Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 3347–3351
Bioorganic & Medicinal Chemistry Letters

(2*R*)-2-Methylchromane-2-carboxylic acids: Discovery of selective PPARα agonists as hypolipidemic agents

Hiroo Koyama,[a,*] Julia K. Boueres,[a] Daniel J. Miller,[a] Joel P. Berger,[a] Karen L. MacNaul,[b] Pei-ran Wang,[c] Marc C. Ippolito,[c] Samuel D. Wright,[c] Arun K. Agrawal,[d] David E. Moller[b] and Soumya P. Sahoo[a,*]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000 Rahway, NJ 07065, USA*
[b]*Department of Metabolic Disorders-Diabetes, Merck Research Laboratories, PO Box 2000 Rahway, NJ 07065, USA*
[c]*Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, PO Box 2000 Rahway, NJ 07065, USA*
[d]*Department of Drug Metabolism, Merck Research Laboratories, PO Box 2000 Rahway, NJ 07065, USA*

Received 15 April 2005; revised 6 May 2005; accepted 10 May 2005
Available online 9 June 2005

Abstract—A SAR study was conducted on chromane-2-carboxylic acid toward selective PPARα agonisim. As a result, highly potent, and selective PPARα agonists were discovered. The optimized compound **43** exhibited robust lowering of total cholesterol levels in hamster and dog animal models.

Atherosclerosis is a chronic disease characterized by the accumulation of lipids and fibrous connective tissue on the arterial wall. Atherosclerosis is a major cause of cardiovascular diseases such as myocardial infarction and stroke, and significantly contributes to the mortality and morbidity in industrialized nations.[1,2] Epidemiological studies have indicated that dyslipidemia and coagulation disturbances are among the most significant risk factors of the development of atherosclerotic condition. Current pharmacological treatment of atherosclerosis includes the use of the statin class HMG-CoA reductase inhibitors[3] and the fibrate class PPARα agonists[4–10] (Fig. 1). These two classes of agents mainly cause their beneficial effects correcting atherogenic dyslipidemia (elevated levels of triglyceride and small LDL-particles, and low HDL-c level). Statins mainly work by lowering the serum LDL-c levels, and their effect on HDL-c level is relatively modest. Fibrates have been used in the clinic over the last three decades and their mode of action has been recently identified as PPARα activation.[11–15] Activation of PPARα causes: (1) lowering of serum triglyceride level via accelerated β-oxidation of fatty acid and down-regulation of apo CIII gene, and (2) elevation of HDL-c level via up-regulation of apoAI gene. In addition, more recent studies have suggested that PPARα activation might have direct effects on the arterial wall treating the inflammation aspect of atherosclerosis.[6,8]

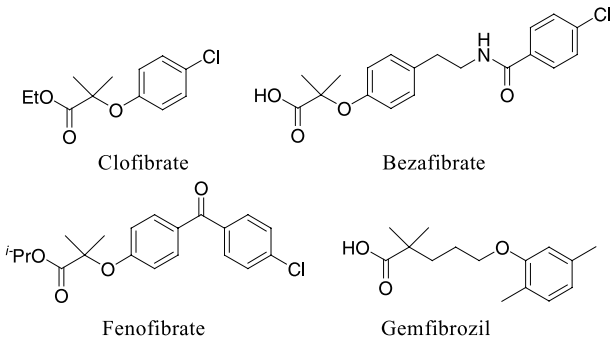


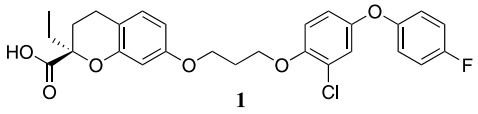
Figure 1. The fibrate class of hypolipidemic agents.

In contrast with the significant level of interest in PPARγ agonists as a new class of antidiabetic agents in the pharmaceutical industry,[12,16–22] the level of interest in the development of new PPARα agonists as hypolipidemic agents appears to be moderate.[23–27] Although fibrates' effectiveness in the reduction of cardiovascular events has been amply demonstrated in

Keywords: PPAR; Chromane-2-carboxylic acid; Atherosclerosis.
* Corresponding authors. Tel.: +1 732 594 3004; fax: +1 732 594 9556; e-mail: hiroo_koyama@merck.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.05.028

large clinical trials and fibrates have enjoyed generally good safety profiles, concomitant use of fibrates and statins has met with serious safety concerns as exemplified by the withdrawal of Cerivastatin in 2001. Furthermore, a more recent study revealed that fibrates are not selective agonists of PPARα and their effects on other isoforms of PPARs are rather complex.[12] With this background, the authors thought that there would be room for new selective PPARα agonists for the treatment of atherogenic dyslipidemia.



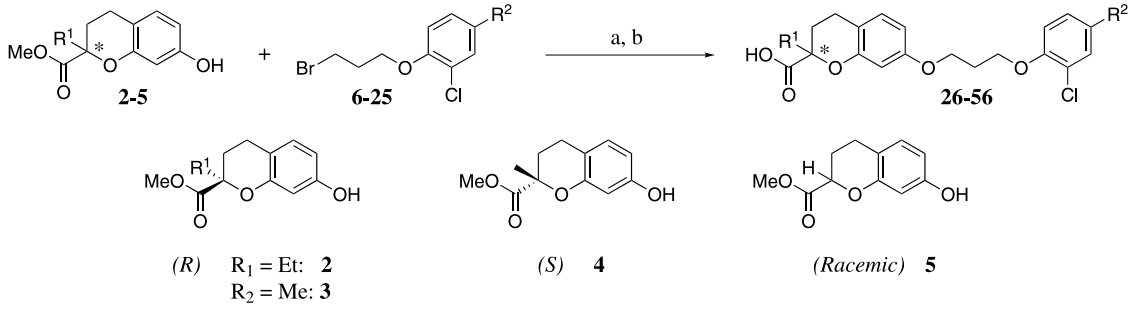
1

hPPAR TA EC_{50} [μM]: α 0.04; δ >15; γ 0.17

Figure 2. Chromane-2-carboxylic acid as a PPARα/γ dual agonist.

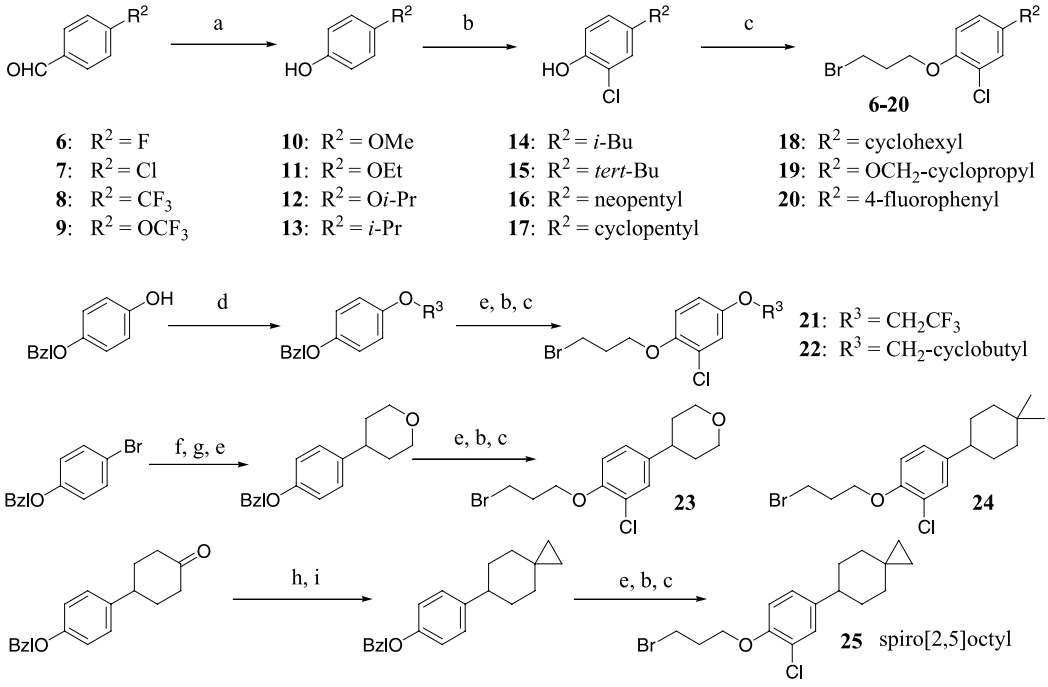
During the course of our SAR studies of chromane-2-carboxylic acid toward PPARα/γ dual agonism culminating in the discovery of compound **1** (Fig. 2),[28] it became clear that the phenoxy group at the end of the molecule was critically important for PPARγ activity. Conversely, it appeared that removal of the phenoxy group might generate selective PPARα agonists. Based on this assumption, we set out to conduct a SAR study on chromane-2-carboxylic acid toward selective PPARα agonism with an emphasis on the replacement of the 4-fluorophenoxy group of compound **1**.

General synthesis of chromane-2-carboxylic acids **26–56** is shown in Scheme 1. Chromane-2-carboxylates **2–5** were synthesized following the published procedure.[28–30] Synthesis of compounds **26–56** was accomplished by an ether bond formation between the phenols **2–5** and the bromides **6–25** followed by hydrolysis of the methyl ester. Synthesis of the bromides is described in Scheme 2. Bromides **6–20** were synthesized from appropriately



(R) R_1 = Et: **2**; R_2 = Me: **3** *(S)* **4** *(Racemic)* **5**

Scheme 1. Reagents and conditions: (a) Cs_2CO_3, DMF, 65 °C, 68–90%; (b) 5 N NaOH, *i*-PrOH, 70 °C, 12 h, 85–95%.



6: R^2 = F; **7**: R^2 = Cl; **8**: R^2 = CF_3; **9**: R^2 = OCF_3

10: R^2 = OMe; **11**: R^2 = OEt; **12**: R^2 = O*i*-Pr; **13**: R^2 = *i*-Pr

14: R^2 = *i*-Bu; **15**: R^2 = *tert*-Bu; **16**: R^2 = neopentyl; **17**: R^2 = cyclopentyl

18: R^2 = cyclohexyl; **19**: R^2 = OCH_2-cyclopropyl; **20**: R^2 = 4-fluorophenyl

6-20

21: R^3 = CH_2CF_3; **22**: R^3 = CH_2-cyclobutyl

23 **24** **25** spiro[2,5]octyl

Scheme 2. Reagents: (a) mCPBA, 56–76%; (b) SO_2Cl_2, diisobutylamine, 62–91%; (c) 1,3-dibromopropane, Cs_2CO_3, 65–85%; (d) 2,2,2-trifluoroethyl trifluoromethane sulfonate or bromomethylcyclobutane, Cs_2CO_3, 56–73%; (e) H_2, 10%, Pd/C, 95%; (f) Mg turnings, tetrahdyro-2*H*-pyran-4-one 65%; (g) HCl/MeOH, 91%; (h) $Ph_3P{=}CH_2$, 90%; (i) CH_2N_2, $Rh_2(OAc)_4$, 53%.

substituted ether benzaldehydes or phenols. Bromides **21** and **22** were synthesized by forming an ether bond between 4-(benzyloxy)phenol and appropriate alkylating agents followed by a protocol similar to the synthesis of **6**–**20**. Bromides **23** and **24** were synthesized starting from 4-benzyloxy bromobenzene and tetrahydro-2*H*-pyran-4-one or 4,4-dimethylcyclohexane-1-one via Grignard reaction followed by dehydration and hydrogenation. For the spiro[2,5]octane compound **25**, Wittig exomethylene formation to the cyclohexanone derivative and following cyclopropanation were used to introduce the cyclopropane moiety.

Table 1 summarizes the in vitro activities of compounds **1** and **26**–**56**. For the replacement of the 4-fluorophenoxy group of compound **1**, we decided to investigate the effects of acyclic and cyclic aliphatic groups on the activity and selectivity. By and large, compounds are listed in the order of the size of the substituents. When the activities and selectivities of compounds **26** through **37** are compared, binding affinity and isoform selectivity are sensitive to the size of the R^2 substituent. Among them, compounds **30** ($R^2 = OCH_2CF_3$), **32** (R^2 = *i*-Bu), and **34** (R^2 = cyclohexyl) appeared to have desirable potency (TA PPARα $EC_{50} < 10$ nM) and no significant binding to PPARδ. Compounds **35**–**37** were synthesized in an attempt to improve on a relatively high clearance of **34** in rat pharmacokinetics (Table 2). The 4-position of the cyclohexyl moiety of **34** was sterically unhindered and seemed to be vulnerable to metabolism.[31] Results of the pharmacokinetic studies of **35** and **36** indicated that the addition of 4,4-cyclopropyl (**35**) or 4,4-dimethyl (**36**) groups helped improve the pharmacokinetic profile (clearance or exposure) as compared with **34**. However, this improvement occurred at the expense of the binding affinity, which appeared to be deriving from the size requirement of the receptor and ligand. Tetrahydropyran compound **37** was synthesized with the intention of improving on the pharmacokinetic profile without significantly changing the size of the cyclohexyl group. However, it turned out that **37** had less desirable pharmacokinetic profile than **34** in addition to reduced PPARα activity.

Table 1. In vitro human PPAR activities of compounds **1** and **26**–**56**

Compound	*R*/*S*	R^1	R^2	Binding IC_{50} (μM)[a]			Transactivation EC_{50} (μM)[b]	
				α	δ	γ	α	γ
26	*R*	Et	F	>15	>15	4.3	NA[c]	3
27	*R*	Et	Cl	0.40	4.1	2.9	0.13	1
28	*R*	Et	CF_3	0.09	2.3	4.3	0.036	1
29	*R*	Et	OCF_3	0.037	1.9	2.6	0.006	0.5
30	*R*	Et	OCH_2CF_3	0.066	>50	0.99	0.004	0.4
31	*R*	Et	*i*-Pr	0.038	>15	2.9	0.024	1.2
32	*R*	Et	*i*-Bu	0.029	>50	1.8	0.007	0.6
33	*R*	Et	*tert*-Bu	0.18	>50	2.8	0.028	1
34	*R*	Et	Cyclohexyl	0.015	>50	1.4	0.005	0.4
35	*R*	Et	Spiro[2,5]octyl-6yl	0.61	>50	3.7	0.3	0.5
36	*R*	Et	4,4-Dimethyl cyclohexyl	1.7	>50	5.7	0.7	1.4
37	*R*	Et	4-Tetrahydropyranyl	0.71	>50	>15	0.022	NA
38	*R*	Me	F	>15	>50	>15	NT	NT[d]
39	*R*	Me	OMe	3.9	>50	>15	NT	NT
40	*R*	Me	OCF_3	0.057	0.49	>15	0.02	NA
41	*R*	Me	OEt	1.38	>15	>15	0.22	NA
42	*R*	Me	O*i*-Pr	0.24	7.4	>15	0.04	NA
43	*R*	Me	OCH_2CF_3	0.11	>15	6.0	0.04	3
44	*R*	Me	OCH_2-cyclopropyl	0.6	>15	>15	0.24	NA
45	*R*	Me	OCH_2-cyclobutyl	0.39	>15	2.0	0.14	0.7
46	*R*	Me	*i*-Pr	0.048	>15	5.0	0.023	3
47	*R*	Me	*i*-Bu	0.016	7.6	3.0	0.006	0.5
48	*R*	Me	*tert*-Bu	0.23	>50	>15	0.08	NA
49	*R*	Me	Neopentyl	0.007	14	>15	0.004	NA
50	*R*	Me	Cyclopentyl	0.04	10.5	3.8	0.009	0.7
51	*R*	Me	Cyclohexyl	0.028	>15	5.8	0.002	0.7
52	*R*	Me	Spiro[2,5]octyl-6yl	1.6	>50	4.5	0.42	1
53	*R*	Me	4,4-Dimethyl cyclohexyl	1.7	>50	6.4	1	1
1	*R*	Et	4-Fluorophenoxy	0.06	>15	0.26	0.04	0.17
54	*R*	Me	4-Fluorophenoxy	0.14	5.0	0.90	0.061	0.24
55	*S*	Me	OCH_2CF_3	>50	>50	2.7	NA	NA
56	Racemic	H	OCH_2CF_3	0.81	6.9	4.1	0.12	3

All data SD ± 15% ($n = 3$).

[a] Binding affinities were measured using radioligands following published procedure.[32]

[b] Agonist activities were measured in human PPAR-GAL4 chimeric COS-1 cells following published procedure.[33] The EC_{50} refers to the concentration yielding a 50% response relative to the standard. All compounds were full agonists.

[c] Not active (less than 20% activation at 10 μM).

[d] Not tested.

Table 2. Pharmacokinetic profiles of **34–37**, **43, 44**, **46**, **47**, and **50**

Compound	Species	iv (0.5 mg/kg)		po (2 mg/k)	
		Clp[a] (ml/min/kg)	$t_{1/2}$[b] (h)	*n*AUC[c] (μM h)	*F*[d] (%)
34	Rat	8.2 ± 1.5	1.2 ± 0.2	2.5 ± 1.1	57
35	Rat	0.62 ± 0.1	4.5 ± 0.2	2.0 ± 0.5	37
36	Rat	2.7 ± 0.7	6.8 ± 1.0	15.6 ± 3.5	95
37	Rat	15.6 ± 2.5	0.9 ± 0.1	1.8 ± 0.7	77
43	Rat	5.1 ± 1.8	2.7 ± 0.2	4.6 ± 1.1	60
43	Dog	5.8 ± 1.5	6.2 ± 0.7	16.5 ± 4.2	100
43	Monkey	5.6 ± 1.4	2.5 ± 0.4	8.4 ± 4.9	88
44	Rat	5.1 ± 2.5	2.9 ± 1.3	6.6 ± 1.3	76
46	Rat	3.2 ± 0.6	1.5 ± 0.7	8.3 ± 1.4	65
47	Rat	2.6 ± 0.2	2.9 ± 0.2	13.1 ± 3.0	87
50	Rat	6.8 ± 1.0	1.3 ± 0.2	3.0 ± 0.1	54

Mean value ± SD is shown. Fasted male Sprague–Dawley rats ($n = 3$), male adult beagle dogs ($n = 3$), and male adult Rhesus monkeys ($n = 3$) received an oral gavage dose of 2 mg/kg, or intravenous dose of 0.5 mg/kg by bolus injection.
[a] Clearance.
[b] Half-life.
[c] Dose-normalized AUC.
[d] Bioavailability.

Next, we shifted our attention to the effect of the R_1 group. Since methyl or ethyl groups were the most desirable substituents in our previous SAR studies on chromane-2-carboxylic acids, compounds with R^1 = methyl were investigated. It is interesting to note that in some cases, compounds with R^1 = methyl group had slightly higher PPARα/PPARγ selectivity than the corresponding ones with R^1 = ethyl in binding affinity (**29** vs **40**, **30** vs **43**, and **33** vs **48**), which appears to be mainly due to the decreased PPARγ binding affinity of the R_1 = methyl series. Otherwise, a similar SAR was found in the R^1 = methyl series as in the R^1 = ethyl series. For reference purposes, the enantiomer of **43** (compd **55**) and a des-methyl compound **56** were also synthesized and studied for their in vitro activities (Table 1).

Compounds with good in vitro profiles were selected for rat pharmacokinetic studies and hamster lipid studies. Table 2 summarizes the results of pharmacokinetic studies. Compounds **43**, **44**, **46**, **47**, and **50** showed desirable pharmacokinetic profiles in rat. Table 3 summarizes the results of hamster lipid studies. All compounds tested showed robust lowering of total cholesterol level. Finally, compound **43** was selected for a dog model study because of its superior PPARα functional activity, receptor isoform selectivity, pharmacokinetic profile, and efficacy in the hamster study.

Table 3. In vivo efficacy of **43, 44, 46, 47**, and **50** in hamster

Compound	Dose (mpk)	Total cholesterol[a] (%)	Triglyceride[b] (%)
43	10	−60	−54
44	10	−39	−13
46	10	−40	−18
47	10	−50	−29
50	10	−40	−21
Fenofibrate	100	−43	−23

Golden Syrian hamsters (120–150 g weight, $n = 10$) were fed normal rodent chow with free access to water and received once-a-day oral dosing of the sodium salts of tested compounds by gavage with vehicle (0.5% methylcellulose) for 9 days.
[a] SD ± 15%.
[b] SD ± 20%.

Figure 3 describes the time course of total cholesterol level in dog when **43** was dosed at three different dose levels for 14 days. Compound **43** caused robust cholesterol lowering in a dose-dependent manner when administered orally. The cholesterol lowering effect of fenofibrate and simvastatin, a statin class HMG-CoA reductase inhibitor, was also shown for comparison purposes. Given that the statins are widely used to treat hypercholesterolemia, simvastatin and **43** were co-administered with the hope of achieving a higher level of efficacy. The experimental results seem to indicate the cholesterol lowering effect of **43** and simvastatin was additive when they were administered simultaneously. Importantly, the pharmacokinetic profiles such as exposure levels, half-life, and clearance of neither **43** nor sim-

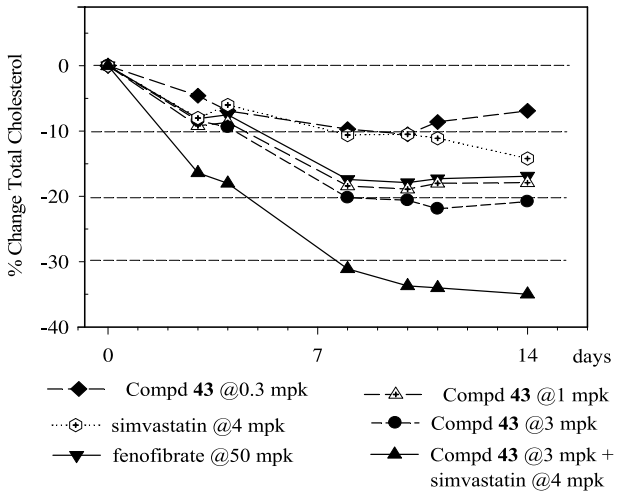


Figure 3. In vivo efficacy of **43** in dog. Mature male beagle dogs (12–18 kg weight, $n = 5$) were fed a cholesterol-free chow diet ad libitum with free access to water. Test compounds were suspended in 0.5% methyl cellulose and gavaged daily for 14 days. Mean values are shown. Data at the final day were $p < 0.05$ against vehicle control.

vastatin were significantly altered by co-administration.[34] It appears that the two different mechanisms of cholesterol lowering, PPARα activation and HMG-CoA reductase inhibition, can work in concert.

In conclusion, by taking advantages of our accumulated knowledge of chromane-2-carboxylic acid SAR with PPARα and γ, we were able to identify a class of highly potent and selective PPARα agonists. The optimized compound **43** exhibited robust cholesterol lowering in the hamster and dog models.[35]

Acknowledgments

Authors thank Mr. Joseph F. Leone, Mr. Robert A. Frankshun, and Dr. Philip Eskola for large scale synthetic support, and Drs. William P. Feeney and Susan A. Iliff for their support in pharmacological evaluation of compounds.

References and notes

1. Biondi-Zoccai, G. G. L.; Abbate, A.; Liuzzio, G.; Biasucci, L. M. *J. Am. Coll. Cardiol.* **2003**, *41*, 1071.
2. Ginsberg, H. N.; Stalenhof, A. F. *J. Cariovasc. Risk* **2003**, *10*, 121.
3. Scandinavian Simvastatin Survival Study Group *Lancet*, **1994**, *344*, 1383.
4. Vosper, H.; Khoudoli, A. G.; Graham, T. L.; Palmer, C. N. A. *Pharm. Therap.* **2002**, *95*, 47.
5. Fruchart, J.-C.; Staels, B.; Duriez, P. *Curr. Pharm. Res.* **2001**, *5*, 345.
6. Francis, G. A.; Annicotte, J.-S.; Auwerx, J. *Curr. Opin. Pharmacol.* **2003**, *41*, 393.
7. Neve, B. P.; Fruchart, J.-C.; Staels, B. *Biochem. Pharmacol.* **2000**, *60*, 1245.
8. Duval, C.; Chinetti, G.; Trottein, F.; Fruchart, J.-C.; Staels, B. *Trends Mol. Med.* **2002**, *8*, 422.
9. Fruchart, J.-C. *Am. J. Cardiol.* **2001**, *88*, 24N.
10. Barish, G. D.; Evans, R. M. *Trends Endocri. Metabol.* **2004**, *15*, 158.
11. Issemann, I.; Green, S. *Nature* **1990**, *347*, 645.
12. Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527.
13. Berger, J. P.; Moller, D. E. *Annu. Rev. Med.* **2002**, *53*, 527.
14. Kersten, S.; Desvergne, B. *Nature* **2000**, *405*, 421.
15. Desvergne, B.; Wahli, W. *Endocr. Rev.* **1999**, *20*, 649.
16. Yanagisawa, H.; Takamura, M.; Yamada, E.; Fujita, S.; Fujiwara, T.; Yachi, M.; Isobe, A.; Hagisawa, Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 373.
17. Momose, Y.; Maekawa, T.; Yamano, T.; Kawada, M.; Okada, H.; Ikeda, H.; Sohda, T. *J. Med. Chem.* **2002**, *45*, 1518.
18. Thor, M.; Beierlein, K.; Dykes, G.; Gustavsson, A.-L.; Heidrich, J.; Jendeberg, L.; Lindqvist, B.; Pegurier, C.; Roussel, P.; Slater, M.; Svesson, S.; Sydow-Bäckman, M.; Thornström, U.; Uppenberg, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3565.
19. Koyama, H.; Boureres, J. K.; Han, W.; Metzger, E. J.; Bergman, J. P.; Gratale, D. F.; Miller, D. J.; Tolman, R. L.; MacNaul, K. L.; Berger, J. P.; Doebber, T. W.; Leung, K.; Moller, D. E.; Heck, J. V.; Sahoo, S. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1801.
20. Rybczynski, P. J.; Zeck, R. E.; Combs, D. W.; Turchi, I.; Burris, T. P.; Xu, J. X.; Yang, M.; Dermarest, K. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2359.
21. Kuroda, M.; Mimaki, Y.; Sashida, Y.; Mae, T.; Kishida, H.; Nishiyama, T.; Tsukagawa, M.; Konishi, E.; Takahashi, K.; Kawada, T.; Nakagawa, K.; Kitahara, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4267.
22. Acton III, J. J.; Black, R. M.; Jones, A. B.; Moller, D. E.; Colwell, L.; Doebber, T. W.; MacNaul, K. L.; Berger, J.; Wood, H. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 357.
23. Brown, P. J.; Wingar, D. A.; Plunket, K. D.; Moore, L. B.; Lewis, M. C.; Wilson, J. G.; Sundseth, S. S.; Koble, C. S.; Wu, Z.; Chapman, J. M.; Lehmann, J. M.; Kliewer, S. A.; Willson, T. M. *J. Med. Chem.* **1999**, *42*, 3785.
24. Brown, P. J.; Stuart, L. W.; Hurley, K. P.; Lewis, M. C.; Winegar, D. A.; Wilson, J. G.; Wilkinson, W. O.; Ittoop, O. R.; Willson, T. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1225.
25. Miyachi, H.; Nomura, M.; Tanase, T.; Takahashi, Y.; Ide, T.; Tsunoda, M.; Murakami, K.; Awano, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 77.
26. Nomura, M.; Tanase, T.; Ide, T.; Tsunoda, M.; Suzuki, M.; Uchiki, H.; Murakami, K.; Miyachi, H. *J. Med. Chem.* **2003**, *46*, 3581.
27. Xu, Y.; Mayhugh, D.; Saeed, A.; Wang, X.; Thompson, R. C.; Dominanni, S. J.; Kauffman, R. F.; Singh, J.; Bean, J. S.; Bensch, W. R.; Barr, R. J.; Osborne, J.; Montrose-Rafizadeh, C.; Zink, R. W.; Yumbie, N. P.; Huang, N.; Luffer-Atlas, D.; Runga, D.; Maise, D. E.; Mantlo, N. B. *J. Med. Chem.* **2003**, *46*, 5121.
28. Koyama, H.; Miller, D. J.; Boueres, J. K.; Desai, R. C.; Jones, A. B.; Berger, J. P.; MacNaul, K. L.; Kelly, L. J.; Doebber, T. W.; Wu, M. S.; Zhou, G.; Wang, P.-R.; Ippolito, M. C.; Chao, Y.-S.; Agrawal, A. K.; Franklin, R.; Heck, J. V.; Wright, S. D.; Moller, D. E.; Sahoo, S. P. *J. Med. Chem.* **2004**, *47*, 3255.
29. Sahoo, S. P.; Koyama, H.; Miller, D. J.; Boueres, J. K.; Desai, R. C. US Patent 6,645,997, 2003; *Chem. Abstr.* **2002**, *136*, 279341.
30. Sahoo, S. P.; Koyama, H.; Boueres, J. K.; Miller, D. J.; Desai, R. C. US Patent 6,713,508, 2004; *Chem. Abstr.* **2002**, *137*, 140435.
31. Agrawal, A. K.; Hop, C. E. C. A.; Pang, J.; Elipe, M. V. S.; Desai, R. C.; Leung, K. H.; Franklin, R. B. *J. Pharm. Biomed. Anal.* **2005**, *37*, 351.
32. Berger, J. P.; Petro, A. E.; MacNaul, K. L.; Kelly, L. J.; Zhang, B. B.; Richards, K.; Elbrecht, A.; Johnson, B. A.; Zhou, G.; Doebber, T. W.; Biswas, C.; Parikh, M.; Sharma, N.; Tanem, M.; Thompson, M.; Venture, J.; Adams, A. D.; Mosely, R.; Surwit, R. S.; Moller, D. E. *Mol. Endocrinol.* **2003**, *17*, 662.
33. Berger, J.; Leibowitz, M. D.; Doebber, T. W.; Elbrecht, A.; Zhang, B.; Zhou, G.; Biswas, C.; Cullinan, C. A.; Hayes, N. S.; Li, Y.; Tanem, M.; Venture, J.; Wu, S. M.; Berger, G. D.; Mosley, R.; Marquis, R.; Santini, C.; Sahoo, S. P.; Tolman, R. L.; Smith, R. G.; Moller, D. E. *J. Biol. Chem.* **1999**, *274*, 6718.
34. Agrawal, A. K. private communication.
35. Sahoo, S. P. New Therapies for Atherosclerosis. Part of this work was presented at the 225th American Chemical Society National Meeting, New Orleans, LA, March 2003; Oral paper 153.