Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 5567–5572
Bioorganic & Medicinal Chemistry Letters

Pyrazole inhibitors of HMG-CoA reductase: An attempt to dramatically reduce synthetic complexity through minimal analog re-design

Scott D. Larsen,* Toni-Jo Poel, Kevin J. Filipski, Jeffrey T. Kohrt, Jeffrey A. Pfefferkorn, Roderick J. Sorenson, Bradley D. Tait, Valerie Askew, Lisa Dillon, Jeffrey C. Hanselman, Gina H. Lu, Andrew Robertson, Catherine Sekerke, Mark C. Kowala and Bruce J. Auerbach

Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, USA

Received 11 July 2007; revised 30 July 2007; accepted 1 August 2007
Available online 11 August 2007

Abstract—An extraordinarily potent and hepatoselective class of HMG-CoA reductase inhibitors containing a pyrazole core was recently reported; however, its development was hampered by a long and difficult synthetic route. We attempted to circumvent this obstacle by preparing closely related analogs wherein the key dihydroxyheptanoic acid sidechain was tethered to the pyrazole core via an oxygen linker ('oxypyrazoles'). This minor change reduced the total number of synthetic steps from 14 to 7. Although the resulting analogs maintained much of the in vitro and cell activity of the pyrazoles, inferior in vivo activity precluded further development. Caco-2 cell permeability data suggest that enhanced cellular efflux of the oxypyrazoles relative to the pyrazoles may be responsible for the poor in vivo activity.

Hydroxymethylglutaryl-Coenzyme A (HMG-CoA) reductase catalyzes the rate-limiting step in cholesterol biosynthesis. Inhibitors of this enzyme (statins, e.g., atorvastatin (**1**) and rosuvastatin (**2**)) are highly effective therapeutic agents for the treatment of hypercholesterolemia and have become the standard of care in the management and prevention of coronary heart disease.[1] Recent data from several large clinical trials suggest that more aggressive LDL-lowering beyond current target guidelines will have additional benefits[2]; however, achieving these reductions with marketed agents requires higher doses or combination therapy. There is now substantial evidence that elevated doses of statins are associated with mild to moderate myalgia,[3] a type of muscle pain or weakness that negatively impacts quality of life and can erode patient compliance. Low tolerance to statin therapy is particularly evident in individuals who exercise vigorously.[4] Consequently there exists a need for new statins that are better tolerated at higher doses and by physically active individuals.

The mechanism(s) responsible for statin-induced myalgia remain unclear, but likely entail disruption of mevalonate metabolism in muscle.[5] Myalgia can be exacerbated by factors that inadvertently increase blood levels of the statin or render patients more sensitive to treatment, for example, drug–drug interactions or genetic polymorphisms.[6] A logical strategy for avoiding statin biochemical effects in muscle is to design agents that are more effective in hepatic tissue than non-hepatic tissue. At the cellular level, this has been successfully achieved through simple reduction in statin lipophilicity.[7] Hydrophilic statins do not passively diffuse well into cells, requiring some level of active transport to achieve good efficacy. Hepatic cells possess organic anion transporting polypeptides (OATPs), for which statins are known to be viable substrates.[8] Muscle cells, on the other hand, are devoid of OATPs, so they should be less susceptible to the effects of hydrophilic statins, an attribute that has been confirmed experimentally.[9]

Keywords: HMG-CoA reductase; Cholesterol; Atherosclerosis; Statin.
* Corresponding author. Tel.: +1 734 323 1187; e-mail: sdlarsen@umich.edu

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.08.004

We recently reported the discovery of a potent and hepatoselective new class of pyrazole-based statins **3** (Fig. 1).[10] Extensive SAR work led to the eventual selection of PF-3052334 (**3f**, Table 1) for progression into advanced pre-clinical studies. Despite their highly favorable PK profiles and in vivo efficacy, development of this class of compounds was impeded by a lengthy and challenging synthetic route (total of 14 steps).[10] It occurred to us that the synthesis of such pyrazole-based statins could be simplified by the replacement of the methylene unit linking the dihydroxy acid sidechain to the heterocyclic core with an ether oxygen. It was anticipated that the resulting 'oxypyrazoles' **4** would maintain most, if not all, of the closely related pyrazoles' biological activity due to the minimal structural change and to favorable literature precedent for ether-linked statins with good biological activity.[11]

We planned to limit our SAR investigation of the oxypyrazoles to variations of the carboxamide substituent, as it had been well established that the dihydroxyacid sidechain, the *iso*-propyl group, and the 4-fluorophenyl group of **4** are optimal in heterocycle-based statins. The preparation of oxypyrazole carboxamides **4** is summarized in Scheme 1. Deprotonation of ester **5** with LDA, followed by acylation with dibenzyl oxalate, provided the keto diester **6**. Condensation of **6** with 4-fluorophenyl hydrazine at elevated temperature then regioselectively afforded the desired hydroxypyrazole ester **7** in good yield. The key attachment of the dihydroxyacid sidechain was accomplished under Mitsunobu conditions, using the commercially available ketal-protected trihydroxy ester **11**. After hydrogenolysis of the resulting benzyl ester **8**, carboxylic acid **9** was converted to various amide analogs **10** using EDCI-mediated coupling conditions. Final analogs **4** were obtained as sodium salts following removal of the diol protecting group with methanolic HCl and subsequent saponification of the *tert*-butyl ester. The total number of linear steps in this sequence is seven, a significant improvement over the 13 linear steps required for the corresponding pyrazole analogs **3**.[10] Furthermore, the sidechain could be installed using the commercially available alcohol **11**, whereas the pyrazole synthesis requires conversion of **11** to the corresponding aldehyde. Thus we were successful in dramatically facilitating the preparation of analogs in the pyrazole series by altering the design of the sidechain linker and truncating the overall synthesis.

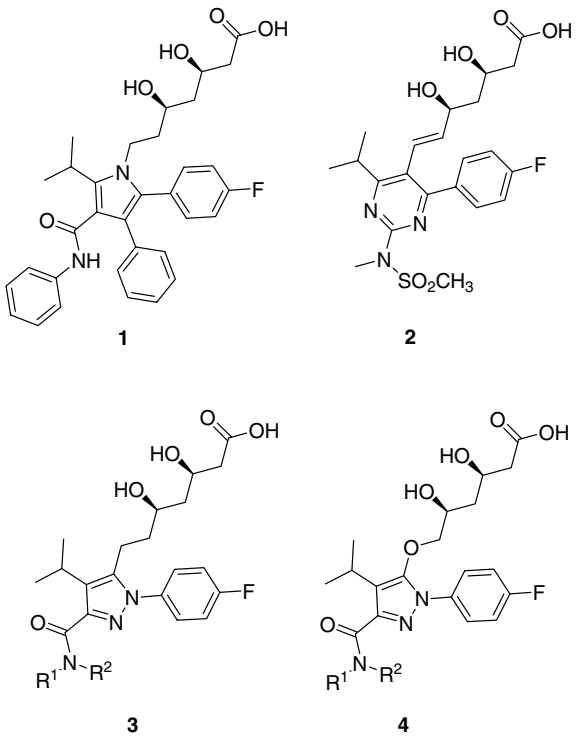


Figure 1. Atorvastatin (**1**), rosuvastatin (**2**), and pyrazole (**3**) and oxypyrazole (**4**) HMG-CoA reductase inhibitors.

New analogs were evaluated in a rat liver microsomal assay for HMG-CoA reductase activity, followed by two rat cellular assays for inhibition of cholesterol synthesis.[10] Both hepatic and non-hepatic (L6 myocyte) cells were employed to provide an estimate of the ability of the compounds to inhibit cholesterol synthesis selectively in the liver. Results are summarized in Table 1. Data for rosuvastatin and selected pyrazoles **3** are included for comparison.

Compounds were selected for synthesis based largely on the SAR of the related pyrazole series.[10] Thus, emphasis was placed on substituted benzyl amides and alkyl amides that had performed well in that series. The first prototype oxypyrazole prepared was simple benzyl amide **4a**, which did not meet our criteria for hepatoselectivity [L6 myocyte $IC_{50} > 1000$ nM and/or (L6 IC_{50}/hepatocyte $IC_{50}) > 1000$]. To our surprise, simple N-methylation of the benzyl amide (to give **4b**) effected a significant improvement in hepatocyte activity. This trend proved to be fairly general, as illustrated with the following compound pairs: **4c/4d**, **4j/4u**, **4m/4r**. In some cases, N-methylation also attenuated the activity in myocytes, dramatically improving the hepatoselectivity (e.g., **4b**). A quick survey of substituents at the 2-, 3-, and 4-positions of the primary benzyl amide (**4f**–**4n**) revealed that 3-substitution produced the best level of activity in the microsomal and/or hepatocyte assays, and that simple methyl proved more effective than methoxy or halogen in hepatocytes. Among the other substituents examined at that position, methoxymethyl (**4jj**) also possessed superior hepatocyte activity.

Within a series of 3-substituted *N*-methylbenzyl amides (**4o**–**4u**), the nature of the substitution did not seem to significantly impact the hepatocyte activity. In this series, halogen appeared to be among the best, so it was explored further with analogs **4v**–**4x**. Homologation of the unsubstituted benzyl amide (**4z**), α-methyl substitution (**4y**), and increasing the size of the *N*-methyl group to ethyl (**4aa**) all were detrimental to microsomal activity relative to prototypes **4a** and **4b**. Alkyl amides in general performed poorly (three examples shown: **4bb**, **4cc**, **4hh**) except for selected tertiary alkyl amides (e.g., *N*-methyl cyclohexylmethyl analog **4dd**). Conformational restriction of the benzyl amide was investigated with analogs **4ee**–**4gg**. (*R*)-3-Phenylpiperidine analog **4gg** was of par-

Table 1. In vitro biological activity of oxypyrazoles **4** and selected pyrazoles **3**

Compound	R^1	R^2	HMGR[a] IC_{50}	Hepato[b] IC_{50}	L6 myo[c] IC_{50}
4a	$PhCH_2$	H	3.8	14	880
4b	$PhCH_2$	Me	5.2	1.1	6720
4c	2,3-DiF–$PhCH_2$	H	2.0	19	120
4d	2,3-DiF–$PhCH_2$	Me	14	2.8	860
4e	4-Me–$PhCH_2$	Me	37	1.2	1250
4f	4-Me–$PhCH_2$	H	15	1.8	2110
4g	3-Me–$PhCH_2$	H	4.9	0.99	280
4h	2-Me–$PhCH_2$	H	17	0.88	2850
4i	4-MeO–$PhCH_2$	H	12	37	nd
4j	3-MeO–$PhCH_2$	H	16	8.4	8750
4k	2-MeO–$PhCH_2$	H	22	83	nd
4l	4-Cl–$PhCH_2$	H	6.7	44	nd
4m	3-Cl–$PhCH_2$	H	5.4	9.9	nd
4n	2-Cl–$PhCH_2$	H	9.5	76	8450
4o	3-EtO–$PhCH_2$	Me	16	2.8	3550
4p	3,5-DiMeO–$PhCH_2$	Me	43	7.1	nd
4q	3-F–$PhCH_2$	Me	14	1.9	2470
4r	3-Cl–$PhCH_2$	Me	8.3	1.8	2120
4s	3-Me–$PhCH_2$	Me	37	2.5	18500
4t	3-F_3C–$PhCH_2$	Me	31	12	nd
4u	3-MeO–$PhCH_2$	Me	21	1.6	9460
4v	3,4-DiF–$PhCH_2$	Me	5.7	8.0	4570
4w	2-F–$PhCH_2$	Me	8.7	3.2	11600
4x	4-F–$PhCH_2$	Me	18	3.8	2800
4y	(*R*)-$PhCH(CH_3)$	Me	21	11	nd
4z	$PhCH_2CH_2$	H	15	14	760
4aa	$PhCH_2$	Et	14	4.7	2660
4bb	*c*-C_6H_{11}–CH_2	H	17	56	nd
4cc	*n*-Bu	H	76	39	nd
4dd	*c*-C_6H_{11}–CH_2	Me	6.2	1.3	2510
4ee	2-Ph-Pyrrolidine		14	8	4340
4ff	Tetrahydroisoquinoline		10	2.5	1720
4gg	(*R*)-3-Ph-Piperidine		4.8	1.5	1110
4hh	Piperidine		47	3.8	32200
4ii	2-Pyr-CH_2	H	25	7.5	nd
4jj	3-($MeOCH_2$)–$PhCH_2$	H	31	1.1	3600
Rosuvastatin			2.1	0.23	210
3b	$PhCH_2$	Me	6.2	0.31	2870
3f	4-Me–$PhCH_2$	H	2.5	1.1	800
3q	3-F–$PhCH_2$	Me	4.1	0.16	1900
3gg	(*R*)-3-Ph–Piperidine		2.1	0.28	310

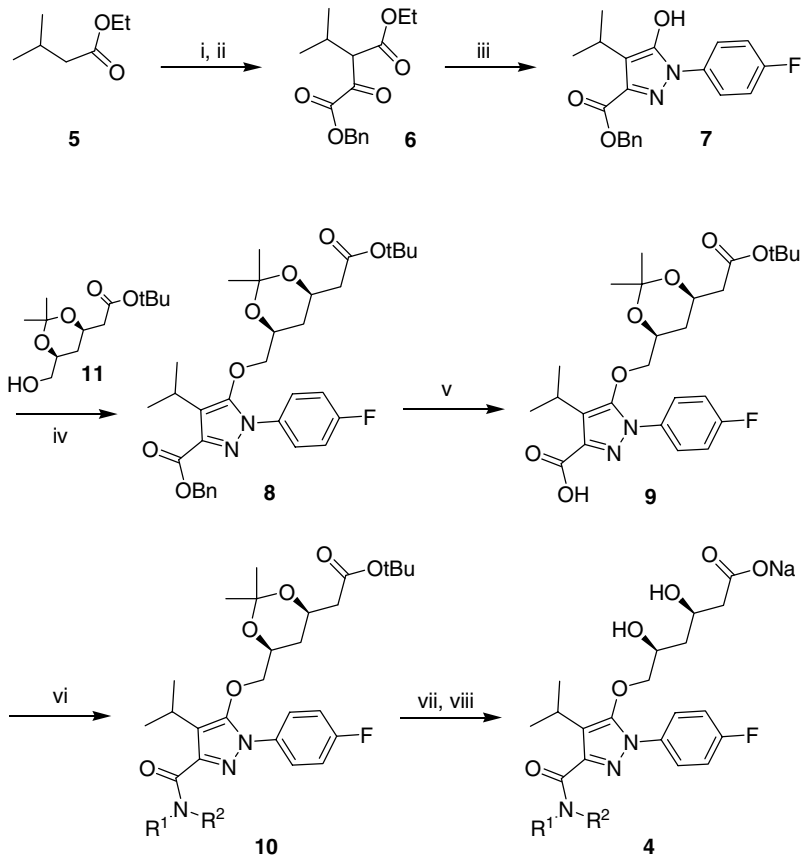
nd, not determined.
[a] Inhibition of HMG-CoA reductase in rat liver microsomes (nM).
[b] Inhibition of cholesterol synthesis in rat hepatocytes (nM).
[c] Inhibition of cholesterol synthesis in L6 myocytes (nM).

ticular interest, as the corresponding pyrazole analog **3gg** was among the most active within that series. Finally, an attempt to replace the phenyl ring of the benzyl amide with a heterocycle (**4ii**) was detrimental to microsomal activity.

A direct comparison of oxypyrazoles **4b**, **4f**, **4q**, and **4gg** with the corresponding pyrazoles **3b**, **3f**, **3q**, and **3gg** indicates that overall the oxypyrazoles, while clearly being potent inhibitors of HMG-CoA reductase, were nevertheless somewhat less active in both the microsomal and hepatocyte assays relative to their pyrazole counterparts.

Selected compounds were tested in vivo for their ability to acutely inhibit cholesterol synthesis in male Syrian Golden hamsters.[10] Animals were administered a single 10 mg/kg po dose of the test compound, followed by a bolus of sodium ^{14}C-acetate at one of three time points: 2, 3 or 4 h after the test compound dosing. After an ensuing 2-h time period, the amount of label incorporated into plasma cholesterol was determined. Results are summarized in Table 2 as percent change in label incorporation relative to vehicle. Measuring cholesterol synthetic rate over time provides an estimate of each compound's duration of action after an acute dose, which we considered a good predictor of chronic LDL-lowering activity. Among marketed statins, long half-lives in vivo are associated with the greatest degree of chronic efficacy.[12] Data for rosuvastatin and selected pyrazoles are provided in the table for comparison.

It is immediately apparent from Table 2 that the oxypyrazoles were distinctly less active in vivo than their pyr-



Scheme 1. Reagents and conditions: (i) 1.1 equiv LDA, THF, −78 °C; (ii) dibenzyl oxalate; (iii) 4-F–Ph–$NHNH_2$·HCl, AcOH/toluene, 50–90 °C, 32–37% overall for steps i–iii; (iv) Ph_3P, DEAD, THF, −5 °C → rt, 88%; (v) H_2, Pd/C, MeOH, rt, >95%; (vi) R^1R^2NH, EDC, HOBt, DCM, 18 h, rt, >88%; (vii) HCl, MeOH, rt, 82–90%; (viii) NaOH, MeOH, rt, 75–90%. Detailed experimental procedures are provided in Ref. 16.

Table 2. In vivo biological activity of oxypyrazoles **4** and selected pyrazoles **3**

Compound	R^1	R^2	HAICS[a] (2–4 h)	HAICS (3–5 h)	HAICS (4–6 h)
4a	$PhCH_2$	H			+41%
4b	$PhCH_2$	Me	−49%		+26%
4f	4-Me–$PhCH_2$	H	−30%		+9%
4h	2-Me–$PhCH_2$	H			+39%
4j	3-MeO–$PhCH_2$	H			+37%
4q	3-F–$PhCH_2$	Me	−41%		−1%
4r	3-Cl–$PhCH_2$	Me		0%	
4u	3-MeO–$PhCH_2$	Me			+53%
4v	3,4-DiF–$PhCH_2$	Me		−5%	
4w	2-F–$PhCH_2$	Me		−4%	
4x	4-F–$PhCH_2$	Me			+91%
4dd	*c*-C_6H_{11}	Me		+23%	
4gg	(*R*)-3-Ph-Piperidine		−15%		
4jj	3-($MeOCH_2$)–$PhCH_2$	H		−6%	
Rosuvastatin			−76%		−46%
3b	$PhCH_2$	Me	−61%		−16%
3f	4-Me–$PhCH_2$	H	−74%		−15%
3q	3-F–$PhCH_2$	Me	−66%		−12%
3gg	(*R*)-3-Ph-Piperidine		−78%	−57%	

[a] Acute inhibition of cholesterol synthesis in hamsters following a single oral dose (10 mg/kg) during the indicated 2-h period (2–4 h) post-dose.

azole counterparts. Each of the four pyrazole comparator examples in the table maintained their ability to inhibit cholesterol synthesis in vivo for at least 5 h post-dose. On the other hand, none of the oxypyrazoles were active beyond 4 h post-dose. Short term activity in vivo was observed with several oxypyrazole analogs (2–4 h), but none of these could maintain efficacy past 4 h. It is interesting to note the apparent *increases* in cholesterol synthetic rate at some of the longer timepoints. These data suggest the compounds were working acutely and

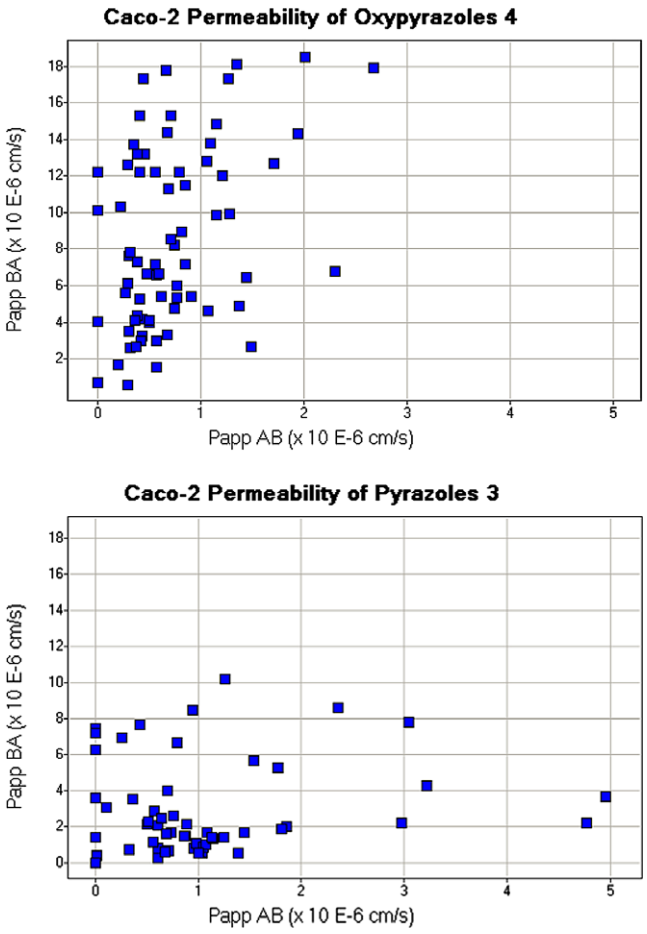


Figure 2. Spotfire® plots of Caco-2 permeability data for oxypyrazoles **4** and pyrazoles **3**.

then getting cleared rapidly, followed by a 'rebound' of HMG-CoA reductase activity above baseline levels. While this phenomenon has not been an issue with statins clinically, there is precedent for a supernormal excursion of HMG-CoA reductase activity in rats within 6 h of a single dose of statin.[13] This suggests that we were indeed observing the effects of short-lived statins rather than an experimental anomaly.

Although the lower intrinsic activity of the oxypyrazoles relative to the corresponding pyrazoles may have accounted at least in part for their inferior in vivo activity, we observed a striking divergence in their Caco-2 permeability properties that could be an additional contributing factor. As a class, the oxypyrazoles had far higher ratios of P_{app} BA/P_{app} AB than the pyrazoles (Fig. 2). This is often indicative of active efflux,[14] which could present a significant impediment to intestinal absorption. Furthermore, since several of the efflux transporters in the small intestine are also expressed at the canalicular membrane of the liver,[15] the greater efflux rate of oxypyrazoles from intestinal cells relative to the pyrazoles might also indicate a greater tendency to be excreted actively into the bile from the liver, thereby shortening their liver residence times and leading to the observed rapid rebound of cholesterol synthesis rates. Unfortunately, due to the poor performance of this class of compounds in vivo, no detailed PK studies were undertaken to confirm this hypothesis.

In summary, we were successful in designing a greatly simplified synthesis of pyrazole-centered statins by incorporating a minor change in the sidechain linkage. While the resulting oxypyrazoles retained much of the pyrazoles' in vitro activity, they were distinctly inferior in vivo, possibly due to a greater susceptibility to active efflux from the gut and/or liver.

References and notes

1. For reviews, see: (a) McKenney, J. M. *Clin. Cardiol.* **2003**, *26*(Suppl. III), 32; (b) Speidal, K. M.; Hilleman, D. E. *Expert Opin. Pharmacother.* **2006**, *7*, 1291.
2. (a) LaRosa, J. C.; Grundy, S. M.; Walters, D. D.; Shear, C.; Barter, P.; Fruchart, J.-C.; Gotto, A. M.; Greten, H.; Kastelein, J. J. P.; Shepard, J.; Wenger, N. K. *N. Engl. J. Med.* **2005**, *352*, 1425; (b) Schwartz, G.; Olsson, A. G.; Ezekowitz, M. D.; Ganz, P.; Oliver, M. F.; Waters, D.; Zeiher, A.; Chaitman, B. R.; Leslie, S.; Stern, T. *JAMA* **2001**, *285*, 1711; (c) Cannon, C. P.; Braunwald, E.; McCabe, C. H.; Rader, D. J.; Rouleau, J. L.; Belder, R.; Joyal, S. V.; Hill, K.; Pfeffer, M. A.; Skene, A. M. *N. Engl. J. Med.* **2004**, *350*, 1495.
3. (a) Bruckert, E.; Hayem, G.; Dejager, S.; Yau, C.; Begaud, B. *Cardiovasc. Drugs Ther.* **2006**, *19*, 403; (b) Paiva, H.; Thelen, K. M.; Van Coster, R.; Smet, J.; De Paepe, B.; Mattila, K. M.; Laakso, J.; Lehtimaki, T.; von Bergmann, K.; Lutjohann, D.; Laaksonen, R. *Clin. Pharmacol. Ther.* **2005**, *78*, 60; (c) Franc, S.; Dejager, S.; Bruckert, E.; Chauvenet, M.; Giral, P.; Turpin, G. *Cardiovasc. Drugs Ther.* **2003**, *17*, 459; (d) Thompson, P. D.; Clarkson, P.; Karas, R. H. *JAMA* **2003**, *289*, 1681; (e) Hansen, K. E.; Hildebrand, J. P.; Ferguson, E. F.; Stein, J. H. *Arch. Intern. Med.* **2005**, *165*, 2671.
4. (a) Sinzinger, H.; O'Grady, J. *Br. J. Clin. Pharmacol.* **2004**, *57*, 525; (b) Athar, H.; Shah, A. R.; Thompson, P. D. *Future Lipidol.* **2006**, *1*, 143; (c) Sinzinger, H.; Wolfram, R.; Peskar, B. A. *J. Cardiovasc. Pharmacol.* **2002**, *40*, 163.
5. (a) Urso, M. L.; Clarkson, P. M.; Hittel, D.; Hoffman, E. P.; Thompson, P. D. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 2560; (b) Dirks, A. J.; Jones, K. M. *Am. J. Physiol. Cell Physiol.* **2006**, *291*, 1208.
6. (a) Laaksonen, R. *Clin. Pharmacol. Ther.* **2006**, *79*, 529; (b) Oh, J.; Ban, M. R.; Miskie, B. A.; Pollex, R. L.; Hegele, R. A. *Lipids Health Dis.* **2007**, *6*, 7.
7. Roth, B. D.; Bocan, T. M. A.; Blankley, C. J.; Chucholowski, A. W.; Creger, P. L.; Creswell, M. W.; Ferguson, E.; Newton, R. S.; O'Brien, P.; Picard, J. A.; Roark, W. H.; Sekerke, C. S.; Sliskovic, D. R.; Wilson, M. W. *J. Med. Chem.* **1991**, *I*, 466 (b).
8. (a) Hsiang, B.; Zhu, Y.; Wang, Z.; Wu, Y.; Sasseville, V.; Yang, W.-P.; Kirchgessner, T. G. *J. Biol. Chem.* **1999**, *274*, 37161; (b) Nezasa, K.; Higaki, K.; Nakano, M.; Koike, M. *Xenobiotica* **2003**, *33*, 379.
9. (a) Masters, B. A.; Palmoski, M. J.; Flint, O. P.; Gregg, R. E.; Wang-Iverson, D.; Durham, S. K. *Toxicol. Appl. Pharmacol.* **1995**, *131*, 163; (b) Veerkamp, J. H.; Smit, J. W. A.; Benders, A. A. G. M.; Oosterhof, A. *Biochim. Biophys. Acta* **1996**, *1315*, 217.
10. Pfefferkorn, J. A.; Choi, C.; Larsen, S. D.; Auerbach, B.; Hutchings, R.; Park, W.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lin, Z.; Lu, G. H.; Robertson, A.; Sekerke, C.; Harris, M. S.; Pavlovsky, A.; Bainbridge, G.; Caspers, N.;

Kowala, M.; Tait, B. D. *J. Med. Chem*., submitted for publication.
11. Jendralla, H.; Granzer, E.; Kerekjarto, B. V.; Krause, R.; Schacht, E.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L.-J.; Granata, S.; Herchen, H.; Kleine, H.; Schussler, H.; Wagner, K. *J. Med. Chem.* **1991**, *34*, 2962.
12. (a) Naoumova, R. P.; Dunn, S.; Rallidis, L.; Abu-Muhana, O.; Neuwirth, C.; Rendell, N. B.; Taylor, G. W.; Thompson, G. R. *J. Lipid Res.* **1997**, *38*, 1496; (b) Bellosta, S.; Paoletti, R.; Corsini, A. *Circulation* **2004**, *109*(Suppl. III), III-50.
13. (a) Aoki, T.; Nishimura, H.; Nakagawa, S.; Kojima, J.; Suzuki, H.; Tamaki, T.; Wada, Y.; Yokoo, N.; Sato, F.; Kimata, H.; Kitahara, M.; Toyoda, K.; Sakashita, M.; Saito, Y. *Arzneim.-Forsch./Drug Res.* **1997**, *47*, 904; (b) Hiyoshi, H.; Yanagimachi, M.; Ito, M.; Ohtsuka, I.; Yoshida, I.; Saeki, T.; Tanaka, H. *J. Lipid Res.* **2000**, *41*, 1136; (c) Jones, P. J. H. *J. Lab. Clin. Med.* **2003**, *141*, 235.
14. Polli, J. W.; Wring, S. A.; Humphreys, J. E.; Huang, L.; Morgan, J. B.; Webster, L. O.; Serabjit-Singh, C. S. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 620.
15. (a) Shitara, Y.; Horie, T.; Sugiyama, Y. *Eur. J. Pharm. Sci.* **2006**, *27*, 425; (b) Lin, J. H. *Curr. Drug Metab.* **2006**, *7*, 39.
16. Poel, T.-J.; Larsen, S. D.; Pfefferkorn, J. A.; Kohrt, J. T.; Filipski, K. J.; Sorenson, R. J. Patent Application WO 2006/087630; *Chem. Abstr* **2006**, *145*, 271771.