Staels, B.; Fruchart, J. C. *Diabetes* **2005**, *54*, 2460; (g) Evans, R. M.; Barish, G. D.; Wang, Y. X. *Nat. Med.* **2004**, *10*, 355; (h) Desvergne, B.; Michalik, L.; Wahli, W. *Mol. Endocrinol.* **2004**, *18*, 1321.
4. Kendall, D. M.; Rubin, C. J.; Mohideen, P.; Ledeine, J. M.; Belder, R.; Gross, J.; Norwood, P.; O'Mahony, M.; Sall, K.; Sloan, G.; Roberts, A.; Fiedorek, F. T.; DeFronzo, R. A. *Diabetes Care.* **2006**, *29*, 1016.
5. Liao, J.; Soltani, Z.; Ebenezer, P.; Isidro-Carrión, A. A.; Zhang, R.; Asghar, A.; Aguilar, E.; Francis, J.; Hu, X.; Ferder, L.; Reisin, E. *Nephron. Exp. Nephrol.* **2010**, *114*, 61.
6. (a) Matralis, A. N.; Katselou, M. G.; Nikitakis, A.; Kourounakis, A. P. *J. Med. Chem.* **2011**, *54*, 5583; (b) Asano, S.; Ban, H.; Tsuboya, N.; Uno, S.; Kino, K.; Ioriya, K.; Kitano, M.; Ueno, Y. *J. Med. Chem.* **2010**, *53*, 3284; (c) Bailey, C. J. *Diab. Vasc. Dis. Res.* **2007**, *4*, 161; (d) Pourcet, B.; Fruchart, J. C.; Staels, B.; Glineur, C. *Expert. Opin. Emerg. Drugs* **2006**, *11*, 379; (e) Chaput, E.; Saladin, R.; Silvestre, M.; Edgar, A. D. *Biochem. Biophys. Res. Commun.* **2000**, *271*, 445.
7. (a) Huang, T. H.; Teoh, A. W.; Lin, B. L.; Lin, D. S.; Roufogalis, B. *Pharmacol. Res.* **2009**, *60*, 195; (b) Itokawa, H.; Morris-Natschke, S. L.; Akiyama, T.; Lee, K. H. *J. Nat. Med.* **2008**, *62*, 263.
8. (a) Cornick, C. L.; Strongitharm, B. H.; Sassano, G.; Rawlins, C.; Mayes, A. E.; Joseph, A. N.; O'Dowd, J.; Stocker, C.; Wargent, E.; Cawthorne, M. A.; Brown, A. L.; Arch, J. R. *J. Nutr. Biochem.* **2009**, *20*, 806; (b) Shih, C. C.; Lin, C. H.; Lin, W. L. *Diab. Res. Clin. Pract.* **2008**, *81*, 134; (c) Li, Y.; Qi, Y.; Huang, T. H.; Yamahara, J.; Roufogalis, B. D. *Diabetes. Obes. Metab.* **2008**, *10*, 10; (d) Lee, H. K.; Nam, G. W.; Kim, S. H.; Lee, S. H. *Exp. Dermatol.* **2006**, *15*, 66; (e) Huang, T. H.; Peng, G.; Kota, B. P.; Li, G. Q.; Yamahara, J.; Roufogalis, B. D.; Li, Y. *Toxicol. Appl. Pharmacol.* **2005**, *207*, 160; (f) Huang, T. H.; Yang, Q.; Harada, M.; Li, G. Q.; Yamahara, J.; Roufogalis, B. D.; Li, Y. *J. Cardiovasc. Pharmacol.* **2005**, *46*, 856; (g) Park, S. H.; Ko, S. K.; Chung, S. H. *J. Ethnopharmacol.* **2005**, *102*, 326; (h) Huang, T. H.; Peng, G.; Kota, B. P.; Li, G. Q.; Yamahara, J.; Roufogalis, B. D.; Li, Y. *Br. J. Pharmacol.* **2005**, *145*, 767.
9. Kim, S. N.; Lee, W. J.; Kwon, H. C.; Ham, J.; Ahn, H. R.; Kim, M. S.; Nam, C.-W.; Lee, J.-N.; Lim, J.-S. Patent WO09/014315 A1 (04, June, 2009).
10. (a) Topczewski, J. J.; Callahan, M. P.; Neighbors, J. D.; Wiemer, D. F. *J. Am. Chem. Soc.* **2009**, *131*, 14630; (b) Topczewski, J. J.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2009**, *74*, 6965; (c) Neighbors, J. D.; Salnikova, M. S.; Wiemer, D. F. *Tetrahedron Lett.* **2005**, *46*, 1321; (d) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718.
11. Schopfer, F. J.; Cole, M. P.; Groeger, A. L.; Chen, C. S.; Khoo, N. K.; Woodcock, S. R.; Golin-Bisello, F.; Motanya, U. N.; Li, Y.; Zhang, J.; Garcia-Barrio, M. T.; Rudolph, T. K.; Rudolph, V.; Bonacci, G.; Baker, P. R.; Xu, H. E.; Batthyany, C. I.; Chen, Y. E.; Hallis, T. M.; Freeman, B. A. *J. Biol. Chem.* **2010**, *285*, 12321.
12. Kim, S. N.; Choi, H. Y.; Lee, W.; Park, G. M.; Shin, W. S.; Kim, Y. K. *FEBS Lett.* **2008**, *582*, 3465.
13. PPARα target genes have been mainly concentrated on hepatocytes and PPARα activation upregulates CPT1 (carnitine palmitoyltransferase 1) and ACS (acyl-CoA synthetase) gene expression involved in mitochondrial fatty acid uptake and oxidation. APH-4 treatment strongly increased CPT1 mRNA expression and APH-11 treatment strongly increased ACS mRNA expression involved in fatty acid β-oxidation in HepG2 cells than APH-1. Therefore we suggested that APH-4 and APH-11 had better PPARα agonist activity than APH-1.

14. Luciferase reporter gene assay description: CV-1 cells were seeded into 24-well plates and cultured for twenty four hour before transfection. CV-1 cells were grown in Dulbecco's modified Eagle's medium (DMEM) containing 10% charcoal dextran treated fetal bovine serum (CDT-FBS) and 1% antibiotics. 24 h later, a DNA mixture containing PPRE-luciferase reporter plasmid (0.3 μg), pcDNA3-hPPAR-γ/-α/-δ (30 ng) and internal control plasmid pRL-SV-40 (5 ng) was transfected using TransFast™ transfection reagent (Promega, Madison, WI). After 24 h of transfection, the cells were incubated for an additional 24 h following treatment with positive control or the indicated concentrations of APHs. The luciferase activity of the cell lysates was measured using Dual-Luciferase® Reporter Assay System (Promega, Madison, WI), according to the manufacturer's instruction. Relative luciferase activity was normalized for transfection efficiency using the corresponding Renilla luciferase activity.
15. *Spectroscopic data of representative compounds. Amorphastilbol (**APH 1**)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 2H, J = 7.1 Hz), 7.34 (t, 2H, J = 7.4 Hz), 7.25 (m, 1H), 7.01 (d, 1H, J = 16.5 Hz), 6.94 (d, 1H, J = 16.5 Hz), 6.59 (s, 2H), 5.28 (td, 1H, J = 7.5, 1.5 Hz), 5.08 (s, 2H), 5.05 (m, 1H), 3.44 (d, 2H, J = 7.1 Hz), 2.10 (m, 4H), 1.82 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 139.4, 137.2, 136.9, 132.1, 128.7, 128.1, 127.6, 126.5, 123.7, 121.3, 113.3, 106.6, 39.7, 26.4, 25.7, 22.5, 17.7, 16.3. ^{13}C NMR (100 MHz, Acetone-d_6) δ 156.2, 156.1, 137.6, 135.9, 133.8, 130.7, 129.0, 128.6, 127.3, 126.3, 124.3, 123.2, 105.2, 105.1, 39.7, 26.6, 24.9, 22.2, 16.8, 15.4. FT-IR (ATR): 3376, 2907, 2850, 1612, 1577, 1448, 1425, 1261, 1156, 1039, 960, 827, 748, 688 cm^{-1}. ESI-MS: m/z calcd for $C_{24}H_{28}O_2$ $[M+H]^+$ 348.21, found 348.00. **APH 4:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.62 (d, 1H, J = 7.5 Hz), 7.47 (m, 2H), 7.01 (d, 1H, J = 16.0 Hz), 6.98 (d, 1H, J = 16.0 Hz), 6.59 (s, 2H), 5.27 (m, 3H), 5.05 (t, 1H, J = 7.0 Hz), 3.44 (d, 2H, J = 7.0 Hz), 2.09 (m, 4H), 1.82 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 139.6, 138.0, 136.2, 132.2, 129.9, 129.5, 129.1, 127.1, 124.1, 124.0, 123.7, 123.1, 123.0, 121.1, 113.9, 106.7, 39.7, 26.4, 25.7, 22.6, 17.7, 16.2. FT-IR (ATR): 3338, 2917, 1850, 1622, 1574, 1441, 1324, 1163, 1115, 1068, 1039, 1011, 944, 817, 691, 653 cm^{-1}. ESI-MS: m/z calcd for $C_{25}H_{27}F_3O_2$ $[M+H]^+$ 416.20, found 416.00. **APH 11:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.39 (s, 1H), 6.97 (d, 1H, J = 20.0 Hz), 6.85 (d, 2H, J = 20.0 Hz), 6.62 (s, 1H), 6.51 (s, 2H), 5.27 (t, 1H, J = 5.5 Hz), 5.20 (s, 2H), 5.05 (m, 1H), 3.42 (d, 2H, J = 8.5 Hz), 2.08 (m, 4H), 1.81 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 143.7, 141.0, 139.4, 136.9, 132.1, 127.8, 124.4, 123.7, 121.3, 118.4, 113.0, 107.4, 106.2, 39.7, 26.4, 25.7, 22.5, 17.7, 16.2. FT-IR (ATR): 3392, 2913, 1584, 1422, 1267, 1153, 1017, 960, 868, 824, 779, 650, 586 cm^{-1}. ESI-MS: m/z calcd for $C_{22}H_{26}O_3$ $[M+H]^+$ 338.19, found 337.75.