Benzoxazinones as PPARγ Agonists. 2. SAR of the Amide Substituent and In Vivo Results in a Type 2 Diabetes Model

Philip J. Rybczynski,* Roxanne E. Zeck, Joseph Dudash, Jr., Donald W. Combs, Thomas P. Burris,† Maria Yang, Melville C. Osborne, Xiaoli Chen, and Keith T. Demarest

Johnson and Johnson Pharmaceutical Research and Development, L.L.C., 1000 Route 202, Raritan, New Jersey 08869

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A series of benzoxazinones has been synthesized and tested for PPARγ agonist activity. Synthetic approaches were developed to provide either racemic or chiral compounds. In vitro functional potency could be measured through induction of the aP2 gene, a target of PPARγ. These studies revealed that compounds with large aliphatic chains at the nitrogen of the benzoxazinone were the most potent. Substitution of the chain was tolerated and in many cases enhanced the in vitro potency of the compound. Select compounds were further tested for metabolic stability, oral bioavailability in rats, and efficacy in *db*/*db* mice after 11 days of dosing. In vivo analysis with **13** and **57** demonstrated that the series has potential for the treatment of type 2 diabetes.

Introduction

PPARγ is a member of the peroxisome proliferator-activated receptor family. Its mechanistic role in glucose and lipid homeostasis has been the subject of extensive research.[1] As a result, PPARγ agonism is a current treatment for type 2 diabetes. The receptor is widely distributed in the spleen, colon, adipose tissue, and macrophages and found to a lesser extent in the liver, pancreas, and skeletal muscle.[2] Activation of PPARγ in the cell nucleus initiates heterodimerization with another nuclear receptor, the rexinoid receptor (RXR), with subsequent recruitment of coactivators and induction of genes that are involved in adipogenesis. Target genes that are upregulated or downregulated have been identified from white and brown adipose tissue, skeletal muscle, and the liver[3] (in vitro adipogenesis can be induced by activation of PPARγ alone or in conjunction with C/EBPα, although the latter is not sufficient to promote adipogenesis[4]). The details of how activation leads to glucose homeostasis are not fully understood. Studies suggest that adipogenesis provides increased lipid metabolism and free fatty acid uptake in adipose tissue, leading to increased insulin sensitivity and glucose metabolism in muscle and liver.[1a,5,6] In support of this mechanism, recent evidence shows that a PPARγ agonist induces glycerol kinase gene expression in adipocytes, thus promoting triglyceride formation in that tissue and reducing circulating free fatty acids.[7] Alternatively, altered secretion of adipocytokines in adipose tissue has been proposed as a mechanism of PPARγ agonist-mediated homeostasis.[5] A conflicting report demonstrates, however, that in heterozygous PPARγ deficient mice fed a high fat diet, insulin resistance can be ameliorated with an antagonist of either PPARγ (bisphenol A diglycidyl ether) or RXR (HX531).[8]

Natural ligands of PPARγ have been identified. These endogenous activators include mono- and polyunsaturated fatty acids as well as eicosanoids, with EC_{50} values in the micromolar range.[9] To date, the most potent natural agonist identified is 15d-PGJ2 with a reported $EC_{50} = 1-2\ \mu M$ in cotransfection assays using PPARγ chimera.[10] By comparison, a recent report identified Saurufuran A from the herb *Suarus chinesis* as an agonist with an $EC_{50} = 16.7\ \mu M$ in a pFA-GAL4-PPAR chimera expression construct.[11] These and other natural ligands are considerably less potent than synthetic ligands (vide infra).

Synthetic PPARγ agonists for the treatment of type 2 diabetes[12] have proven successful for glucose control and reduction of HbA_{1c} with the marketed compounds Rosiglitazone[13] and Pioglitazone[14,13b] (Chart 1). However, edema and weight gain have been reported in patients after treatment with PPARγ agonists[13b] (it remains to be seen if this is related to individual compounds or activation of PPARγ, and there continues to be interest in new compounds for clinical development). Additional compounds in clinical and preclinical development have recently been reviewed.[12a,b] Compounds reported to be advanced clinical candidates include Farglitazar (GW262570, Ph III),[15] KRP-297 (Ph II/III),[16] Reglitazar (JTT-501, Ph II/III),[17] Ragaglitazar (DRF-2725, Ph II),[18] and Tesaglitazar (AZ-242, Ph II).[19] We sought a backup for our clinical compound Netoglitazone (MCC-555).[20] This compound contains a thiazolidinedione (TZD) moiety commonly seen in PPARγ agonists. It has remarkable potency in vivo and shows promise for the treatment of type 2 diabetes. In an earlier report, we described our efforts to identify a backup chemical series and the initial structure−activity relationship (SAR) work.[21] At the time of that report and during the work described here, there were no clinical data to dictate the incorporation or avoidance of any structural features. However, we were excited to discover a series devoid of the TZD, since this provided an opportunity to bring a diverse set of ligands

* To whom correspondence should be addressed. Tel: 908.704.4511. Fax: 908.203.8109. E-mail: prybczyn@prdus.jnj.com.
† Current address: Eli Lilly and Co., Indianapolis, IN 46285.

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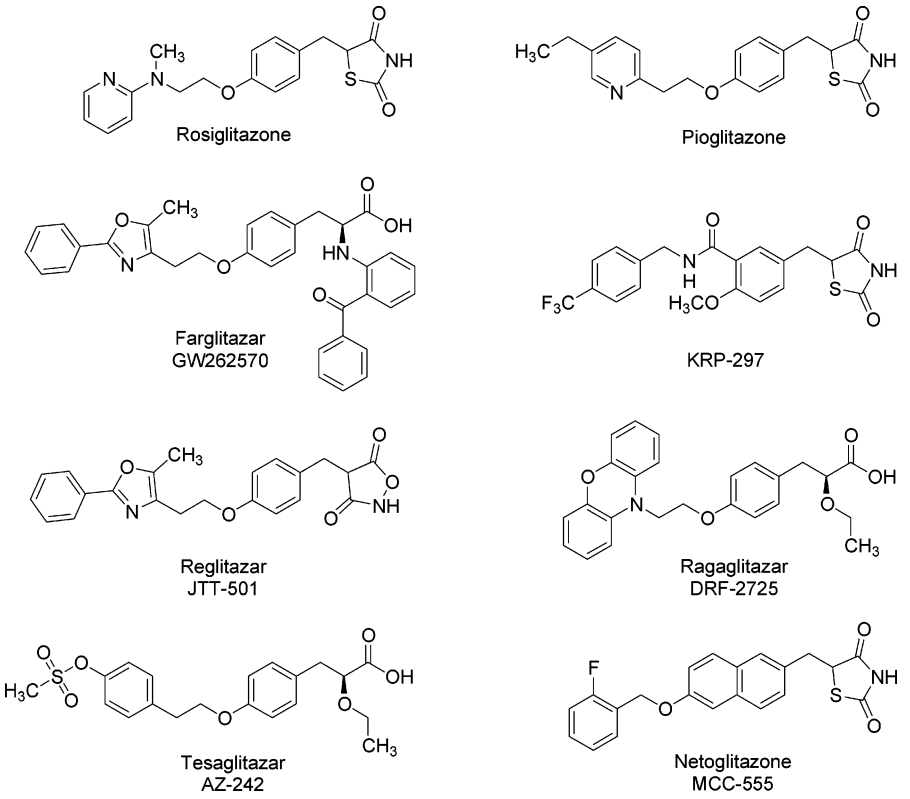
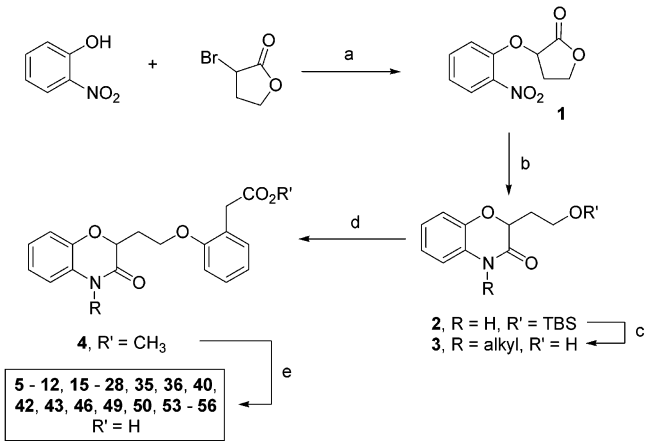
Chart 1. PPARγ Agonists



Scheme 1[a]



[a] Reagents and conditions: (a) K_2CO_3, DMF, 0 °C to room temperature. (b) (i) H_2, Pd/C, EtOH, room temperature; (ii) TBSOTf, imidazole, DMF, 0 °C to room temperature. (c) (i) NaH, alkylating agent, DMF, 0 °C to room temperature; (ii) CH_3SO_3H, MeOH, water, room temperature. (d) (2-Hydroxyphenyl)acetic acid methyl ester, Bu_3P, 1,1′-(azodicarbonyl)dipiperidine (ADDP), PhH, 10 °C to room temperature. (e) NaOH, MeOH, water, 65 °C.

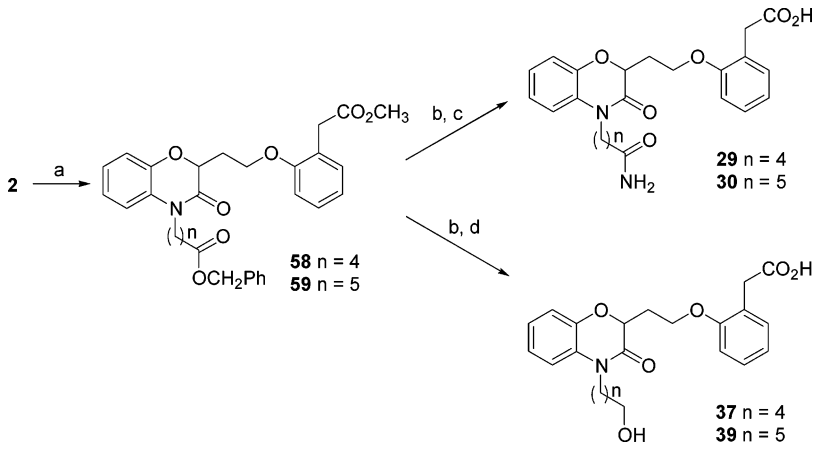
into preclinical development. In this report, we describe further efforts to elaborate the SAR of the benzoxazinone series of compounds.[22] The in vitro potency, in vitro stability toward P450 enzymes in human liver microsomes, bioavailability in rats, and initial in vivo efficacy studies are included.

Chemistry

Racemic compounds were synthesized as shown in Scheme 1. 2-Nitrophenol was alkylated with α-bromo-γ-butyrolactone to provide **1**. Catalytic hydrogenation of the nitro group and concomitant cyclization to the benzoxazinone, followed by protection of the primary alcohol, yielded silyl ether **2**. Alkylation of the amide was achieved by deprotonation of the amide with sodium hydride and then reaction with the alkylating agent specified in each experimental (in the synthesis of **55**, alkylation was accomplished with a primary alcohol under Mitsunobu conditions). A mixture of *N*- and *O*-alkylation products was obtained from **2** under these deprotonation/alkylation conditions. Therefore, deprotection of the *tert*-butyldimethylsilyl (TBS) ether was conducted with aqueous methanesulfonic acid in methanol to hydrolyze the *O*-alkylated products. The N−H and N-alkyl products were readily separated on silica gel to provide **2** and Mitsunobu substrate **3**. Formation of the phenyl ether (**4**) and saponification provided target compounds **5**−**12**, **15**−**28**, **35**, **36**, **40**, **42**, **43**, **46**, **49**, **50**, and **53**−**56**.

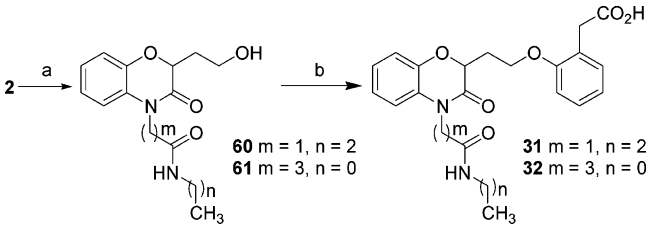
The introduction of some of the substituents in the side chain required additional functional group manipulations. Schemes 2−5 highlight the changes to the chemistry in Scheme 1. The reagents that could not be purchased were synthesized, and the methods are detailed in the Experimental Section. In Scheme 2, **29**, **30**, **37**, and **39** were obtained through manipulation of differentially protected carboxylic acids. Alkylation of **2** with the benzyl esters of 5-bromopentanoic acid or 6-bromohexanoic acid, followed by deprotection of the TBS ethers and Mitsunobu etherification, provided benzyl esters **58** and **59**. A portion of each intermediate was saponified to provide diacids **26** or **27** (see Scheme 1). Alternatively, each benzyl ester was hydrogenated to a mixed methyl ester/carboxylic acid. Activation of the acid moiety with 1,1′-carbonyldiimidazole, exposure to ammonium hydroxide, and saponification of the

Scheme 2[a]



[a] Reagents and conditions: (a) (i) NaH, $Br(CH_2)_nCO_2CH_2Ph$, DMF, 0 °C to room temperature; (ii) CH_3SO_3H, MeOH, water, room temperature; (iii) (2-hydroxyphenyl)acetic acid methyl ester, Bu_3P, ADDP, PhH, 10 °C to room temperature. (b) H_2, Pd/C, EtOH, room temperature. (c) (i) 1,1′-Carbonyldiimidazole, CH_2Cl_2, room temperature, 2 h, and then NH_4OH; (ii) NaOH, MeOH, water, 40 °C. (d) (i) BH_3, THF, −50 to 0 °C; (ii) NaOH, MeOH, water, 40 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) (i) NaH, $Br(CH_2)_mCO_2Et$, DMF, 0−50 °C; (ii) $CH_3(CH_2)_nNH_2$, MeOH, 45 °C; (iii) CH_3SO_3H, MeOH, water, room temperature. (b) (i) (2-Hydroxyphenyl)acetic acid methyl ester, Bu_3P, ADDP, PhH, 10 °C to room temperature; (ii) NaOH, MeOH, water, 40 °C.

methyl ester yielded compound **29** or **30**. Finally, hydrogenation of each benzyl ester, borane reduction of the carboxylic acid, and saponification of the methyl ester provided compound **37** or **39**. In Scheme 3, compounds **31** and **32** were obtained by initial alkylation of amide **2** with either ethyl bromoacetate or ethyl 4-bromobutyrate. Amidation occurred readily upon exposure to propylamine or methylamine. Deprotection with methanesulfonic acid provided **60** and **61**. Mitsunobu etherification and saponification yielded the target compounds. The chemistry in Scheme 4 provided compounds **33** and **34**. Alkylation of **2** with 6-bromohexyl phthalimide and deprotection of the TBS ether provided **62**. Mitsunobu etherification and deprotection of the amine yielded **63**. Amidation with either acetic anhydride or methanesulfonyl chloride and saponification gave the desired products. In Scheme 5, the keto group is used to synthesize four additional target compounds. Grignard addition to **42** with methylmagnesium bromide provided **38**. The oximes in compounds **44** and **45** were obtained from ketone **42** by condensation with hydroxylamines. Compound **41** was obtained by sodium borohydride reduction of the ketone in **64** followed by saponification to the target compound.

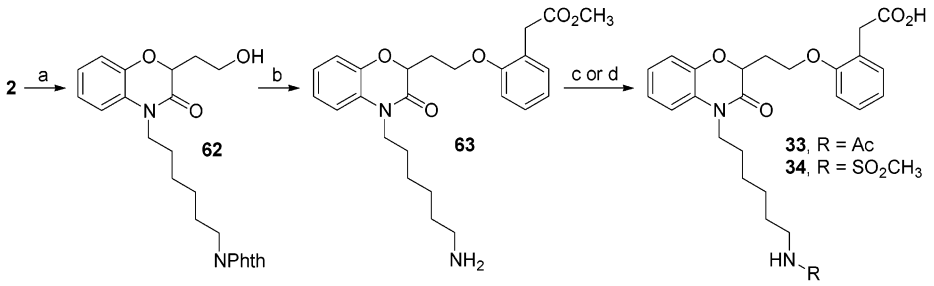
Chiral compounds arise by virtue of the stereogenic center at C-2 of the benzoxazinone ring. The stereochemically pure compounds could be obtained by chromatographic resolution of racemates—as in **13**, **14**, **47**, **48**, **51**, and **52**—or by the stereospecific synthesis shown in Scheme 6 for **13** and **57**. In this variation of the chemistry depicted in Scheme 1, stereochemistry is introduced from the chiral pool and maintained throughout the sequence. Mitsunobu reaction of 2-nitrophenol and (*S*)-2-hydroxy-γ-butyrolactone provided chiral lactone **65**. Reduction of the nitro group, silyl ether formation, alkylation with 1-iodohexane or 1-bromo-4-methoxybutane, and deprotection with aqueous HCl yielded alcohols **66** or **67**. Mitsunobu etherification and saponification with lithium hydroxide provided chiral products **13** or **57**. Chiral high-performance liquid chromatography (HPLC) analysis of racemic and chiral intermediates in each case confirmed the presence of a single enantiomer. In both cases, it was observed that the more potent of the two enantiomers could be obtained from the (*S*)-lactone, with elaboration to final products. From this, it was inferred that these compounds had (*R*) absolute configuration, by inversion of configuration during the Mitsunobu reaction in the first step.

Results and Discussion

In Vitro SAR Studies. The preliminary results obtained with this series provided impetus for further SAR development on the scaffold.[21] In those studies, it was found that the benzyl substituent of the amide influenced potency (Scheme 1; R = CH_2Ar), the favored position of the carboxylic acid is in the 2-position of the phenyl ether, and substitution on the aromatic portion of the benzoxazinone bicyclic ring is not tolerated. In the previous and present studies, compounds were tested in the PPARγ-mediated aP2 gene induction assay. This target gene of PPARγ has been evaluated in these laboratories and shown to undergo a large induction in the presence of agonists.[23] As such, it is a useful marker of in vitro activation of the receptor. Select compounds were tested for in vitro metabolic stability and rat oral bioavailability. Racemic and chiral compounds with acceptable profiles were further tested for in vivo efficacy.

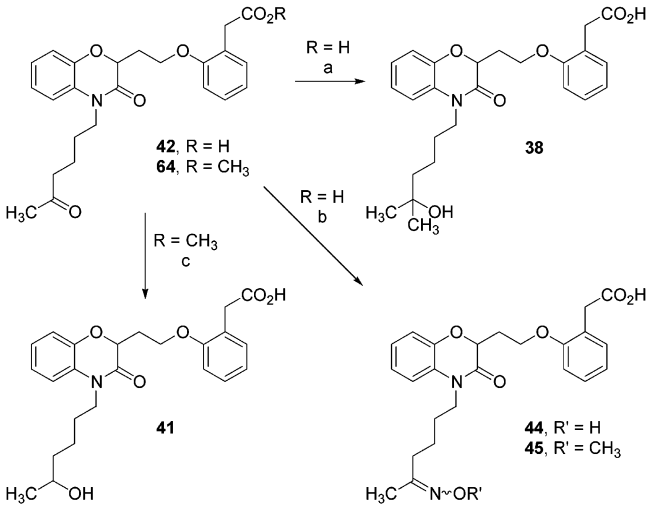
Substitution on the amide of the benzoxazinone started with unsubstituted alkyl side chains, either branched or linear (Table 1). The effect of homologation

Scheme 4[a]



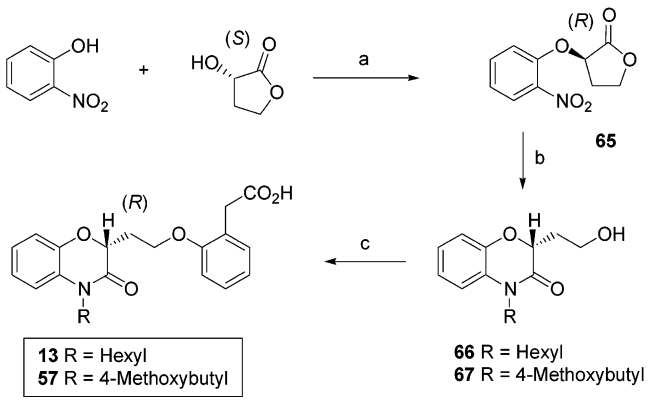
[a] Reagents and conditions: (a) NaH, 6-bromohexyl phthalimide, DMF, 0 °C to room temperature. (b) (i) (2-Hydroxyphenyl)acetic acid methyl ester, Bu_3P, ADDP, PhH, 10 °C to room temperature; (ii) NH_2NH_2, EtOH, 60 °C. (c) (i) Ac_2O, room temperature; (ii) NaOH, MeOH, water, 40 °C. (d) (i) CH_3SO_2Cl, TEA, CH_2Cl_2, room temperature; (ii) NaOH, MeOH, water, 40 °C.

Scheme 5[a]



[a] Reagents and conditions: (a) Two equiv of CH_3MgBr, THF, −78 °C to room temperature. (b) $H_2NOR{\cdot}HCl$, lutidine, EtOH, room temperature. (c) (i) $NaBH_4$, EtOH, 0 °C to room temperature; (ii) NaOH, MeOH, water, 40 °C.

Scheme 6[a]



[a] Reagents and conditions: (a) Ph_3P, DEAD, THF, −20 °C to room temperature. (b) (i) H_2, Pd/C, EtOH, room temperature; (ii) TBSOTf, imidazole, DMF, 0 °C to room temperature; (iii) NaH, alkyl halide, DMF, 0−65 °C; (iv) 6 N HCl, MeOH, room temperature. (c) (i) (2-Hydroxyphenyl)acetic acid methyl ester, Bu_3P, ADDP, PhH, 10 °C to room temperature; (ii) LiOH, THF, water, 0 °C to room temperature.

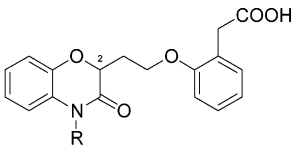
has been well-documented,[24] and those principles were applied to the current scaffold. One to four linear and branched carbon chains provided low potency compounds (**5**−**10**). Extension to the pentyl, hexyl, heptyl, and octyl linear chains provided compounds with EC_{50} values of 243, 100, 234, and 300 nM, respectively (**11**, **12**, **15**, and **16**). The linear nonyl and decyl substituents reduced the potency to over 1 μM (**17** and **18**). Optimal chain length for this scaffold is thus in the range of 5−8 carbons. This was the basis for studies into the role of chain branching, which provided mixed results. There was a steady decline in functional potency as the amide substituent progressed from isoheptyl (**19**) to ethylcyclohexyl (**23**) and on to the 5,5-dimethylhexyl, cyclopentylethyl, and cyclopentylpropyl side chains (**20**−**22**). From these data, it appeared that the receptor has limited space to accommodate the side chains on this scaffold, so that there was little to be gained from the additional steric bulk. The effect of electronics on functional potency will be discussed below.

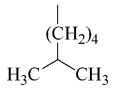
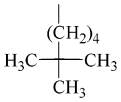
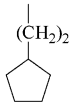
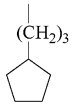
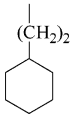
Compound **12** was separated into enantiomers **13** and **14** by chiral chromatography. Enantiomer **13** was the more potent of the two, and it was synthesized by the chemistry in Scheme 6 for in vivo studies (vide infra).

The utility of polar groups in the side chain was investigated with the compounds shown in Table 2. After the first two examples, side chains for the compounds in this study were also in the range of 5−8 atoms. Hydroxyethyl and methylene carboxylate derivatives (**24** and **25**) displayed no improvement over compound **6**. Introducing a carboxylic acid into the side chain (**26**−**28**) likewise provided no advantage. The side chain was also substituted with a primary (**29** and **30**) or secondary amide moiety (**31** and **32**), as well as a reverse amide (**33**) and reverse sulfonamide (**34**). All of these target compounds showed poor potency in the functional assay. The only break in this trend arose from the unsaturated variation of the hexyl chain (**36**).[25] It was apparently similar enough to the hexyl chain of **12** to provide a potent agonist. Unfortunately, the double bond cannot be mimicked by the aforementioned amides. The nitrile-substituted chain in **35** was superior to the corresponding carboxylic acid substituent in **28** but was still not in the potency range obtained from the best linear compounds in Table 1. The highly polar carboxylic acids and amides represented by **24**−**35** indicated that the receptor favors less polar, linear ligands for activation of the receptor.

More interesting results were obtained by substitution of the alkyl chain with hydroxyl, fluoro, or carbonyl groups or by replacement of a methylene with oxygen

Table 1. Benzoxazinones with Linear or Branched Alkyl Substituents



Cpd	R	EC_{50} (nM)[a]	Cpd	R	EC_{50} (nM)[a]
5	CH_3	>5,000	**15**	$(CH_2)_6CH_3$	234
6	CH_2CH_3	>5,000	**16**	$(CH_2)_7CH_3$	300
7	$CH(CH_3)_2$	>5,000	**17**	$(CH_2)_8CH_3$	~5,000
8	$(CH_2)_2CH_3$	~5,000	**18**	$(CH_2)_9CH_3$	1,000
9	$CH_2CH(CH_3)_2$	~5,000	**19**		79
10	$(CH_2)_3CH_3$	~5,000	**20**		1,000
11	$(CH_2)_4CH_3$	243	**21**		~5,000
12	$(CH_2)_5CH_3$	100	**22**		2,700
13	(*R*)-**12**[b]	100	**23**		300
14	(*S*)-**12**[b]	1,200	**Rosiglitazone**		120

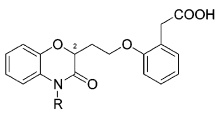
[a] Each value is the mean of three determinations. [b] Chiral at the C2 position of the benzoxazinone ring.

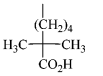
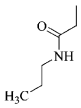
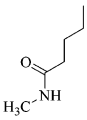
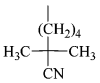
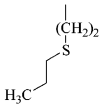
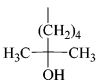
or sulfur. These substitutions provide linear chains that are not as polar as those described above. Introducing a hydroxyl group at the terminus of the pentyl chain reduced potency (**37** vs **11**), and branching to the tertiary alcohol gave a slight improvement (**38** vs **37**). However, the linear 6-hydroxyhexyl and 7-hydroxyheptyl chains (**39** and **40**) brought potency back to the level in the unsubstituted cases (**12** and **15**) while reducing lipophilicity. Simply moving the hydroxy from C6 to C5 of the hexyl substituent reduced potency (**41** vs **39**). By comparison, potent agonists were obtained by the incorporation of a ketone into the hexyl or heptyl side chains (**42** and **43**). Conversion of the 5-ketohexyl chain to the corresponding oxime (**44**, 3.4:1 *E*/*Z* mixture) provided the most potent compound found in this series. Unfortunately, the oxime was hydrolytically labile and rapidly reverted to the ketone under acidic conditions (pH 2). The methyl oxime in **45** (3:1 *E*/*Z* mixture) eliminated all potency, indicating the value of a protic group in this region. Overall, these results point to a polarity factor that can be exploited over and above the sterics explored by the compounds in Table 1.

One or two fluorine atoms could be introduced into the C5 or C6 position of the hexyl chain (**46** and **50**) and the C6 or C7 position of the heptyl chain (**49** and **53**). The best results were obtained from the hexyl analogues **46** and **50**. Both **46** and **50** were separated into enantiomers by chiral chromatography (**46** was separated into **47** and **48** while **50** was separated into **51** and **52**). Enantiomers **47** and **51** were the better of each pair, and both are presumed to have (*R*) absolute stereochemistry from synthesis beginning with the (*S*)-lactone. The most potent enantiomer **51** was taken on for additional studies (vide infra). Finally, oxygen and sulfur were introduced into the chain (**54**−**57**), with the best results arising from **56** and its (*R*)-enantiomer, **57**. Compound **57** was taken on for in vivo studies. It is interesting to note that **57** was the least potent of the compounds taken into secondary studies but had one of the best overall profiles (vide infra).

Pharmacokinetic and in Vivo Studies. Subsequent studies on the series focused on compounds **12**, **13**, **39**, **40**, **42**, **44**, **50**, **51**, and **57** (Table 3). The in vitro metabolic stability was determined by incubation with

Table 2. Benzoxazinones with Substituted Alkyl Chains



Cpd	R	EC_{50} (nM)[a]	Cpd	R	EC_{50} (nM)[a]
24	CH_2CH_2OH	>5,000	**42**		260
25	CH_2CO_2H	>5,000	**43**		264
26		>5,000	**44**		10
27		>5,000	**45**		~5,000
28		1,000	**46**		179
29		>5,000	**47**	(*R*)-**46**[b]	295
30		~5,000	**48**	(*S*)-**46**[b]	1,000
31		>5,000	**49**		534
32		>5,000	**50**		117
33		>5,000	**51**	(*R*)-**50**[b]	152
34		>5,000	**52**	(*S*)-**50**[b]	570
35		359	**53**		718
36		208	**54**		380
37		1000	**55**		~5,000
38		644	**56**		274
39		200	**57**	(*R*)-**56**[b]	274
40		149	**Rosiglitazone**		120
41		1,000			

[a] Each value is the mean of three determinations. [b] Chiral at the C2 position of the benzoxazinone ring.

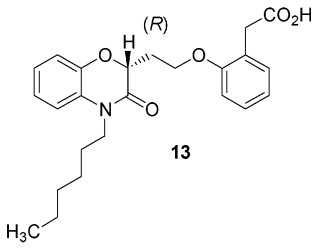
Table 3. Human Liver Microsome Stability and Rat Oral Bioavailability of Benzoxazinones

		rat oral bioavailability[b]		
entry	HLM[a] $t_{1/2}$ (min)	%	AUC (μM h)	$t_{1/2}$ (h)
12	53	115	406	14.0
13	73	95	327	14.5
39	57	4	2.5	0.6
40	76	13	2.3	7.0
42	51	27	5.8	9.8
44	148	16	19.9	4.2
50	76	100	84	16.0
51	111	39	93	7.9
57	>500	41	88	6.7

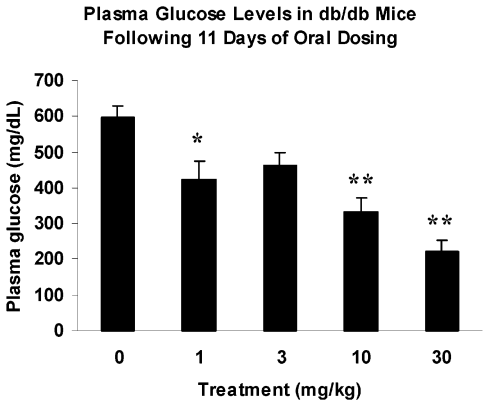
[a] Incubated at 37 °C with test compound at 5 μM and 1 mg protein/mL microsomal prep. [b] Dosed at 30 mg/kg po as a suspension in methocel, 3 mg/kg iv. See Experimental Section for details.

human liver microsomes. In this system, values above 30 min were considered acceptable, and all compounds had high metabolic stability. The analogue with the hexyl chain (**12**) and the more potent (*R*)-enantiomer (**13**) had a half-life of 53 and 73 min, respectively. Other analogues showed little variation by the introduction of a primary alcohol, ketone, oxime, or fluorine. A noteworthy difference came from replacing a methylene (**13**) with an oxygen (**57**). It was expected that the methyl ether would be cleaved, but the compound was not degraded by the P450s present in the microsomes. Rat oral bioavailability showed greater variation across the set of functional agonists. All compounds were dosed individually at 30 mg/kg po in 0.5% aqueous methocel for comparison to iv dosing at 3 mg/kg. This test of exposure after oral dosing showed that racemic **12** provided high exposure at 406 μM h AUC, corresponding to approximately 100% bioavailability, and the half-life was 14 h. The high exposure held for the (*R*)-enantiomer (**13**) where the AUC reached 327 μM h, and the half-life remained at 14.5 h. Continuing through the series, compounds **39** and **40** showed low exposure after oral dosing. The analogue **39** had an AUC of 2.5 μM h and a half-life of 0.6 h. The analogue **40** had an AUC of 2.3 μM h and a half-life of 7 h. The results from the in vitro microsome test indicated that the compounds were not susceptible to phase I metabolism. It was not ascertained whether the low exposure was due to phase II metabolism or poor uptake from the gut, but these results demonstrated that the hydroxyl group added a liability to the scaffold. The keto compound **42** provided similar low exposure after oral dosing, with an AUC of 5.8 μM h and a half-life of 9.8 h. The poor bioavailability was also presumed to be due to phase II metabolism or poor uptake. Compound **44** followed this trend with an AUC of 19.9 μM h and a half-life of 4.2 h. Higher exposure was obtained from the fluorohexyl compounds **50** and **51** where the exposure seen with the racemic compound was mirrored by the (*R*)-enantiomer. Racemic **50** provided an AUC of 84 μM h and a half-life of 16 h, and chiral **51** had an AUC of 93 μM h and a half-life of 7.9 h. Finally, **57** (the (*R*)-enantiomer of **55**) gave an AUC of 88 μM h and a half-life of 6.7 h.

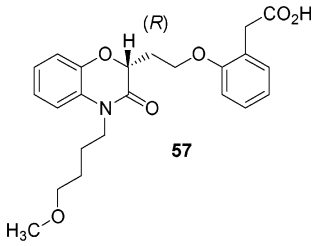
Two compounds, **13** and **57**, were taken into the 11 day *db*/*db* mouse model of type 2 diabetes (Figure 1). Compound **13** showed a dose-dependent decrease in plasma glucose over a dose range of 1−30 mg/kg po, single daily dose. By comparison, **57** showed near



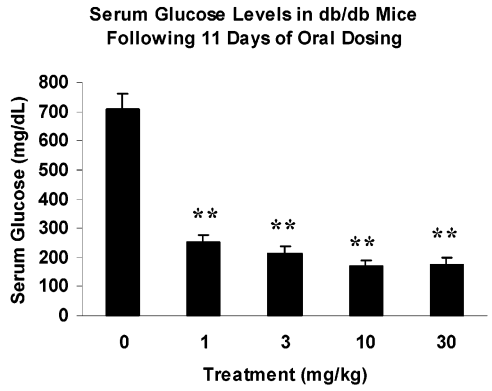
PPARγ EC_{50} = 110 nM
Human Liver Microsome $t_{1/2}$ = 73 min
Rat oral bioavailability = 95%, $t_{1/2}$ = 14.5 h
@ 30 mg/kg oral, 3 mg/kg iv



* p<0.05 and ** p<0.01 compared to vehicle group



PPARγ EC_{50} = 274 nM
Human Liver Microsome $t_{1/2}$ > 500 min
Rat oral bioavailability = 41%, $t_{1/2}$ = 6.7 h
@ 30 mg/kg oral, 3 mg/kg iv



** p<0.01 compared to vehicle group

Figure 1. Biological profile of two compounds.

maximal effect at doses of 1−30 mg/kg. At this time, it is not clear why **57** offered such an advantage over **13**, but studies are continuing with these compounds.

In conclusion, the SAR of a PPARγ agonist series has been developed. Previous work has determined the optimal location for the carboxylic acid in the phenyl ether and that substitution of the benzoxazinone aryl ring was not tolerated.[21] This work has demonstrated that substitution on the amide of the heterocyclic ring offered enhancement of receptor activation while generally maintaining bioavailability and resistance to oxidative metabolism. Lipophilic side chains provided the most potent agonists, and the optimal chain length was 5−8 atoms. These chains could be substituted with hydroxy, fluorine, carbonyl, or oxime groups. However, carboxylic acids and amides were not tolerated. Sulfur and oxygen could be successfully introduced as a member of the chain. The stereochemistry of the compound was critical to potency. The preferred stereochemistry was inferred to be (*R*) by virtue of the route used to obtain enantiomerically pure compounds. Furthermore, two compounds have in vivo efficacy in a *db*/*db* mouse model of type 2 diabetes (Figure 1). Future communications on this series will describe additional efficacy testing and preclinical evaluation of the compounds.

Experimental Section

General Chemistry. Purchased reagents and anhydrous solvents were used as received. Proton NMRs were obtained with a Bruker 300 MHz in the indicated solvent with chemical shifts (δ) reported in ppm vs tetramethylsilane and coupling constants (J) in Hz. Positive and negative ion loop mass spectra were obtained with an Agilent 1100 LC/MSD. Elemental analyses were obtained by Quantitative Technologies, Inc. (Whitehouse, NJ) on a Perkin-Elmer 2400 Elemental Analyzer.

The synthesis of the compounds in Scheme 1 is exemplified by the synthesis of compounds **1**−**5**. The alkylating agent used for each target compound is noted in the Experimental Section. If the alkylating agent was synthesized, the experimental details immediately precede the experimental section for the target compound where it was used.

3-(2-Nitrophenoxy)dihydrofuran-2-one (1). A solution of 2-nitrophenol (50 g, 0.36 mol) in dry dimethyl formamide (DMF) (200 mL), under N_2, was cooled to 0 °C. Potassium carbonate (74.5 g, 0.54 mol) was added, followed by dropwise addition of α-bromo-γ-butyrolactone (36 mL, 0.43 mol) in dry DMF (36 mL). The reaction was stirred at room temperature for 17 h. Acetic acid (60 mL) was added slowly to control the CO_2 evolution, the mixture was poured into water (4 L) containing NaCl (200 g), and the solution was washed with EtOAc. The organic layer was washed with water (5 × 100 mL) and brine (100 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The phenolic ether (**1**) was isolated as a pale yellow solid (50 g, 0.22 mol, 62%). ^{1}H ($CDCl_3$): 7.86 (d, J = 8.1, 1H), 7.58 (t, J

= 8.6, 1H), 7.50 (d, *J* = 7.8, 1H), 7.16 (t, *J* = 7.4, 1H), 5.04 (t, *J* = 7.4, 1H), 4.58 (m, 1H), 4.40 (q, *J* = 7.4, 1H), 2.8−2.6 (m, 2H).

2-(2-*tert*-Butyldimethylsiloxyethyl)-4*H*-benzo[1,4]-oxazin-3-one (2). The intermediate **1** (50 g, 0.22 mol) was suspended in EtOH (550 mL) and then shaken for 3 h with 10% Pd/C and H_2 (45 psi) at room temperature. The solution was filtered through Celite, and the solvent was removed in vacuo. The amide was obtained as a solid. A solution of the amide (42.5 g, 0.22 mol) in dry DMF (400 mL), under N_2, was cooled to 0 °C. Imidazole (37.4 g, 0.55 mol) was added in one portion, followed by addition of TBS chloride (39.8 g, 0.26 mol) in one portion. The mixture was stirred for 15 h as the ice bath was thawed to room temperature. The reaction was poured into water (2 L) containing NaCl (100 g) and washed with 7:3 Et_2O/CH_2Cl_2 (5 × 120 mL). The organic layer was washed with water (4 × 100 mL) and brine (100 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product **2** was isolated by silica gel chromatography with hexane/EtOAc and then crystallized from hexane. The silyl ether was obtained as a pale yellow solid (46.8 g, 0.15 mol, 69% for two steps). ^{1}H ($CDCl_3$): 6.89 (m, 3H), 6.80 (m, 1H), 4.70 (m, 1H), 3.78 (m, 2H), 2.15 (m, 1H), 1.94 (m, 1H), 0.83 (s, 9H), 0.07 (s, 6H). *m*/*z* (MH^+) 308.0. Note: The solid is volatile and sublimes when dried under vacuum for long periods.

2-(2-Hydroxyethyl)-4-methyl-4*H*-benzo[1,4]oxazin-3-one (3). A solution of **2** (1.0 g, 3.25 mmol) in dry DMF (35 mL), under N_2, was cooled to 0 °C. Sodium hydride (75% dispersion in oil, 0.105 g, 3.25 mmol) was added, and the solution was stirred for 30 min at 0 °C. Iodomethane (0.2 mL, 3.25 mmol) was added, the ice bath was removed, and the solution was stirred overnight. The mixture was poured into water (180 mL) and washed with Et_2O (3 × 60 mL). The organic layer was washed with water (4 × 40 mL) and brine (50 mL). The organic layer was then dried (Na_2SO_4) and filtered, and solvent was removed in vacuo. The silyl ether (0.821 g, 2.6 mmol) was dissolved in methanol (15 mL) and water (0.5 mL) and then treated with CH_3SO_3H (0.5 mL) and stirred for 30 min at room temperature. The solvent was removed, and the product was purified on silica by gel chromatography with hexane/EtOAc. The product **3** was obtained as a colorless oil (0.478 g, 2.3 mmol, 70% for two steps). ^{1}H ($CDCl_3$): 7.01 (m, 4H), 4.72 (dd, *J* = 7.2, 5.7, 1H), 3.88 (m, 2H), 3.38 (s, 3H), 2.31−2.10 (m, 2H). *m*/*z* (MH^+) 208.0.

Methyl-2-[2-(4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]-oxazin-2-yl)ethoxy]phenylacetate (4). A solution of **3** (0.134 g, 0.65 mmol), (2-hydroxyphenyl)acetic acid methyl ester (0.16 g, 0.96 mmol), and tributylphosphine (0.24 mL, 0.96 mmol) in dry benzene (15 mL), under N_2, was cooled to 10 °C. 1,1′-(Azodicarbonyl)dipiperidine (0.244 g, 0.96 mmol) was added in one portion, and the solution was stirred at room temperature overnight. The organic layer was washed with 5 N aqueous NaOH (4 × 5 mL) and brine (5 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was purified by silica gel chromatography with hexane/EtOAc. The ester **4** was obtained as a colorless oil (0.148 g, 0.42 mmol, 64%). ^{1}H ($CDCl_3$): 7.28−7.18 (m, 2H), 7.09−6.89 (m, 6H), 4.79 (dd, *J* = 9.5, 3.9, 1H), 4.24 (m, 2H), 3.60 (m, 5H), 3.38 (s, 3H), 2.52 (m, 1H), 2.24 (m, 1H). *m*/*z* (MNa^+) 378.1.

2-[2-(4-Methyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (5). A solution of **4** in MeOH (15 mL) and 2 N aqueous NaOH (2 mL) was heated to 65 °C for 2.5 h, cooled to 0 °C, diluted with 10 mL of water, and acidified with concentrated HCl (0.5 mL). The product was obtained as a solid by filtration and dried in vacuo at 45 °C (0.083 g, 0.24 mmol, 78%). ^{1}H ($CDCl_3$): 7.28−7.18 (m, 2H), 7.07−6.89 (m, 6H), 4.87 (dd, *J* = 9.0, 3.7, 1H), 4.23 (m, 2H), 3.62 (dd, *J* = 21.2, 15.9, 2H), 3.37 (s, 3H), 2.46 (m, 1H), 2.25 (m, 1H). *m*/*z* (MH^+) 340.1. Anal. ($C_{19}H_{19}NO_5 \cdot 0.15H_2O$) C, H, N.

2-[2-(4-Ethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (6). Alkylating agent = iodoethane. ^{1}H ($CDCl_3$): 7.28−7.18 (m, 2H), 7.05−6.89 (m, 6H), 4.85 (dd, *J* = 9.1, 3.6, 1H), 4.23 (m, 2H), 3.99 (m, 2H), 3.63 (dd, *J* = 20.9, 15.9, 2H), 2.43 (m, 1H), 2.23 (m, 1H), 1.28 (t, *J* = 7.2, 3H). *m*/*z* (MH^+) 354.2. Anal. ($C_{20}H_{21}NO_5 \cdot 0.25H_2O$) C, H, N.

2-[2-(4-Isopropyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (7). Alkylating agent = 2-iodopropane. ^{1}H ($CDCl_3$): 7.28−7.13 (m, 2H), 7.05−6.89 (m, 6H), 4.74 (m, 2H), 4.21 (m, 2H), 3.63 (dd, *J* = 20.2, 16.0, 2H), 2.41 (m, 1H), 2.19 (m, 1H), 1.54 (d, *J* = 7.2, 6H). *m*/*z* (MH^+) 368.1. Anal. ($C_{21}H_{23}NO_5 \cdot 0.25H_2O$) C, H, N.

2-[2-(3-Oxo-4-propyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (8). Alkylating agent = 1-iodopropane ^{1}H ($CDCl_3$): 7.26−7.17 (m, 2H), 7.06−6.89 (m, 6H), 4.82 (dd, *J* = 9.2, 3.8, 2H), 4.20 (m, 2H), 3.88 (t, *J* = 7.5, 2H), 3.61 (dd, *J* = 19.1, 16.2, 2H), 2.45 (m, 1H), 2.23 (m, 1H), 1.68 (hex, *J* = 7.6, 2H), 0.97 (t, *J* = 7.4, 6H). *m*/*z* (M − 1) 368.3. Anal. ($C_{20}H_{21}NO_5$) C, H, N.

2-[2-(4-Isobutyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (9). Alkylating agent = 1-bromo-2-methylpropane. ^{1}H ($CDCl_3$): 7.28−7.17 (m, 2H), 7.05−6.89 (m, 6H), 4.84 (dd, *J* = 9.3, 3.7, 2H), 4.22 (m, 2H), 3.79 (m, 2H), 3.61 (dd, *J* = 19.1, 16.1, 2H), 2.44 (m, 1H), 2.24 (m, 1H), 2.08 (hept, *J* = 7.0, 1H), 0.94 (m, 6H). *m*/*z* (M − 1) 382.3. Anal. ($C_{22}H_{25}NO_5 \cdot 0.15H_2O$) C, H, N.

2-[2-(4-Butyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (10). Alkylating agent = 1-bromobutane. ^{1}H ($CDCl_3$): 7.28−7.17 (m, 2H), 7.04−6.88 (m, 6H), 4.81 (dd, *J* = 9.1, 3.8, 2H), 4.20 (m, 2H), 3.92 (t, *J* = 7.5, 2H), 3.61 (dd, *J* = 19.0, 16.2, 2H), 2.45 (m, 1H), 2.23 (m, 1H), 1.63 (m, 2H), 1.41 (m, 2H), 0.96 (t, *J* = 7.3, 3H). *m*/*z* (M − 1) 382.3. Anal. ($C_{22}H_{25}NO_5 \cdot 0.1H_2O$) C, H, N.

2-[2-(3-Oxo-4-pentyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (11). Alkylating agent = 1-bromopentane. ^{1}H ($CDCl_3$): 7.28−7.16 (m, 2H), 7.06−6.88 (m, 6H), 4.81 (dd, *J* = 9.2, 3.8, 2H), 4.20 (m, 2H), 3.90 (t, *J* = 7.6, 2H), 3.61 (dd, *J* = 19.2, 16.1, 2H), 2.46 (m, 1H), 2.23 (m, 1H), 1.65 (m, 2H), 1.34 (m, 4H), 0.96 (t, *J* = 6.8, 3H). *m*/*z* (M − 1) 396.4. Anal. ($C_{23}H_{27}NO_5$) C, H, N.

2-[2-(4-Hexyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (12). Alkylating agent = 1-iodohexane. ^{1}H ($CDCl_3$): 7.28−7.18 (m, 2H), 7.07−6.89 (m, 6H), 4.83 (dd, *J* = 9.1, 3.7, 1H), 4.20 (m, 2H), 3.91 (t, *J* = 7.6, 2H), 3.62 (dd, *J* = 20.6, 16.0, 2H), 2.44 (m, 1H), 2.23 (m, 1H), 1.65 (m, 2H), 1.33 (m, 6H), 0.88 (t, *J* = 6.7, 3H). *m*/*z* (MH^+) 412.3. Anal. ($C_{24}H_{29}NO_5$) C, H, N.

Compound **12** was resolved into enantiomers **13** and **14** by chiral chromatography with a Chiralcel AD column (2 cm × 25 cm). The mobile phase was 80:20:0.1 hexane/2-propanol/TFA, and the flow rate was 6 mL/min. Retention times: (*R*) = 23.3 min; (*S*) = 29.8 min.

(*R*)-2-[2-(4-Hexyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (13). ^{1}H ($CDCl_3$): 7.26−7.19 (m, 2H), 7.03−6.89 (m, 6H), 4.87 (dd, *J* = 9.2, 3.5, 1H), 4.22 (m, 2H), 3.91 (t, *J* = 7.7, 2H), 3.63 (dd, *J* = 21.4, 16.0, 2H), 2.39 (m, 1H), 2.23 (m, 1H), 1.65 (m, 2H), 1.33 (m, 6H), 0.89 (m, 3H). *m*/*z* (MH^+) 412.3. Anal. ($C_{24}H_{29}NO_5$) C, H, N.

(*S*)-2-[2-(4-Hexyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (14). ^{1}H ($CDCl_3$): 7.26−7.19 (m, 2H), 7.03−6.89 (m, 6H), 4.87 (dd, *J* = 9.2, 3.5, 1H), 4.22 (m, 2H), 3.91 (t, *J* = 7.7, 2H), 3.63 (dd, *J* = 21.4, 16.0, 2H), 2.39 (m, 1H), 2.23 (m, 1H), 1.65 (m, 2H), 1.33 (m, 6H), 0.89 (m, 3H). *m*/*z* (MH^+) 412.3. Anal. ($C_{24}H_{29}NO_5$) C, H, N.

2-[2-(4-Heptyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (15). Alkylating agent = 1-iodoheptane. ^{1}H ($CDCl_3$): 7.27−7.19 (m, 2H), 7.06−6.88 (m, 6H), 4.80 (dd, *J* = 9.0, 4.0, 1H), 4.20 (m, 2H), 3.90 (t, *J* = 7.6, 2H), 3.62 (s, 2H), 2.46 (m, 1H), 2.24 (m, 1H), 1.75−1.28 (m, 10H), 0.92 (m, 3H). *m*/*z* (M − 1) 424.1. Anal. ($C_{25}H_{31}NO_5 \cdot 1.4H_2O \cdot 1.0C_6H_{14} \cdot 1.0C_4H_8O_2$) C, H, N.

2-[2-(4-Octyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (16). Alkylating agent = 1-bromooctane. ^{1}H ($CDCl_3$): 7.26−7.18 (m, 2H), 7.06−6.88 (m, 6H), 4.80 (dd, *J* = 9.1, 3.9, 1H), 4.20 (m, 2H), 3.90 (t, *J* = 7.6,

2H), 3.61 (dd, J = 18.5, 16.3, 2H), 2.43 (m, 1H), 2.24 (m, 1H), 1.76−1.27 (m, 12H), 0.88 (m, 3H). m/z (M − 1) 438.3. Anal. ($C_{26}H_{33}NO_5 \cdot 0.2H_2O \cdot 0.3C_6H_{14} \cdot 0.6C_4H_8O_2$) C, H, N.

2-[2-(4-Nonyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (17). Alkylating agent = 1-bromononane. ^{1}H ($CDCl_3$): 7.27−7.19 (m, 2H), 7.06−6.88 (m, 6H), 4.80 (dd, J = 9.2, 4.0, 1H), 4.20 (m, 2H), 3.90 (t, J = 7.5, 2H), 3.61 (s, 2H), 2.46 (m, 1H), 2.24 (m, 1H), 1.75−1.26 (m, 14H), 0.92 (m, 3H). m/z (M − 1) 452.2. Anal. ($C_{27}H_{35}NO_5 \cdot 1.4H_2O \cdot 1.0C_6H_{14} \cdot 0.8C_4H_8O_2$) C, H, N.

2-[2-(4-Decyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (18). Alkylating agent = 1-bromodecane. ^{1}H ($CDCl_3$): 7.26−7.18 (m, 2H), 7.06−6.88 (m, 6H), 4.80 (dd, J = 9.1, 3.9, 1H), 4.20 (m, 2H), 3.90 (t, J = 7.6, 2H), 3.61 (dd, J = 18.5, 16.2, 2H), 2.45 (m, 1H), 2.24 (m, 1H), 1.75−1.18 (m, 16H), 0.88 (m, 3H). m/z (M − 1) 466.3. Anal. ($C_{25}H_{31}NO_5 \cdot 0.3C_6H_{14} \cdot 0.6C_4H_8O_2$) C, H, N.

2-[2-(4-(5-Methylhexyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (19). Alkylating agent = 1-bromo-5-methylhexane. ^{1}H ($CDCl_3$): 7.25 (m, 1H), 7.18 (d, J = 7.3, 1H), 7.06−6.88 (m, 6H), 4.81 (dd, J = 9.0, 3.8, 1H), 4.20 (m, 2H), 3.90 (t, J = 7.7, 2H), 3.61 (dd, J = 20.0, 16.1, 2H), 2.45 (m, 1H), 2.26 (m, 1H), 1.68−1.49 (m, 3H), 1.36 (m, 2H), 1.22 (m, 2H), 0.87 (t, J = 6.6, 3H). m/z (M − 1) 424.1. Anal. ($C_{25}H_{31}NO_5$) C, H, N.

1-Bromo-5,5-dimethylhexane. THF, *tert*-butylmagnesium chloride, and CuCN were reacted as described in the literature to provide (5,5-dimethylhexyloxy)trimethylsilane (*Tetrahedron Lett.* **1989**, *30*, 6393). The silyl ether was cleaved by the hydrolysis method described in example **3** to provide 5,5-dimethylhexan-1-ol. The alcohol (0.6 g, 4.6 mmol) was combined with 48% aqueous HBr (10 mL) and heated to reflux for 3 h. The aqueous layer was washed with 1:1 Et_2O/CH_2Cl_2 (3 × 25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) and brine (25 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. 1-Bromo-5,5-dimethylhexane was obtained as a colorless oil and used in the synthesis of **20**.

2-[2-(4-(5,5-Dimethylhexyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (20). Alkylating agent = 1-bromo-5,5-dimethylhexane. ^{1}H ($CDCl_3$): 7.28−7.17 (m, 2H), 7.03−6.88 (m, 6H), 4.83 (dd, J = 9.1, 3.6, 1H), 4.20 (m, 2H), 3.91 (t, J = 7.5, 2H), 3.63 (dd, J = 20.0, 16.1, 2H), 2.44 (m, 1H), 2.23 (m, 1H), 1.62 (m, 2H), 1.33 (m, 2H), 1.24 (m, 2H), 0.87 (s, 9H). m/z (M − 1) 438.1. Anal. ($C_{26}H_{33}NO_5 \cdot 0.4H_2O$) C, H, N.

2-[2-(4-(2-Cyclopentylethyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (21). Alkylating agent = (2-hydroxyethyl)cyclopentane. In the alkylation of the amide (Scheme 1), a solution of **2** (0.5 g, 1.6 mmol) in THF (5 mL) was cooled to −10 °C. Triphenylphosphine (0.46 g, 1.76 mmol) and diethylazodicarboxylate (DEAD, 0.28 mL, 1.76 mmol) were added, and the solution was stirred overnight at room temperature. The reaction was diluted with EtOAc (25 mL) and then extracted with 2 N NaOH (2 × 5 mL), water (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4) and filtered, and then, the solvent was removed in vacuo. The reaction product was elaborated to compound **21** with the chemistry in Scheme 1. ^{1}H ($CDCl_3$): 7.28−7.18 (m, 2H), 7.01−6.88 (m, 6H), 4.85 (dd, J = 9.3, 3.5, 1H), 4.23 (m, 2H), 3.92 (t, J = 7.8, 2H), 3.62 (dd, J = 20.0, 16.0, 2H), 2.43 (m, 1H), 2.21 (m, 1H), 1.84 (m, 3H), 1.65 (m, 6H) 1.17 (m, 2H). m/z (MH^+) 424.0. Anal. ($C_{25}H_{29}NO_5 \cdot 0.25H_2O$) C, H, N.

2-[2-(4-(3-Cyclopentylpropyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (22). Alkylating agent = (3-hydroxypropyl)cyclopentane. See the synthesis of **21** for the synthetic method. ^{1}H ($CDCl_3$): 7.28−7.18 (m, 2H), 7.03−6.89 (m, 6H), 4.85 (dd, J = 9.2, 3.6, 1H), 4.22 (m, 2H), 3.90 (t, J = 7.7, 2H), 3.63 (dd, J = 20.3, 15.9, 2H), 2.43 (m, 1H), 2.23 (m, 1H), 1.76−1.52 (m, 10H), 1.39 (m, 3H). m/z (MH^+) 438.1. Anal. ($C_{26}H_{31}NO_5 \cdot 0.12CH_2Cl_2$) C, H, N.

2-[2-(4-(2-Cyclohexylethyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (23). Alkylating agent = 1-bromo-2-cylohexylethane. ^{1}H ($CDCl_3$): 7.28−7.18 (m, 2H), 7.06−6.88 (m, 6H), 4.82 (dd, J = 9.0, 3.7, 1H), 4.20 (m, 2H), 3.93 (t, J = 8.0, 2H), 3.62 (dd, J = 20.0, 16.0, 2H), 2.43 (m, 1H), 2.23 (m, 1H), 1.80−0.88 (m, 13H). m/z (MH^+) 438.3. Anal. ($C_{24}H_{29}NO_5$) C, H, N.

2-[2-(4-(2-Hydroxyethyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (24). Alkylating agent = 2-bromoethyl acetate. ^{1}H ($CDCl_3$): 7.28−6.89 (m, 8H), 4.86 (dd, J = 8.8, 4.2, 1H), 4.22 (m, 4H), 3.91 (m, 4H), 2.49 (m, 1H), 2.25 (m, 1H). m/z (M-1) 370.1. Anal. ($C_{20}H_{21}NO_6 \cdot 0.2H_2O$) C, H, N.

(2-[2-(2-Carboxymethylphenoxy)ethyl]-3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-yl)acetic Acid (25). Alkylating agent = ethyl bromoacetate. ^{1}H (DMSO-d_6): 7.24 (d, J = 7.6, 1H), 7.18 (d, J = 7.4, 1H), 7.06 (m, 4H), 7.02 (d, J = 8.1, 1H), 6.89 (t, J = 7.3, 1H), 4.87 (dd, J = 9.1, 4.2, 1H), 4.64 (m, 2H), 4.16 (m, 2H), 3.35 (s, 2H), 2.26 (m, 1H), 2.12 (m, 1H). m/z (M-1) 384.1. Anal. ($C_{20}H_{19}NO_7 \cdot 0.2H_2O$) C, H, N.

5-Bromopentanoic Benzyl Ester. Benzyl alcohol (6.3 mL, 60.7 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (11.6 g, 60.7 mmol) were combined in CH_2Cl_2 (110 mL) and cooled to 0 °C. *N*,*N*-(Dimethylamino)-pyridine (0.67 g, 5.5 mmol) and 5-bromovaleric acid (10.0 g, 55.2 mmol) were added, and the reaction was stirred at room temperature for 7 h. The reaction was poured into water and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), water (50 mL), and brine (50 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained as a colorless oil and used in the synthesis of **26** and **37**.

5-(2-[2-(2-Carboxymethylphenoxy)ethyl]-3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-yl)pentanoic Acid (26). ^{1}H (CD_3OD): 7.25−7.15 (m, 2H), 7.09−6.86 (m, 6H), 4.87 (dd, J = 9.5, 4.2, 1H), 4.18 (m, 2H), 3.98 (m, 2H), 3.57 (dd, J = 19.1, 16.2, 2H), 2.33 (m, 3H), 2.21 (m, 1H), 1.68 (m, 4H). m/z (M − 1) 426.1. Anal. ($C_{23}H_{25}NO_7$) C, H, N.

6-(2-[2-(2-Carboxymethylphenoxy)ethyl]-3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-yl)hexanoic Acid (27). Alkylating agent = benzyl 6-bromohexanoate. ^{1}H (CD_3OD): 7.25−6.87 (m, 8H), 4.81 (m, 1H), 4.19 (m, 2H), 3.97 (m, 2H), 3.57 (m, 2H), 2.39−2.17 (m, 4H), 1.64 (m, 4H), 1.40 (m, 2H). m/z (M − 1) 440.0. Anal. ($C_{24}H_{27}NO_7$) C, H, N.

6-(2-[2-(2-Carboxymethylphenoxy)ethyl]-3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-yl)-2,2-dimethylhexanoic Acid (28). Alkylating agent = 6-bromo-2,2-dimethylhexanitrile. Exposure to NaOH saponified the ester and the nitrile. ^{1}H ($CDCl_3$): 7.26 (m, 1H), 7.15 (d, J = 6.4, 1H), 7.05−6.89 (m, 6H), 4.79 (dd, J = 9.9, 3.6, 1H), 4.31 (m, 1H), 4.17 (m, 1H), 4.00 (m, 2H), 3.62 (m, 2H), 2.32 (m, 1H), 2.17 (m, 1H), 1.71−1.19 (m, 6H), 1.16 (s, 3H), 1.14 (s, 3H). m/z (M − 1) 468.1. Anal. ($C_{26}H_{31}NO_7$) C, H, N.

(2-[2-(4-(4-Cyano-4,4-dimethylbutyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (35). Alkylating agent = 6-bromo-2,2-dimethylhexanitrile. The corresponding intermediate **4** was saponified with excess LiOH in THF/water. ^{1}H ($CDCl_3$): 7.26 (m, 1H), 7.18 (d, J = 7.2, 1H), 7.08−6.89 (m, 6H), 4.82 (dd, J = 9.1, 3.8, 1H), 4.20 (m, 2H), 3.95 (m, 2H), 3.61 (dd, J = 19.5, 16.1, 2H), 2.46 (m, 1H), 2.23 (m, 1H), 1.70 (m, 2H), 1.57 (m, 4H), 1.33 (s, 6H). m/z (M − 1) 449.2. Anal. ($C_{26}H_{30}N_2O_5$) C, H, N.

2-[2-(4-Hex-5-enyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]-oxazin-2-yl)ethoxy]phenylacetic Acid (36). Alkylating agent = 6-bromo-1-hexene. ^{1}H ($CDCl_3$): 7.25−7.16 (m, 2H), 7.01−6.88 (m, 6H), 5.79 (m, 1H), 5.03 (m, 1H), 4.96 (m, 1H), 4.81 (dd, J = 9.1, 3.8, 1H), 4.20 (m, 2H), 3.91 (t, J = 7.5, 2H), 3.62 (m, 2H), 2.47 (m, 1H), 2.22 (m, 1H) 2.10 (q, J = 7.1, 2H), 1.67 (m, 2H), 1.47 (p, J = 7.2, 2H). m/z (MH^+) 432.1. Anal. ($C_{24}H_{27}NO_5$) C, H, N.

7-Bromoheptyl Acetate. Acetic anhydride (1.5 mL, 15.4 mmol) and 7-bromo-1-heptanol (1.6 mL, 10.3 mmol) were combined in CH_2Cl_2 (30 mL). DMAP (0.6 g, 10.3 mmol) was added, and the reaction was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 (30 mL) and washed with 1 N HCl (50 mL), 1 N NaOH (50 mL), saturated

$NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained as a colorless oil and used in the synthesis of **40**.

(2-[2-(4-(7-Hydroxyheptyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (40). ^{1}H ($CDCl_3$): 7.27−7.17 (m, 2H), 7.06−6.88 (m, 6H), 4.84 (dd, J = 9.7, 3.5, 1H), 4.21 (m, 2H), 3.92 (m, 2H), 3.61 (m, 4H), 2.43 (m, 1H), 2.21 (m, 1H), 1.66 (m, 2H), 1.55 (m, 2H), 1.36 (s, 6H). *m/z* (MH^+) 442.0. Anal. ($C_{25}H_{31}NO_6$) C, H, N.

(2-[2-(3-Oxo-4-(5-oxohexyl)-3,4-dihydro-2*H*-benzo[1,4]-oxazin-2-yl)ethoxy]phenylacetic Acid (42). Alkylating agent = 1-chloro-5-hexanone. ^{1}H ($CDCl_3$): 7.28−7.18 (m, 2H), 7.05−6.89 (m, 6H), 4.85 (dd, J = 9.1, 3.7, 1H), 4.22 (m, 2H), 3.94 (m, 2H), 3.62 (dd, J = 20.5, 15.9, 2H), 2.50 (m, 2H), 2.41 (m, 1H), 2.23 (m, 1H), 2.13 (s, 3H), 1.64 (m, 4H). *m/z* (MH^+) 426.1. Anal. ($C_{24}H_{27}NO_6$) C, H, N.

(2-[2-(3-Oxo-4-(6-oxoheptyl)-3,4-dihydro-2*H*-benzo[1,4]-oxazin-2-yl)ethoxy]phenylacetic Acid (43). Alkylating agent = 1-bromo-6 heptanone. ^{1}H ($CDCl_3$): 7.28−7.17 (m, 2H), 7.03−6.89 (m, 6H), 4.81 (dd, J = 9.3, 3.7, 1H), 4.21 (m, 2H), 3.92 (m, 2H), 3.61 (dd, J = 19.3, 16.1, 2H), 2.43 (t, J = 7.3, 3H), 2.23 (m, 1H), 2.13 (s, 3H), 1.64 (m, 4H), 1.38 (m, 2H). *m/z* (M − 1) 438.1. Anal. ($C_{25}H_{29}NO_6$) C, H, N.

1-Chloro-5,5-difluorohexane. Caution: (Diethylamino)-sulfur trifluoride (DAST) reacts violently with water. 1-Chloro-5-oxohexane (1.37 g, 10.2 mmol) and DAST (2.6 mL, 19.7 mmol) were mixed at room temperature and then stirred at 50 °C overnight. The reaction was poured into ice (150 mL), adjusted to pH 5, and extracted with Et_2O (3 × 50 mL). The organic layer was washed with water (50 mL) each and brine (50 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained as a colorless oil, contaminated with <10% of the starting ketone. The material was used without purification in the synthesis of **46**.

(2-[2-(4-(5,5-Difluorohexyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (46). ^{1}H ($CDCl_3$): 7.30−7.18 (m, 2H), 7.08−6.89 (m, 6H), 4.85 (dd, J = 9.1, 3.7, 1H), 4.25 (m, 2H), 3.96 (t, J = 8.0, 2H), 3.66 (dd, J = 20.5, 15.9, 2H), 2.46 (m, 2H), 2.23 (m, 1H), 1.96−1.52 (m, 9H). *m/z* (MH^+) 448.1. Anal. ($C_{24}H_{27}F_2NO_5$) C, H, N.

Compound **46** was resolved into enantiomers **47** and **48** by chiral chromatography with a Chiralpak AD column (2 cm × 25 cm). The mobile phase was 80:20:0.1 hexane/2-propanol/TFA, and the flow rate was 9 mL/min. Retention times: (*R*) = 19.0 min; (*S*) = 24.4 min.

(*R*)-(2-[2-(4-(5,5-Difluorohexyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (47). ^{1}H ($CDCl_3$): 7.25 (m, 1H), 7.17 (m, 1H), 7.02−6.88 (m, 6H), 4.80 (dd, J = 9.1, 3.8, 1H), 4.21 (m, 2H), 3.93 (t, J = 7.5, 2H), 3.60 (dd, J = 20.4, 16.1, 2H), 2.45 (m, 1H), 2.24 (m, 1H), 1.88 (m, 2H), 1.70 (m, 1H), 1.57 (m, 5H). *m/z* (MH^+) 448.1. Anal. ($C_{24}H_{27}F_2NO_5$) C, H, N.

(*S*)-(2-[2-(4-(5,5-Difluorohexyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (48). ^{1}H ($CDCl_3$): 7.25 (m, 1H), 7.17 (m, 1H), 7.03−6.88 (m, 6H), 4.80 (dd, J = 9.1, 3.8, 1H), 4.21 (m, 2H), 3.93 (t, J = 7.5, 2H), 3.60 (dd, J = 20.4, 16.1, 2H), 2.45 (m, 1H), 2.22 (m, 1H), 1.87 (m, 2H), 1.70 (m, 1H), 1.57 (m, 5H). *m/z* (MH^+) 448.0. Anal. ($C_{24}H_{27}F_2NO_5$·$0.75H_2O$) C, H, N.

1-Bromo-6,6-difluoroheptane. Caution: DAST reacts violently with water. 1-Bromo-6-oxoheptane (1.1 g, 5.7 mmol) and DAST (1.5 mL, 11.4 mmol) were mixed at room temperature and then stirred at 50 °C overnight. The reaction was poured into ice (150 mL), adjusted to pH 4, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with water (50 mL) and brine (50 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained as a colorless oil, contaminated with <10% of the starting ketone. The material was used without purification in the synthesis of **49**.

(2-[2-(4-(6,6-Difluoroheptyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (49). ^{1}H ($CDCl_3$): 7.28−7.17 (m, 2H), 7.05−6.89 (m, 6H), 4.81 (dd, J = 9./, 3.7, 1H), 4.20 (m, 2H), 3.92 (t, J = 7.6, 2H), 3.62 (dd, J = 19.1, 16.2, 2H), 2.44 (m, 1H), 2.23 (m, 1H), 1.90−1.41 (m, 11H). *m/z* (MH^+). Anal. ($C_{25}H_{29}F_2NO_5$) C, H, N.

1-Bromo-6-fluorohexane. Caution: DAST reacts violently with water. 1-Bromohexan-6-ol (2.0 mL, 15.2 mmol) and DAST (4.0 mL, 30.5 mmol) were mixed at room temperature and then stirred at 35 °C for 4 h. The reaction was poured into ice (150 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained by silica gel chromatography with CH_2Cl_2 and used in the synthesis of **50**.

(2-[2-(4-(6-Fluorohexyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (50). ^{1}H ($CDCl_3$): 7.29−7.19 (m, 2H), 7.03−6.89 (m, 6H), 4.87 (dd, J = 9.0, 3.5, 1H), 4.52 (t, J = 6.0, 1H), 4.36 (t, J = 6.0, 1H), 4.23 (m, 2H), 3.93 (t, J = 7.6, 2H), 3.63 (dd, J = 21.8, 15.8, 2H), 2.40 (m, 1H), 2.23 (m, 1H), 1.68 (m, 4H), 1.45 (m, 4H). *m/z* (MH^+) 430.0. Anal. ($C_{24}H_{28}FNO_5$) C, H, N.

Compound **50** was resolved into enantiomers **51** and **52** by chiral chromatography with a Chiralpak AD column (2 cm × 25 cm). The mobile phase was 80:20:0.1 hexane/2-propanol/TFA, and the flow rate was 9 mL/min. Retention times: (*R*) = 19.5 min; (*S*) = 24.6 min.

(*R*)-(2-[2-(4-(6-Fluorohexyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (51). ^{1}H ($CDCl_3$): 7.29−7.19 (m, 2H), 7.03−6.89 (m, 6H), 4.87 (dd, J = 9.0, 3.5, 1H), 4.52 (t, J = 6.0, 1H), 4.36 (t, J = 6.0, 1H), 4.23 (m, 2H), 3.93 (t, J = 7.6, 2H), 3.63 (dd, J = 21.8, 15.8, 2H), 2.40 (m, 1H), 2.23 (m, 1H), 1.68 (m, 4H), 1.45 (m, 4H). *m/z* (MH^+) 430.0. Anal. ($C_{24}H_{28}FNO_5$) C, H, N.

(*S*)-(2-[2-(4-(6-Fluorohexyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (52). ^{1}H ($CDCl_3$): 7.25−7.16 (m, 2H), 7.01−6.88 (m, 6H), 4.80 (dd, J = 9.2, 3.8, 1H), 4.48 (t, J = 6.0, 1H), 4.36 (t, J = 6.0, 1H), 4.20 (m, 2H), 3.91 (t, J = 7.6, 2H), 3.61 (dd, J = 21.8, 15.8, 2H), 2.44 (m, 1H), 2.23 (m, 1H), 1.67 (m, 4H), 1.45 (m, 4H). *m/z* (MH^+) 430.0. Anal. ($C_{24}H_{28}FNO_5$·$0.25H_2O$) C, H, N.

1-Bromo-7-fluoroheptane. Caution: DAST reacts violently with water. 1-Bromohexan-7-ol (1.2 mL, 7.7 mmol) and DAST (1.5 mL, 11.5 mmol) were mixed at room temperature and then stirred at 50 °C for 4 h. The reaction was poured into ice (150 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained by silica gel chromatography with CH_2Cl_2 and used in the synthesis of **53**.

(2-[2-(4-(7-Fluoroheptyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (53). ^{1}H ($CDCl_3$): 7.28−7.17 (m, 2H), 7.06−6.88 (m, 6H), 4.82 (dd, J = 9.2, 3.7, 1H), 4.50 (t, J = 6.1, 1H), 4.35 (t, J = 6.1, 1H), 4.21 (m, 2H), 3.91 (t, J = 7.6, 2H), 3.62 (dd, J = 19.6, 16.0, 2H), 2.44 (m, 1H), 2.23 (m, 1H), 1.66 (m, 4H), 1.39 (m, 6H). *m/z* (M − 1) 442.1. Anal. ($C_{25}H_{30}FNO_5$) C, H, N.

(2-[2-(3-Oxo-(2-propylsulfanylethyl)-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (54). Alkylating agent = 2-chloroethyl-*n*-propylsulfide. ^{1}H ($CDCl_3$): 7.28−7.17 (m, 2H), 7.05−6.89 (m, 6H), 4.82 (dd, J = 9.2, 3.7, 1H), 4.21 (m, 2H), 4.10 (q, J = 9.3, 6.3, 2H), 3.62 (dd, J = 19.0, 16.1, 2H), 2.74 (dd, J = 8.7, 6.9, 2H), 2.59 (t, J = 7.3, 2H), 2.46 (m, 1H), 2.24 (m, 1H), 1.64 (hex, J = 7.3, 2H), 1.00 (t, J = 7.3, 3H). *m/z* (MNa^+) 451.9. Anal. ($C_{23}H_{27}NO_5S$) C, H, N.

(2-[2-(4-(3-Ethoxypropyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (55). Alkylating agent = 3-ethoxy-1-propanol. See the synthesis of **21** for the synthetic method. ^{1}H ($CDCl_3$): 7.28−6.89 (m, 8H), 4.82 (dd, J = 9.1, 3.7, 1H), 4.19 (m, 2H), 4.03 (m, 2H), 3.62 (dd, J = 18.5, 16.3, 2H), 3.46 (m, 4H), 2.44 (m, 1H), 2.23 (m, 1H), 1.94 (quint, J = 6.5, 2H), 1.21 (t, J = 7.1, 3H). *m/z* (M − 1) 412.1. Anal. ($C_{23}H_{27}NO_6$) C, H, N.

(2-[2-(4-(4-Methoxybutyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (56). Alkylating agent = 1-bromo-4-methoxybutane. ^{1}H ($CDCl_3$): 7.26−6.74 (m, 8H), 4.81 (m, 1H), 4.04 (m, 2H), 3.85 (m, 2H), 3.32 (m, 4H),

3.26 (s, 3H) 2.29 (m, 1H), 2.05 (m, 1H), 1.59 (m, 4H). *m/z* (MNa^+) 436.0. Anal. ($C_{23}H_{27}NO_6 \cdot 0.75\ H_2O$) C, H, N.

(2-[2-(4-(4-Carbamoylbutyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (29). Compound **58** (2.0 g, 3.8 mmol, see the synthesis of **26**) was dissolved in EtOH (50 mL) and debenzylated via hydrogenation with 10% Pd/C at 50 psi for 3.0 h. The reaction was filtered through Celite, and the solvent was removed in vacuo. A portion of the product (0.3 g, 0.68 mmol) was dissolved in CH_2Cl_2 (15 mL). 1,1′-Carbonyldiimidazole (0.22 g, 1.4 mmol) was added, and the solution was stirred for 2 h. Ammonium hydroxide (0.1 mL, 1.4 mmol) was added, and the reaction was stirred overnight at room temperature. The reaction was diluted with water (25 mL), and the pH was adjusted to 7 with 1 N HCl. The aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layer was washed with water (25 mL) and brine (25 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The methyl ester was saponified by the method for example **5** to yield **29**. ^1H (CD_3OD): 7.26−7.15 (m, 2H), 7.09−6.86 (m, 6H), 4.82 (dd, J = 9.4, 4.1, 1H), 4.18 (m, 2H), 3.99 (m, 2H), 3.57 (dd, J = 19.7, 16.2, 2H), 2.39 (m, 1H), 2.25 (m, 3H), 1.67 (m, 4H). *m/z* (M-1) 425.0. Anal. ($C_{23}H_{26}N_2O_6$) C, H, N.

(2-[2-(4-(5-Carbamoylpentyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (30). Compound **30** was prepared using the methods described for compound **29**. ^1H (DMSO-d_6): 7.26−7.17 (m, 2H), 7.11−6.98 (m, 5H), 6.89 (t, J = 7.4, 1H), 4.80 (dd, J = 9.2, 4.0, 1H), 4.15 (m, 2H), 3.90 (t, J = 7.3, 2H), 3.50 (s, 2H), 2.27 (m, 1H), 2.02 (m, 3H), 1.53 (m, 4H), 1.28 (m, 2H). *m/z* (M-1) 439.1. Anal. ($C_{24}H_{28}N_2O_6$) C, H, N.

(2-[2-(4-(5-Hydroxypentyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (37). Compound **58** (2.0 g, 3.8 mmol, see the synthesis of **26**) was dissolved in EtOH (50 mL) and debenzylated via hydrogenation with 10% Pd/C at 50 psi for 3.0 h. The reaction was filtered through Celite, and the solvent was removed in vacuo. A portion of the product (0.15 g, 0.34 mmol) was dissolved in dry THF (10 mL) and chilled to −50 °C. Borane−THF (0.7 mL, 0.68 mmol) was added, and the reaction was stirred while warming to 0 °C over 8 h. The reaction was quenched with 0.05 N aqueous HCl. THF was removed in vacuo, and the crude product was dissolved in EtOAc (150 mL). The organic layer was washed with water (50 mL) and brine (50 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The methyl ester was saponified by the method for example **5** to yield **37**. ^1H (CD_3OD): 7.25−6.87 (m, 8H), 4.82 (dd, J = 9.4, 4.0, 1H), 4.18 (m, 2H), 3.98 (t, J = 7.5, 2H), 3.54 (m, 4H), 2.39 (m, 1H), 2.18 (m, 1H), 1.72−1.42 (m, 6H). *m/z* (M − 1) 412.1. Anal. ($C_{23}H_{27}NO_6$) C, H, N.

(2-[2-(4-(6-Hydroxyhexyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (39). Compound **39** was prepared using the methods described for compound **37** via intermediate **59**. ^1H ($CDCl_3$): 7.27−7.16 (m, 2H), 7.02−6.88 (m, 6H), 4.86 (dd, J = 9.3, 3.3, 1H), 4.22 (m, 2H), 3.94 (m, 2H), 3.61 (m, 4H), 2.40 (m, 1H), 2.20 (m, 1H), 1.70−1.36 (m, 8H). *m/z* (M − 1) 426.1. Anal. ($C_{25}H_{31}NO_6$) C, H, N. Anal. ($C_{24}H_{29}NO_6$) C, H, N.

2-[2-(3-Oxo-4-propylcarbamoylmethyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (31). A solution of the amide **2** (0.8 g, 2.6 mmol) in dry DMF (5 mL) was added to a suspension of sodium hydride (0.087 g, 2.86 mmol) in dry DMF (5 mL) at 0 °C. After 30 min at 0 °C, ethyl bromoacetate (0.35 mL, 3.12 mmol) was added and the reaction was stirred for 30 min at 0 °C and then overnight at 50 °C. The reaction was quenched with 1 N HCl (5 mL), diluted with water (10 mL), and extracted with EtOAc (2 × 15 mL). The organic layer was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The crude product (**60**, 1 g, 2.54 mmol) was dissolved in MeOH (10 mL), and propylamine (1.46 mL, 17.78 mmol) was added. The reaction was stirred overnight at 45 °C. The mixture was diluted with EtOAc (25 mL) and washed with saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was elaborated to compound **31** by the methods described for compounds **3**−**5**. ^1H ($CDCl_3$): 7.32−7.22 (m, 2H), 7.19−6.91 (m, 6H), 6.20 (bs, 1H), 4.94 (dd, J = 8.5, 4.4, 1H) 4.72 (d, J = 16.0, 1H), 4.36 (d, J = 16.0, 1H), 4.32−4.26 (m, 2H), 3.62 (s, 2H), 3.57−3.18 (m, 2H), 2.61−2.54 (m, 2H), 2.34−2.27 (m, 1H), 1.52−1.43 (m, 2H), 0.86 (t, J = 7.4, 3H). *m/z* (MNa^+) 449.4. Anal. ($C_{23}H_{26}N_2O_6$) C, H, N.

2-[2-(4-(3-Methylcarbamoylpropyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (32). Compound **32** was prepared by the methods described for compound **31** via intermediate **61**. ^1H ($CDCl_3$): 7.31−6.91 (m, 8H), 5.94 (bs, 1H), 4.88 (dd, J = 9.1, 3.8, 1H), 4.29−4.19 (m, 2H), 4.08−3.93 (m, 2H), 3.65 (d, J = 3.4, 2H), 2.81 (d, J = 5.1, 3H), 2.49−2.41 (m, 1H), 2.29−2.21 (m, 3H), 2.08−1.99 (m, 2H). *m/z* (MNa^+) 449.4. Anal. ($C_{23}H_{26}N_2O_6$) C, H, N.

(2-[2-(4-(6-Acetylaminohexyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (33). A solution of the amide **2** (3.0 g, 9.8 mmol) in dry DMF (10 mL) was added to a suspension of sodium hydride (0.352 g, 11.7 mmol) in dry DMF (15 mL) at 0 °C. After 30 min at 0 °C, 6-bromohexyl phthalimide (4.0 g, 12.7 mmol) was added. The reaction was stirred for 30 min at 0 °C and then overnight at 50 °C. The reaction was quenched with 1 N aqueous HCl (15 mL), diluted with water (15 mL), and extracted with EtOAc (3 × 30 mL). The organic layer was washed with water (2 × 20 mL) and brine (20 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The crude material (6.2 g, 11.6 mmol) was dissolved in methanol (150 mL) and water (20 mL) and then treated with CH_3SO_3H (4 mL) and stirred for 2 h at room temperature. The mixture was diluted with EtOAc (150 mL), and then, the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to yield **62**. A solution of **62** (5.0 g, 11.8 mmol), (2-hydroxyphenyl)acetic acid methyl ester (3.9 g, 17.8 mmol), and tributylphosphine (4.4 mL, 17.8 mmol) in dry benzene (200 mL), under N_2, was cooled to 10 °C. 1,1′-(Azodicarbonyl)dipiperidine (4.5 g, 17.8 mmol) was added in one portion, and the solution was stirred at room temperature overnight. The organic layer was washed with 5 N aqueous NaOH (4 × 25 mL) and brine (25 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained as a yellow solid by silica gel chromatography with hexane/EtOAc (3.1 g, 5.4 mmol). Hydrazine (0.17 mL, 5.48 mmol) was added to a suspension of the purified product (2.6 g, 4.57 mmol) in EtOH (13 mL) and THF (13 mL). The reaction was stirred at 60 °C overnight and then diluted with MeOH and filtered. The solvent was evaporated to give **63** (1.46 g, 3.3 mmol) as a white solid. Compound **63** (0.2 g, 0.45 mmol) was stirred in acetic anhydride (6 mL) overnight. MeOH (10 mL) was added, and the solvent was removed in vacuo. Purification by reverse phase HPLC gave the desired acetamide (0.066 g, 0.14 mmol) as a clear oil. NaOH (1 N, 1 mL, 1 mmol) was added to a solution of the acetamide (0.066 g, 0.14 mmol) in 5 mL of MeOH. The reaction was stirred at 45 °C overnight and then acidified to pH 5 with 1 N HCl and extracted with EtOAc (10 mL). The organic layer was washed with water (5 mL) and brine (5 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. Compound **33** was obtained as a clear oil (40 mg, 0.08 mmol). ^1H ($CDCl_3$): 8.16 (bs, 1H), 7.24−7.16 (m, 2H), 7.06−6.87 (m, 6H), 5.29 (bs, 1H), 4.83 (dd, J = 9.2, 3.7, 1H), 4.27−4.19 (m, 2H), 3.99−3.85 (m, 2H), 3.61 (s, 2H), 3.19 (dd, J = 12.8, 6.7, 2H), 2.49−2.39 (m, 1H), 2.27−2.16 (m, 1H), 1.96 (s, 3H), 1.68−1.63 (m, 2H), 1.49−1.43 (m, 2H), 1.35−1.23 (m, 4H). *m/z* (MNa^+) 491.2. Anal. ($C_{26}H_{32}N_2O_6 \cdot 1.0Na \cdot 0.75H_2O$) C, H, N.

(2-[2-(4-(6-Methanesulfonylaminohexyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (34). Compound **34** was prepared by the methods described for compound **33**. ^1H ($CDCl_3$): 7.28−7.16 (m, 2H), 7.07−6.88

(m, 6H), 4.82 (dd, J = 9.1, 3.6, 1H), 4.25−4.16 (m, 2H), 3.98−3.87 (m, 2H), 3.61 (s, 2H), 3.09 (dd, J = 13.2, 6.6, 2H), 2.92 (s, 3H), 2.46−2.40 (m, 1H), 2.27−2.17 (m, 1H), 1.72−1.62 (m, 2H), 1.59−1.46 (m, 2H), 1.41−1.25 (m, 4H). m/z (MNa^+) 527.3. Anal. ($C_{25}H_{32}N_2O_7S$) C, H, N.

(2-[2-(4-(5-Hydroxy-5-methylhexyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (38). Compound **42** (0.4 g, 1 mmol) was dissolved in dry THF (10 mL), and the solution was cooled to −78 °C. Methylmagnesium bromide (0.7 mL, 3.0 M in ether) was added, and the reaction was stirred for 5 h at room temperature. Excess reagent was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with 1:1 Et_2O/CH_2Cl_2 (3 × 25 mL). The organic layer was washed with water (25 mL) and brine (25 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was isolated as a colorless oil. ^1H ($CDCl_3$): 7.28−7.08 (m, 2H), 6.93−6.81 (m, 6H), 4.78 (m, 1H), 4.21−3.97 (m, 3H), 3.78 (m, 1H), 3.51 (m, 2H), 2.44 (m, 1H), 2.12 (m, 1H), 1.69−1.36 (m, 6H), 1.15 (m, 6H). m/z (M − 1) 440.0. Anal. ($C_{25}H_{31}NO_6 \cdot 0.75H_2O$) C, H, N.

(2-[2-(4-(5-Hydroxyiminohexyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (44). Compound **42** (4.72 g, 11 mmol) was stirred at room temperature as a slurry in EtOH (200 mL). Lutidine (2.6 mL, 22 mmol) and hydroxylamine (3.8 g, 55 mmol) were added. The mixture rapidly became clear, and the reaction was complete in 2 h. Solvent was removed in vacuo, and the residue was dissolved in EtOAc (100 mL) and water (50 mL). The organic layer was washed with 0.1 N aqueous HCl (2 × 50 mL), water (50 mL), and brine (50 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained as a pale yellow solid (4.65 g, 10.5 mmol, 95%) and as a 3.4:1 E/Z mixture of oximes. ^1H ($CDCl_3$): 7.30−7.17 (m, 2H), 7.05−6.90 (m, 6H), 4.87 (dd, J = 9.4, 3.7) and 4.76 (dd, J = 10.0, 3.3) 1H, 4.27 (m, 2H), 4.15 (m, 1H), 3.88 (m, 1H), 3.61 (dd, J = 24.0, 15.4, 2H), 2.56 (m, 1H), 2.38−2.14 (m, 3H), 1.90 (s) and 1.82 (s) 3H, 1.78−1.46 (m, 4H). m/z (MH^+) 441.1. Anal. ($C_{24}H_{28}N_2O_6$) C, H, N.

(2-[2-(4-(5-Methoxyiminohexyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (45). Compound **42** (0.1 g, 0.24 mmol) was stirred at room temperature as a slurry in EtOH (5 mL). Pyridine (0.1 mL, 1.23 mmol) and *O*-methylhydroxylamine (0.098 g, 1.17 mmol) were added. The mixture rapidly became clear, and the reaction was complete in 0.5 h. Solvent was removed in vacuo, and the residue was dissolved in EtOAc (20 mL) and water (10 mL). The organic layer was washed with 0.1 N aqueous HCl (2 × 50 mL), water (50 mL), and brine (50 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained as a pale yellow solid (0.087 g, 0.19 mmol, 80%) and as a 3:1 E/Z mixture of oximes. ^1H ($CDCl_3$): 7.28−7.15 (m, 2H), 7.05−6.82 (m, 6H), 4.85 (dd, J = 9.1, 3.6, 1H), 4.21 (m, 2H), 3.82 (s) and 3.80 (s) 3H, 3.62 (dd, J = 20.4, 16.0, 2H), 2.43 (m, 1H), 2.21 (m, 3H), 1.84 (s) and 1.81 (s) 3H, 1.62 (m, 4H). m/z (MH^+) 455.0. Anal. ($C_{25}H_{30}N_2O_6 \cdot 0.4H_2O$) C, H, N.

(2-[2-(4-(5-Hydroxyhexyl)-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (41). ^1H ($CDCl_3$): 7.26−7.17 (m, 2H), 7.00−6.86 (m, 6H), 4.87 (m, 1H), 4.29 (m, 2H), 4.07 (m, 2H), 3.85 (m, 2H), 3.59 (m, 2H), 2.49 (m, 1H), 2.21 (m, 1H), 1.72 (m, 2H), 1.50 (m, 6H), 1.19 (m, 3H). m/z (MH^+) 428.0. Anal. ($C_{24}H_{29}NO_6 \cdot 0.5H_2O$) C, H, N.

Stereospecific Synthesis. Analytical chiral HPLC was performed on a Hewlett-Packard1090 Series II AminoQuant HPLC fitted with a Daicel Chemical Industries, LTD Chiralpak AD column (4.6 mm × 25 cm). The sample concentration was 1 mg/mL in eluting solvent, the flow rate was 1 mL/min, and UV detection was at 254 nm. Solvent and retention time of the chiral and racemic are listed with the individual experimental.

(*R*)-3-(2-Nitrophenoxy)dihydrofuran-2-one (65). A solution of 2-nitrophenol (27.8 g, 0.2 mol), (*S*)-(−)-α-hydroxy-γ-butyrolactone (15.3 mL, 0.2 mol), and triphenylphosphine (78.6 g, 0.3 mol) in dry THF (550 mL), under N_2, was cooled to −20 °C. A room temperature solution of DEAD (47.5 mL, 0.3 mol) in THF (20 mL) was added dropwise over 30 min. The reaction was stirred for 17 h as the cold bath thawed. The mixture was poured into water (3L) containing NaCl (200 g), and the solution was washed with a 1:1 ratio of Et_2O/EtOAc (6 × 100 mL). The organic layer was washed with water (5 × 100 mL) and brine (100 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was purified by silica gel chromatography with CH_2Cl_2/EtOAc and then crystallized from hexane/EtOAc to yield **65** as a pale yellow solid (21.16 g, 95 mmol, 47%). ^1H ($CDCl_3$): 7.86 (d, J = 8.1, 1H), 7.58 (t, J = 8.6, 1H), 7.50 (d, J = 7.8, 1H), 7.16 (t, J = 7.4, 1H), 5.04 (t, J = 7.4, 1H), 4.58 (m, 1H), 4.40 (q, J = 7.4, 1H), 2.8−2.6 (m, 2H). By HPLC, the enantiomeric purity was >99% for the crystalline sample (8:2 hexane/2-propanol, retention time chiral = 13.8 min, retention time racemic = 11.1 min, 13.7 min).

(*R*)-4-Hexyl-2-(2-hydroxyethyl)-4*H*-benzo[1,4]oxazin-3-one (66). The phenolic ether **65** (21.16 g, 0.095 mol) was suspended in EtOH (400 mL) and then shaken for 3 h at room temperature with 10% Pd/C and H_2 (45 psi). The solution was filtered through Celite, and the solvent was removed in vacuo. The crude benzoxazinone was dissolved in dry DMF (200 mL), imidazole (16.3 g, 0.24 mol) was added, and the solution was cooled to 0 °C. TBS chloride (28.6 g, 0.19 mol) was added as a solid, and the reaction was stirred overnight, under N_2, as the bath thawed. The reaction was poured into water (1.4 L) containing NaCl (200 g) and washed with a 4:1 ratio of Et_2O/CH_2Cl_2 (4 × 150 mL). The organic layer was washed with water (6 × 100 mL) and brine (100 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was isolated by silica gel chromatography with hexane/EtOAc. Note: The solid is volatile and sublimes when dried under vacuum for long periods.

A solution of the silyl ether (26.75 g, 87 mmol) in dry DMF (435 mL), under N_2, was cooled to 0 °C. Sodium hydride (75% dispersion in oil, 2.48 g, 83 mmol) was added in four portions of 0.62 g with 5 min intervals between additions. The solution was stirred for an additional 40 min at 0 °C. 1-Iodohexane (12.8 mL, 87 mmol) in dry DMF (25 mL) was added dropwise, the ice bath was replaced with an oil bath, and the solution was stirred at 65 °C overnight. The mixture was cooled to room temperature and poured into water (3 L) containing NaCl (200 g). The aqueous mixture was washed with a ratio of 1:1 Et_2O/EtOAc (4 × 125 mL). The organic layer was washed with water (6 × 125 mL) and brine (125 mL). The organic layer was then dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was obtained as a colorless oil by silica gel chromatography with hexane/EtOAc (26.8 g, 68 mmol, 79%). The silyl ether was dissolved in MeOH (150 mL). HCl (6 N, 0.5 mL) was added, and the mixture was stirred at room temperature for 5 h. The solvent was removed in vacuo, and the product was isolated by silica gel chromatography with hexane/EtOAc. The primary alcohol **66** was obtained as a colorless oil (16.7 g, 60 mmol, 88%). ^1H ($CDCl_3$): 7.01 (m, 4H), 4.69 (t, J = 7.0, 1H), 3.88 (m, 4H), 2.44 (t, J = 5.8, 1H), 2.20 (m, 2H), 1.65 (m, 2H), 1.33 (m, 6H), 0.89 (br t, 3H). m/z (MH^+) 278.0. By HPLC, the enantiomeric purity was 97.4:2.1 (9:1 hexane/2-propanol, retention time chiral = 7.5 min, retention time racemic = 7.6 min, 8.5 min).

(*R*)-2-[2-(4-Hexyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (13). A solution of **66** (16.7 g, 0.06 mol), (2-hydroxyphenyl)acetic acid methyl ester (15 g, 0.09 mol), and tributylphosphine (22.4 mL, 0.09 mol) in dry benzene (1 L), under N_2, was cooled to 10 °C. 1,1′-(Azodicarbonyl)dipiperidine (22.7 g, 0.09 mol) was added in one portion, and the solution was stirred, with an overhead stirrer, at room temperature overnight. Water (130 mL) was added, and stirring was continued for 40 min. The mixture was transferred to a separatory funnel. The organic layer was washed with water (4 × 100 mL) and brine (100 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The product was purified by silica gel

chromatography with hexane/EtOAc. The ester was obtained as a colorless oil (24.3 g, 0.057 mol, 95%). ^{1}H ($CDCl_3$): 7.28−6.89 (m, 8H), 4.76 (dd, J = 9.4, 4.0, 1H), 4.28−4.21 (m, 2H), 3.92 (t, J = 7.7, 2H), 3.60 (m, 5H), 2.49 (m, 1H), 2.23 (m, 1H), 1.66 (m, 2H), 1.34 (m, 6H), 0.89 (m, 3H). A solution of the ester (24.3 g, 0.057 mol) in THF (500 mL) was cooled to 0 °C. Aqueous LiOH (0.85 N, 200 mL, 0.17 mol LiOH) at 10 °C was added in one portion. The solution was stirred at room temperature overnight, open to air. The solution was poured into water (1 L), and the solution was brought to pH 4 by portionwise addition of 28.5 mL of 6 N HCl. The aqueous layer was extracted with CH_2Cl_2 (4 × 120 mL). The organic layer was washed with 2:1 water/brine (3 × 150 mL). The organic layer was then dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. The oily residue was diluted with pentane (1 L) and Et_2O (200 mL), heated on a steam bath, and scratched with a glass rod until the material became a white solid. The mixture was cooled to 0 °C for 1.5 h and then filtered and washed with pentane (2 × 100 mL). The amorphous white solid was dried under vacuum at 40 °C (17.5 g, 0.043 mol, 75%). mp 80.0−81.5 °C. $[\alpha]^D_{25}$ = +31.2 °c = 1, $CHCl_3$. ^{1}H ($CDCl_3$): 7.28−6.89 (m, 8H), 4.84 (dd, 1H), 4.20 (m, 2H), 3.91 (t, 2H), 3.62 (dd, 2H), 2.43 (m, 1H), 2.23 (m, 1H), 1.65 (m, 2H), 1.33 (m, 6H), 0.88 (m, 3H). By HPLC, the enantiomeric purity was 99:1 (80:20:0.1 hexane/2-propanol/trifluoroacetic acid, retention time chiral = 7.2 min, retention time racemic = 7.2 min, 8.7 min).

(*R*)-(2-[2-(4-(4-Methoxybutyl)-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-yl)ethoxy]phenylacetic Acid (57). Alkylating agent = 1-bromo-4-methoxybutane. ^{1}H ($CDCl_3$): 7.26−6.74 (m, 8H), 4.81 (m, 1H), 4.04 (m, 2H), 3.85 (m, 2H), 3.32 (m, 4H), 3.26 (s, 3H) 2.29 (m, 1H), 2.05 (m, 1H), 1.59 (m, 4H). m/z (MH^+) 436.0. Anal. ($C_{23}H_{27}NO_6$) C, H, N.

General Biology. The PPARγ in vitro aP2 induction assay was run as described in ref 23. Incubations with human liver microsomes were run by Absorption Systems (Exton, PA).

Bioavailability. Rats were dosed intravenously (IV) at 3 mg/kg and by oral gavage at 30 mg/kg. The test compound was formulated for IV dosing as a solution in 10% w/v Solutol in 5% dextrose in sterile water vehicle (D5W) and formulated for oral dosing as a uniform suspension in 0.5% methylcellulose vehicle. Blood samples (0.5 mL) were collected into heparinized tubes postdose via orbital sinus puncture and then centrifuged for cell removal. Precisely 200 μL of plasma supernatant was transferred to a clean vial, frozen with dry ice, and stored at −70 °C prior to analysis. Four hundred microliters of acetonitrile containing internal standard (Propranolol) was added to 200 μL of plasma to precipitate proteins. Samples were centrifuged at 5000g for 3 min, and the supernatant was removed for analysis by LC-MS-MS. Calibration standards were prepared by adding appropriate volumes of stock solution directly into plasma and treatment identically to collected plasma samples. Calibration standards were typically prepared in the range of 0.1−10 μM for quantitation. LC-MS-MS analysis was performed using either multiple reaction or selected ion monitoring for detection of characteristic ions for each drug candidate and internal standard. Results were calculated by WinNonlin Pro version 3.1. Oral and intravenous areas under the concentration vs time curve (AUC) were compared, to determine the % bioavailability (%F) by the following formula: dose (IV) × AUC (oral)/dose (oral) × AUC (IV).

In Vivo Efficacy. Female *db*/*db* mice (C57 BLK S/J-m$^{+/+}$ Lepr^{db} mice (Jackson Labs, Bar Harbor, ME)), about 7 weeks of age, were maintained on NIH Rat and Mouse/Auto 6F Reduced Fat Diet #5K52 (PMI Nutrition International Inc.). Animals were treated with vehicle or compound for 11 consecutive days by oral gavage (n = 7−8). All mice were weighed on day 1 prior to dosing and then on day 12. Eighteen to twenty-four hours after the final dose, the mice were anesthetized with CO_2/O_2 (70%:30%), bled by retroorbital sinus puncture into 1.7 mL of heparin-containing (for plasma) or clotting activator-containing (for serum) tubes. Plasma or serum samples were prepared and assayed for glucose using Sigma Diagnostics Trinder reagent. All of the in vivo data were analyzed using Prism program (Graphpad, Monrovia, CA), and statistical analysis was performed using the one way analysis of variance with a Dunnett's multiple comparison test.

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