Bioorganic & Medicinal Chemistry Letters 19 (2009) 1883–1886

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Selective, potent PPARγ agonists with cyclopentenone core structure

M. Paz Otero, Efrén Pérez Santín, Fátima Rodríguez-Barrios, Belén Vaz, Ángel R. de Lera *

Departamento de Química Orgánica, Universidade de Vigo, 36310 Vigo, Spain

ARTICLE INFO

Article history:
Received 7 January 2009
Revised 16 February 2009
Accepted 18 February 2009
Available online 23 February 2009

Keywords:
Nuclear receptors
PPARs
Agonists
Cyclopentenones
Prostaglandins

ABSTRACT

A series of analogues of the PPARγ ligand 15-deoxy-$\Delta^{12,14}$-PGJ_2 have been synthesized by functionalization of a 5-alkyl-4-hydroxycyclopentenone core structure obtained by Piancatelli rearrangement of precursor furylcarbinol. Transient transactivation assays indicate that analogues **18** and **20** are selective nanomolar agonists of PPARγ. This subtype selectivity is lost in derivatives (**23**, **24**) with an alkynyl (oct-1-yn) chain at the C3 position, although the cyclopentenone derivative with *cis* relative configuration (**23**) showed greater affinity for PPARα.

Peroxisome proliferator-activated receptors (PPARs)[1,2] are members of the nuclear hormone receptor superfamily.[3] Upon activation by a ligand, these proteins act as transcription factors, regulating multiple physiological pathways including reproduction, growth, differentiation, development, energy metabolism and homeostasis.[1,2] The PPAR subfamily comprises three subtypes (α, γ and δ) that exhibit different tissue distribution and physiological function. Each subtype plays a defined role in lipid, lipoprotein and glucose homeostasis.[2] PPARα (NR1C1) is highly enriched in the liver and other tissues involved in lipid oxidation; upon binding its ligands, such as the fibrates, the activated complex stimulates lipid metabolism downregulating or upregulating genes involved in fatty acid uptake and degradation, and in reverse cholesterol transport. PPARγ (NR1C3) is highly expressed in adipose tissue, macrophages and vascular smooth muscles and acts as regulator of adipocyte differentiation and other processes that affect energy metabolism. Together, the α and γ subtypes regulate the balance between catabolism and storage of long-chain fatty acids. The PPARδ subtype (NR1C2),[4] which is ubiquitously expressed, is a potent transcriptional repressor[4a] that inhibits the ligand-induced transcriptional activity of PPARα and PPARγ. Its activation by a ligand increases HDL cholesterol levels, exerts glycemic control and improves glucose tolerance and insulin resistance in *ob*/*ob* mice.[4b]

Recent work with selective ligands has contributed to unveil the pleiotropic pharmacology of the PPAR subtypes, and confirmed that their activities extend beyond metabolic homeostasis to the treatment of inflammation, cancer and neurodegeneration.[1–3] Therefore, in addition to being relevant biological tools, ligands selective for a particular PPAR subtype hold great therapeutic potential.[5] In this regard, synthetic PPARγ agonists such as the anti-(type II)diabetic thiazolidinedione drugs (TZDs) rosiglitazone **1** and pioglitazone **2** (Fig. 1) induce adipocyte gene expression and stimulate their differentiation in cell culture,[6] although their use is not free from associated side effects, namely body weight gain (including heart weight of rodents), adipose tissue proliferation and fatty acid changes in bone marrow, and also cardiovascular risks.[7]

The identity of the physiological ligand for PPARγ remains a matter of controversy. Some natural ligands with fatty acid and eicosanoid skeletons are known to bind to and activate PPARγ at micromolar concentrations.[8–10] These include linoleic acid, linolenic acid, arachidonic acid, eicosapentaenoic acid (EPA), and metabolites of the 15-lipoxygenase pathway such as 9-HODE and 13-HODE.[8] The most potent natural PPARγ ligand is the prostaglandin derivative 15-deoxy-$\Delta^{12,14}$-PGJ_2 **3** (Fig. 1),[9] which induces differen-

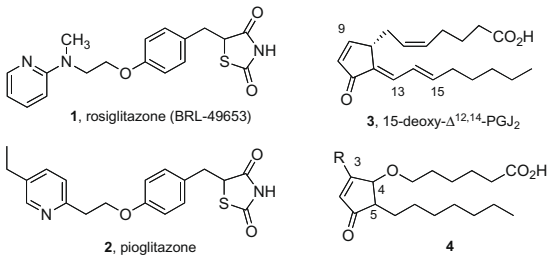


Figure 1. Antidiabetic glitazones (**1**, **2**), 15-deoxy-$\Delta^{12,14}$-PGJ_2 **3** and analogues **4**.

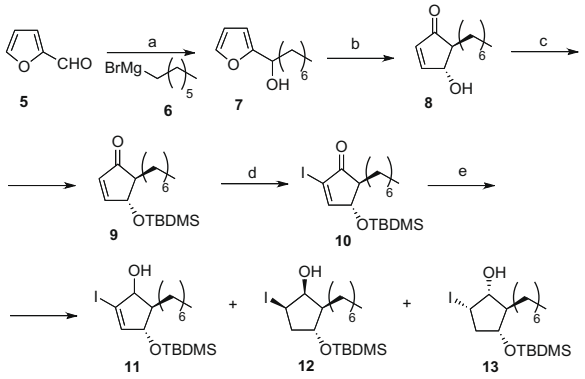
* Corresponding author.
E-mail address: qolera@uvigo.es (Á.R. de Lera).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.02.072

tiation of adipocytes at low micromolar concentrations and represses the expression of several genes in activated macrophages, including iNOS (NO synthase) and TNFα.[10a] Although this metabolite has been considered an endogenous ligand of PPARγ, and as such might exert some of its effects via receptor binding and transactivation, activities that appear to be independent of PPARγ binding are increasingly being discovered.[10b] The functional studies are however limited by the instability of the ligand, which is even greater than that of common prostaglandins since the bis-unsaturated alkylidenecyclopentenone structure of 15-deoxy-$\Delta^{12,14}$-PGJ_2 **3** renders this compound particularly prone to Michael addition. In fact, covalent binding of **3** to PPARγ by addition of a sulfahydryl of a cysteine (Cys285) residue of the LBP to the unsaturated ketone has been demonstrated.[11]

In order to fully exploit the therapeutic potential of these PG-related compounds, more stable cyclopentenones that retain PPAR transcriptional activity are highly desirable. We report herein the preparation of a series of PPAR ligands with cyclopentenone core structure (compounds **4**) having substituents at C3 and C5 as well as a ω-4-alkoxy carboxylic acid side chain. Transient transactivation studies confirmed the PPARγ activation profile of the C3-iodocyclopentenones, which are nanomolar agonists, thus considerably more potent than ligand **3**. This activity is largely independent of the relative configuration of the 4,5-disubstituted cyclopentenone ring but is very sensitive to the substitution of the iodine atom by a hydrogen or a long alkynyl chain.

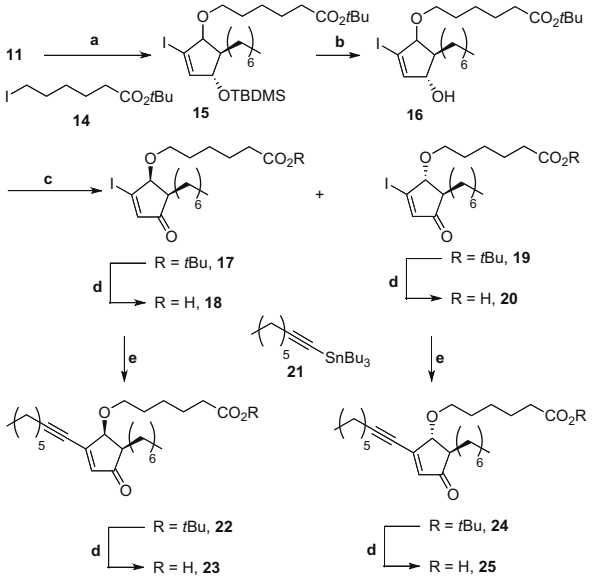
The synthetic sequence started with the preparation of *trans*-5-heptyl-4-hydroxycyclopentenone **8** from alcohol **7** (the addition product of heptylmagnesium bromide **6** to furfural **5**) according to the procedure described by Piancatelli.[12] The transformation of **7**–**8** involves the rearrangement of a hydroxypentadienyl carbocation through a Nazarov-type electrocyclic reaction.[13] In practice, 2-furylcarbinol **7** was heated to 65 °C for 48 h in the presence of substoichiometric quantities of polyphosphoric acid in a 2:1 (v/v) acetone/H_2O mixture. Variable amounts of the starting material were partially recovered and recycled. The corrected yield of the transformation was 50%. The direct alkylation of the C4-hydroxy group of **8** was unsuccessful, and all our attempts led to the rearrangement product with the isomeric 2-alkyl-4-hydroxycyclopentenone skeleton.[12,14] Therefore, protection of **8** as silyl ether **9** with TBDMSCl/DMAP and Et_3N[15] in CH_2Cl_2 was followed by α-iodination to **10** upon addition of a solution of iodine in a CH_2Cl_2/pyridine mixture[16] to a cooled (0 °C) solution of **9** (87% yield). Reduction of the carbonyl group required the use of excess Luche's reagent ($NaBH_4$, $CeCl_3{\cdot}7H_2O$ in MeOH).[17] The diastereomeric alcohols (1*S**,4*S**,5*R**)- and (1*R**,4*S**,5*R**)-**11** were obtained in a 1:1 ratio accompanied by small amounts of products **12** and **13** resulting from overreduction (Scheme 1) (87% overall yield). The inseparable mixture of diastereomers **11** was carried on through the following steps.



Scheme 1. Reagents and reaction conditions: (a) Mg, 1-bromoheptane, diethyl ether, reflux; then 25 °C, 2 h (85%); (b) PPA, acetone/H_2O (2:1 v/v), 65 °C, 48 h (50% brsm); (c) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0–25 °C, 12 h (81%); (d) I_2, pyridine/CH_2Cl_2, 0–25 °C, 2 h (87%); (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 2 h [**11** (64%), **12** (9%), **13** (14%)].

O-alkylation was achieved by treatment[18] of **11** with *tert*-butyl 6-iodohexanoate **14**[19] in DMF at 0 °C (79%). Desilylation was carried out using a solution of *n*-Bu_4NF in THF at 25 °C for 10 h, affording the mixture of alcohols **16** in 99% yield (Scheme 2). Oxidation of **16** with PDC[20] in CH_2Cl_2 required stirring for 12 h at 25 °C (94%) and the mixture of ketones **17** and **19** was separated at this stage by column chromatography.[21] Hydrolysis of the *tert*-butyl esters **17** and **19** was carried out with TFA,[22] affording carboxylic acids **18** and **20**, respectively, in high yields. Copper-promoted Stille cross-coupling[23] [$(CH_3CN)_2PdCl_2$, CuI, $AsPh_3$, NMP, 80 °C, 40 min] with the stannane **21** derived from oct-1-yne[24] provided enynes **22** and **24**, in 89% and 95% yields, respectively. Hydrolysis with TFA produced carboxylic acids **23** and **25** in quantitative yield.

The activity of the cyclopentenones as PPAR ligands was measured in transactivation assays in a cellular context that is more representative of a physiological response than a binding assay. We used a reporter assay with genetically engineered HeLa cell lines that had been stably cotransfected with a chimeric receptor construct and the cognate reporter gene to evaluate the effects of the described cyclopentenones on PPARα, PPARδ, and PPARγ-mediated transactivation. The system is based on fusion proteins, which consist of the ligand-binding domain of the corresponding receptor and the DNA-binding domain of the yeast Gal4 transcription factor. The cells also contain stably integrated luciferase reporters, which are controlled by five Gal4 response elements in front of a minimal β-globin promoter; these are referred to as reporter genes '(17mer)5-βGlob-Luc-SVNeo and Gal-PPAR[DEF](α,δ,γ)-puro'. In this assay, the activation or inhibition of receptors by an agonist (activator) or an inverse agonist (inhibitor) in the cells leads to the induction/repression of the luciferase reporter gene which generates light in the presence of the substrate. The synthesized compounds were evaluated in 96-well plates versus a reference ligand (Fig. 2): GW9578 **26** for PPARα, GW501516 **27** for PPARδ, and rosiglitazone **1** (BRL49653) for PPARγ. Dose



Scheme 2. Reagents and reaction conditions: (a) NaH, DMF, −10 °C to 0 °C, 4 h (79%); (b) *n*-Bu_4NF, THF, 25 °C, 10 h (99%); (c) PDC, CH_2Cl_2, 0–25 °C, 12 h [**17** (47%), **19** (47%)]; (d) TFA, 25 °C, 5–10 min [**18** (99%), **20** (83%), **23** (99%), **25** (99%)]; (e) $(CH_3CN)_2PdCl_2$, $AsPh_3$, CuI, NMP, 80 °C, 40 min [**22** (89%), **24** (95%)].

response curves were constructed and the concentration at which 50% of the maximal activation is achieved was calculated. The EC_{50} values of each compound expressed in nM for the three PPAR subtypes (α,δ,γ) is shown in Table 1.

The diastereomeric C3-iodocyclopentenones **18** and **20** exhibited nanomolar affinities for the PPARγ subtype, with the *cis* isomer **18** transactivating exclusively through PPARγ. There is a change in subtype selectivity for the C3-alkynylsubstituted derivatives **23** and **25**, which showed a higher affinity for PPARα, with **23** exhibiting greater discrimination among subtypes than reference agonist GW9578 **26**. Moreover **25** retains some of the PPARδ activity of iododerivative **20**, which might be associated to the *trans* relative configuration of the substituents at the cyclopentenone core in both structures. The effect of the halogen is most pronounced, since the non-iodinated analogues **28** and **29** (Fig. 2, synthesis not shown) exhibited weak affinity for all the PPAR subtypes (Table 1).

We then addressed by Molecular Docking the interaction of the potent and selective ligands **18** and **20** with PPARγ. Understanding the structural factors responsible for the subtype selectivity is not a trivial endeavor in these nuclear receptors, since the Y-shaped LBP of the PPAR subtypes is a large domain[25] and thus capable of binding a variety of synthetic ligands and fatty acids (and even two fatty acids simultaneously[26]) in alternative conformations as shown in several crystal structures.[27] First, the geometry of the ligands was optimized using the ab initio quantum chemistry program GAUSSIAN 03[28] and the B3LYP/6-31G* basis set, in conjunction with the Stuttgart/Dresden—relativistic-effective core potential for iodine. The choice of the PPARγ-(*R*)-**31** complex crystal structure (PDB code 2i4j)[27c] was prompted by the presence in **31**, an analogue of ureidofibrate GW2331 **30**, of an alicyclic chain connected to a five-membered ring core, which is also found in ligands **18** and **20**. The genetic algorithm[29] implemented in AutoDock[30] with the target PPARγ crystal structure upon removal of the ligand (*R*)-**31** was used to generate different PPARγ-cyclopentenone **18**/**20** conformers by randomly changing torsion angles and the overall orientation of the molecules. A volume for exploration was defined in the shape of a three-dimensional cubic grid with a spacing of 0.3 Å that enclosed the residues that are known to constitute the ligand-binding pocket. At each grid point, the atomic affinity potentials for the carbon, oxygen, iodine and hydrogen atoms present in **18**/**20** were pre-calculated for rapid intra- and intermolecular energy evaluation of the docking solutions. To obtain additional validation of the proposed binding mode for the ligand, GRID[31] was also used to search for sites on the receptor that could be complementary to the functional groups present in the ligand. For the GRID calculations, a 18 Å × 21 Å × 21 Å lattice of points spaced at 0.5 Å was established at the binding site, with C3 (CH_3 group), COO^- (aliphatic carboxylate) and I (iodine) as probes, and dielectric constants of 4.0 for the macromolecule and 80.0 for the bulk water.

Table 1
PPAR-transcriptional activities (EC_{50} in nM) of cyclopentenones and reference agonists

Compound	PPARα	PPARδ	PPARγ
18	NA[a,b]	NA	60
20	1000	500	30
23	500	NA	4000
25	500	2000	8000
28	ND[c]	2000	2000
29	1000	NA	4000
GW9578, **26**	250	1000	250
GW501516, **27**	NA	8	NA
Rosiglitazone, **1**	NA	NA	15

[a] NA: not active.
[b] Activity cut-off: >10,000.
[c] ND: not determined.

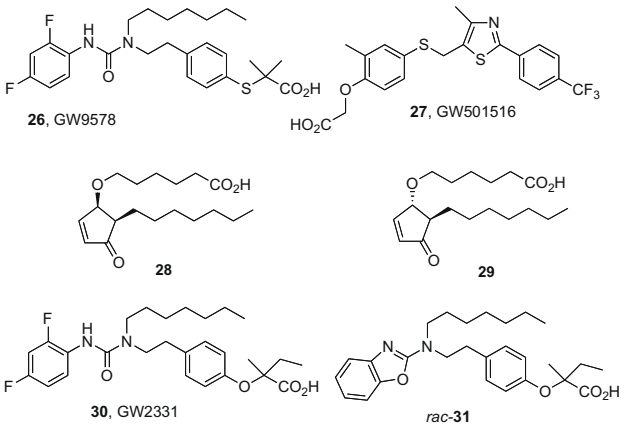


Figure 2. Structures of PPAR reference agonists (**26**, **27**), the non-iodinated cyclopentenones **28** and **29**, and ligands GW4331 **30** and analogue *rac*-**31**.

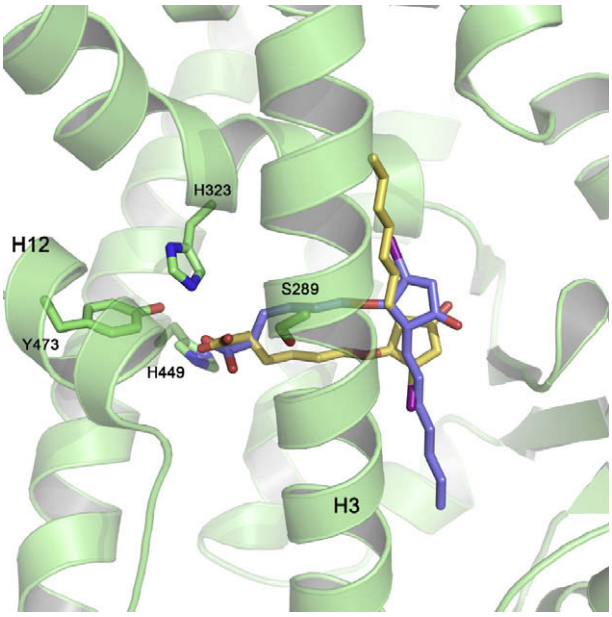


Figure 3. Superimposition of the docking solution for cyclopentenones **18** (in yellow) and **20** (in blue).

A variety of binding modes were found by the automated docking method in the region delimited for exploration, but the majority were judged as unproductive. The highest score for the docking pose PPARγ-**18** and PPARγ-**20** was selected as representative (Fig. 3). The docking was validated by the GRID maps.[32]

Iodocyclopentenones bind in a similar orientation than other PPARγ inhibitors like the ureidofibrate derivatives **31** (in this case, whereas the *R* enantiomer is a full agonist, the *S* enantiomer is a partial agonist in transient transactivation assays).[27c] The carboxylic acid establishes contacts with Tyr_{473} and His_{323} (Fig. 3) as well as with His_{449} and Ser_{289} (not shown for clarity). Diastereomer **20** shows an opposite orientation of the alkyl chain relative to **18**, pointing towards the region that other fatty acid ligands such as DHA occupy (see S.I.).

This binding mode moreover explains the drastic reduction of activity of the derivatives with an alkyne substituent in place of the halogen atom at C3 since the halogen points towards a rather restricted region. The fact that the non-iodinated cyclopentenones **28** and **29** show also reduction in binding affinity despite their smaller size suggests instead the likely involvement of stabilizing 'halogen bonds'[33] or charge-transfer complex from binding pocket heteroatom lone pairs (Lewis base) to the halogen (Lewis acid). A

recent thermodynamic study has highlighted the role of the ligand halogen atoms (identity and position) on protein–ligand binding parameters.[34]

In conclusion, these preliminary results establish proof-of-principle that more stable analogues of 15-deoxy-$\Delta^{12,14}$-PGJ_2 **3** with cyclopentenone structure[35] can be generated that exhibit PPARγ-subtype selectivity and greater potency than the native ligand. Since the synthetic scheme allows for the straightforward incorporation of additional substituents at C3 (other halogens, alkyl, alkenyl, aryl or alkynyl group via Pd-catalyzed cross-coupling reactions) a greater number of PPARγ ligands are being prepared, aided by molecular modeling, in order to better define the requirements of the PPAR subtype selectivity in these series.

Acknowledgments

The authors are grateful to the MEC-Spain (SAF2007-63880-FEDER) and Xunta de Galicia (fellowship to M. Paz Otero, Grant 08CSA052383PR from DXI+D+i; Consolidación 2006/15 from DXPCTSUG). Galderma R&D (Sophia-Antipolis, France) is gratefully acknowledged for financial support of this work and biological evaluation of the cyclopentenones.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.02.072.

References and notes

1. Kliewer, S. A.; Umesono, K.; Noonan, D. J.; Heyman, R. A.; Evans, R. M. *Nature* **1992**, *358*, 771.
2. Mangelsdorf, D. J.; Evans, R. M. *Cell* **1995**, *83*, 841.
3. (a) Devchand, P. R.; Keller, H.; Peters, J. M.; Vazquez, M.; Gonzalez, F. J.; Wahli, W. *Nature* **1996**, *384*, 39; (b) Hertz, R.; Berman, I.; Keppler, D.; Bar-Tana, J. *Eur. J. Biochem.* **1996**, *235*, 242; (c) Spiegelman, B. M. *Cell* **1998**, *93*, 153; (d) Kliewer, S. A.; Lehmann, J. M.; Willson, T. M. *Science* **1999**, *284*, 757; (e) Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527; (f) Kersten, S.; Desvergne, B.; Wahli, W. *Nature* **2000**, *405*, 421; (g) Nencioni, A.; Wesselborg, S.; Brossart, P. *Crit. Rev. Immunol.* **2003**, *23*, 1; (h) Shearer, B. G.; Hoekstra, W. J. *Curr. Med. Chem.* **2003**, *10*, 267; (i) Rangwala, S. M.; Lazar, M. A. *Trends Pharm. Sci.* **2004**, *25*, 331; (j) Evans, R. M.; Barish, G. D.; Wang, Y. X. *Nat. Med.* **2004**, *10*, 355.
4. (a) Oliver, W. R., Jr.; Shenk, J. L.; Snaith, M. R.; Russell, C. S.; Plunket, K. D.; Bodkin, N. L.; Lewis, M. C.; Winegar, D. A.; Sznaidman, M. L.; Lambert, M. H.; Xu, H. E.; Sternbach, D. D.; Kliewer, S. A.; Hansen, B. C.; Willson, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5306; (b) Shi, Y.; Hon, M.; Evans, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 2613; (c) Tanaka, T.; Yamamoto, J.; Iwasaki, S.; Asaba, H.; Hamura, H.; Ikeda, Y.; Watanabe, M.; Magoori, K.; Ioka, R. X.; Tachibana, K.; Watanabe, Y.; Uchiyama, Y.; Sumi, K.; Iguchi, H.; Ito, S.; Doi, T.; Hamakubo, T.; Naito, M.; Auwerx, J.; Yanagisawa, M.; Kodama, T.; Sakai, J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 15924.
5. (a) Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E.; Collins, J. L.; Harrington, W. W., Jr.; Hashim, M. A.; Hull-Ryde, E. A.; Kaldor, I.; Kliewer, S. A.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J. M.; Lenhard, J. M.; Orband-Miller, L. A.; Miller, J. F.; Mook, R. A., Jr.; Noble, S. A.; Oliver, W., Jr.; Parks, D. J.; Plunket, K. D.; Szewczyk, J. R.; Willson, T. M. *J. Med. Chem.* **1998**, *41*, 5020; (b) Collins, J. L.; Blanchard, S. G.; Boswell, G. E.; Charifson, P. S.; Cobb, J. E.; Henke, B. R.; Hull-Ryde, E. A.; Kazmierski, W. M.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J.; Lenhard, J. M.; Orband-Miller, L. A.; Gray-Nunez, Y.; Parks, D. J.; Plunkett, K. D.; Tong, W. Q. *J. Med. Chem.* **1998**, *41*, 5037; (c) Cobb, J. E.; Blanchard, S. G.; Boswell, E. G.; Brown, K. K.; Charifson, P. S.; Cooper, J. P.; Collins, J. L.; Dezube, M.; Henke, B. R.; Hull-Ryde, E. A.; Lake, D. H.; Lenhard, J. M.; Oliver, W., Jr.; Oplinger, J.; Pentti, M.; Parks, D. J.; Plunket, K. D.; Tong, W. Q. *J. Med. Chem.* **1998**, *41*, 5055.
6. (a) Hiragun, A.; Sato, M.; Mitsui, H. *J. Cell. Physiol.* **1988**, *134*, 124; (b) Hauner, H. *Diabetes/Metab. Res. Rev.* **2002**, *18*, S10; (c) Kletzien, R. F.; Clarke, S. D.; Ulrich, R. G. *Mol. Pharmacol.* **1992**, *41*, 393.
7. (a) Tugwood, J. D.; Montague, C. T. *Human Exp. Toxicol.* **2002**, *21*, 429; (b) Pickavance, L. C.; Tadayyon, M.; Widdowson, P. S.; Buckingham, R. E.; Wilding, J. P. H. *Br. J. Pharmacol.* **1999**, *128*, 1570.
8. (a) Krey, G.; Braissant, O.; L'Horset, F.; Kalkhoven, E.; Perrodu, M.; Parker, M. G.; Wahli, W. *Mol. Endocrinol.* **1997**, *11*, 779; (b) Kliewer, S. A.; Sundseth, S. S.; Jones, S. A.; Brown, P. J.; Wisely, G. B.; Koble, C. S.; Devchand, P.; Wahli, W.; Willson, T. M.; Lenhard, J. M.; Lehmann, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 4318.
9. (a) Kliewer, S. A.; Lenhard, J. M.; Willson, T. M.; Patel, I.; Morris, D. C.; Lehmann, J. M. *Cell* **1995**, *83*, 803; (b) Forman, B. M.; Tontonoz, P.; Chen, J.; Brun, R. P.; Spiegelman, B. M.; Evans, R. M. *Cell* **1995**, *83*, 813.
10. (a) Straus, D. S.; Pascual, G.; Li, M.; Welch, J. S.; Ricote, M.; Hsiang, C. H.; Sengchanthalangsy, L. L.; Ghosh, G.; Glass, C. K. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 4844; (b) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185.
11. (a) Shiraki, T.; Kamiya, N.; Shiki, S.; Kodama, T. S.; Kakizuka, A.; Jingami, H. *J. Biol. Chem.* **2005**, *280*, 14145; (b) Soares, A. F.; Nosjean, O.; Cozzone, D.; D'Orazio, D.; Becchi, M.; Guichardant, M.; Ferry, G.; Boutin, J. A.; Lagarde, M.; Géloën, A. *Biochem. Biophys. Res. Commun.* **2005**, *337*, 521.
12. (a) Piancatelli, G.; Scettri, A.; David, G.; D'auria, M. *Tetrahedron* **1978**, *34*, 2775; (b) Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, *17*, 3555; (c) Piancatelli, G.; Scettri, A. *Synth. Commun.* **1977**, *7*, 116; (d) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867.
13. Nieto Faza, O.; Silva Lopez, C.; Alvarez, R.; de Lera, A. R. *Chem. Eur. J.* **2004**, *10*, 4324.
14. These 2-alkyl-4-hydroxycyclopentenones are the starting materials for the synthesis of isoprostanes, phytoprostanes and other polyunsaturated fatty acids (PUFAs). For a recent review, see: Jahn, U.; Galano, J-M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894.
15. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
16. (a) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 7027; (b) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919.
17. (a) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848; (b) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226; (c) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
18. Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.
19. Stewart, C. A.; VanderWerp, C. A. *J. Am. Chem. Soc.* **1954**, *76*, 1259.
20. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
21. The assignment of the relative configurations relied on the value of the coupling constants of 2.0 Hz and 6.4 Hz for **17** and **19**, respectively, corresponding to those computed using the Karplus equation (Crews, P.; Rodriguez, J.; Jaspars, M., *Organic Structure Analysis*. Oxford University Press: New York, 1998; chapter 4) for the C_5–C_4 dihedral (120° and 25°, respectively measured with Spartan; Wavefunction, I. V. K., Suite 370 *PC Spartan, with semiempirical AM1*, Irvine, CA.).
22. Hostetler, E. D.; Fallis, S.; McCarthy, T.; Welch, M. J.; Katzenellenbogen, J. A. *J. Org. Chem.* **1998**, *63*, 1348.
23. (a) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508; (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771; (c) Mitchell, T. N. *Synthesis* **1992**, 803; (d) Farina, V.; Roth, G. P.. In *Advances in Metal–Organic Chemistry*; JAI Press: New York, 1996; Vol. 5; (e) Farina, V.; Krishnamurthy, V.; Scott, W. J., *Organic Reactions*. New York, 1997; Vol. 50, Chapter 1.; (f) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73; (g) Mitchell, T. N. Organotin Reagents in Cross-Coupling Reactions. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 125–161. Chapter 3.
24. (a) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138; (b) Shirakawa, E.; Morita, R.; Tsuchimoto, T.; Kawakami, Y. *J. Am. Chem. Soc.* **2004**, *126*, 13614.
25. Markt, P.; Petersen, R. K.; Flindt, E. N.; Kristiansen, K.; Kirchmair, J.; Spitzer, G.; Distinto, S.; Schuster, D.; Wolber, G.; Laggner, C.; Langer, T. *J. Med. Chem.* **2008**, *51*, 6303.
26. Itoh, T.; Fairall, L.; Amin, K.; Inaba, Y.; Szanto, A.; Balint, B. L.; Nagy, L.; Yamamoto, K.; Schwabe, J. W. R. *Nat. Struct. Mol. Biol.* **2008**, *15*, 924.
27. (a) Cronet, P.; Petersen, J. F. W.; Folmer, R.; Blomberg, N.; Sjöblom, K.; Karlsson, U.; Lindstedt, E.-L.; Bamberg, K. *Structure* **2001**, *9*, 699; (b) Gampe, R. T., Jr.; Lambert, M. H.; Miller, A. B.; Bledsoe, R. K.; Milburn, M. V.; Kliewer, S. A.; Willson, T. M.; Xu, E. *Mol. Cell.* **2000**, *5*, 545; (c) Nolte, R. T.; Wisely, G. B.; Westin, S.; Cobb, J. E.; Lambert, M. H.; Kurokawa, R.; Rosenfeld, M. G.; Willson, T. M.; Glass, C. K.; Milburn, M. V. *Nature* **1998**, *395*, 137; (d) Pochetti, G.; Godio, C.; Mitro, N.; Caruso, D.; Galmozzi, A.; Scurati, S.; Loiodice, F.; Fracchiolla, G.; Tortorella, P.; Laghezza, A.; Lavecchia, A.; Novellino, E.; Mazza, F.; Crestani, M. *J. Biol. Chem.* **2007**, *282*, 17314; The first complete structure of a NR heterodimer, PPARγ-RXRα, including the DNA binding domain has recently been published: (e) Chandra, V.; Huang, P.; Hamuro, Y.; Raghuram, S.; Wang, Y.; Burris, T. P.; Rastinejad, F. *Nature* **2008**, *456*, 350.
28. Pople, J. A. et al. GAUSSIAN 98, revision A.11.2; Gaussian: Pittsburgh, PA, 2001.
29. Morris, G. M.; Goodsell, D. S.; Halliday, R. S.; Huey, R.; Hart, W. E.; Belew, R. K.; Olson, A. J. *J. Comput. Chem.* **1998**, *19*, 1639.
30. AutoDock: Automated docking of flexible ligands to receptors, Version 3.0, The Scripps Research Institute, La Jolla, CA, 1999.
31. Goodford, P. *J. Med. Chem.* **1985**, *28*, 849–857. http://www.moldiscovery.com/.
32. To confirm that the selected protein–ligand complex is suitable for the docking problem we have done redocking of the crystal structure ligand to the protein and determined the good reproducibility of all important ligand–protein interactions of the crystal structure ligand (see S.I., Fig. 1).
33. (a) Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. *Acc. Chem. Res.* **2005**, *38*, 386; (b) Auffinger, P.; Hays, F. A.; Westhof, E.; Ho, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16789.
34. Memic, A.; Spaller, M. R. *ChemMedChem* **2008**, *9*, 2793.
35. A series of alkylidenecyclopentenones with the same skeleton of 15-deoxy-$\Delta^{12,14}$-PGJ_2 **3** have recently been described, but their PPARγ transactivation potency is lower than that of compound **18**, and no studies with the other PPAR paralogues were reported; see: Iqbal, M.; Duffy, P.; Evans, P.; Cloughley, G.; Allan, B.; Lledó, A.; Verdaguer, J.; Riera, A. *Org. Biomol. Chem.* **2008**, *6*, 4649.