Articles

Hypoglycemic Activity of a Series of α-Alkylthio and α-Alkoxy Carboxylic Acids Related to Ciglitazone

Bernard Hulin,* Linda S. Newton, Diana M. Lewis, Paul E. Genereux, E. Michael Gibbs, and David A. Clark

Central Research, Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340

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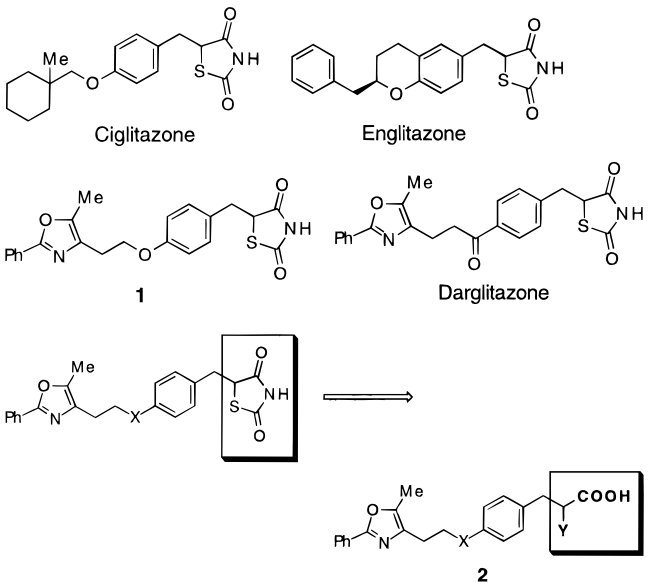
The thiazolidinedione moiety of ciglitazone and its analogues can be replaced by an α-alkoxy or α-thioether carboxylic acid group. The influence of the nature of the R group, the length of the connector to the aromatic backbone of the molecule, and the stereochemistry have been studied. The most potent compounds have glucose-lowering activity at doses as low as 0.01 mg/kg.

Non-insulin-dependent diabetes mellitus (NIDDM) is a metabolic disorder leading to long-term organ complications such as neuropathy, nephropathy, retinopathy and premature atherosclerosis.[1] NIDDM patients are usually treated by a combination of dietary measures and pharmacological agents: sulfonylureas, biguanides, and/or insulin.[2] This conventional treatment suffers from a high failure rate, and attempting to achieve the desired tight control may result in an increase in dangerous hypoglycemic episodes. The recently disclosed results of the Diabetes Control and Complications Trial showed dramatic benefits for IDDM patients on intensive insulin therapy, but at the cost of a 3-fold increase in the risk of severe hypoglycemia.[3] If extrapolated to NIDDM, these results indicate that tight glucose control is desirable in order to decrease the risk of these long-term complications. This tight control must be balanced with the risk of hypoglycemia, particularly with insulin and sulfonylureas. New therapies which normalize blood glucose levels without raising insulin levels are therefore an attractive alternative, and a variety of agents with potential advantages over the existing ones have recently been disclosed.[4,5] Among them, analogs of ciglitazone have been the objects of widespread interest.[5] Ciglitazone, reported in 1982 by Takeda, was shown to normalize hyperglycemia in insulin-resistant models without affecting the glycemia in nondiabetic animals,[6] therefore lowering insulin resistance directly without any effect on insulin secretion. Since then, numerous reports have appeared describing more potent or structurally distinct analogs,[5,7] and positive clinical results have been reported.[5,8]

Compounds containing a (2-phenyloxazol-4-yl)ethyl chain display particularly potent activity, whether in the ether series as in **1**[9] or in the ketone series as in darglitazone.[10] At the other end of the molecule, the thiazolidinedione ring has been replaced mainly by closely related groups such as the oxazolidine-2,4-dione[11] and 1-oxa-2,4-diazolidine-3,5-dione[12] rings and the carbonylated hydroxyurea moiety.[12,13] Our goal in this study was to find derivatives such as **2** where the acidic role is now played by a carboxylic acid function. It was envisioned that an appropriate substituent placed at the α-position could alter the chemical environment around the carboxylic acid function in such a way that the whole group would mimic the thiazolidinedione ring.



Results and Discussion

The choice of the appropriate backbone on which to append the carboxylic acid function was based on work performed in the thiazolidinedione series, where we sought to reduce the conformational freedom of the ether linkage, without creating a stereocenter, as in the benzopyran series where compounds isomeric at C-2 of the benzopyran, such as englitazone,[14] had similar activities. This was accomplished by incorporating the oxygen into a benzofuran ring system substituted at the 2-position. The resulting series of compounds exemplified by **3**, a direct analog of **1**, displayed exceptional potency in the ob/ob mouse. A similar modification in the oxazolidinedione series also led to very potent compounds.[11a]

As the results in Table 1 show, all these compounds display excellent activity at 0.1 mg/kg, and two compounds, **3** and **7**, are fully active at 0.01 mg/kg, i.e. they are at least 50 times more potent than darglitazone, our compound previously selected for clinical studies.[10]

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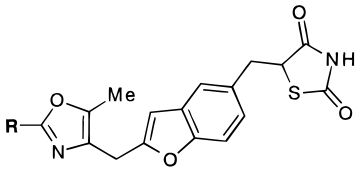
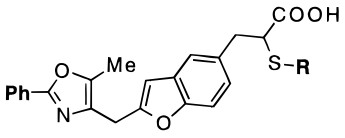
Table 1. Hypoglycemic Activity of Benzofuran Thiazolidinediones



compound		% glucose normalization in ob/ob mouse (mg/kg)[a]		
no.	R	1	0.1	0.01
3	Ph	NT	93*	76*
4	4-ClPh	100*	100*	0
5	3-FPh	100*	88*	12
6	2-MePh	100*	91*	11
7	3-MePh	100*	79*	78*
8	cyclohexyl	100*	90*	IA

[a] *p < 0.05; NT, not tested; IA, inactive.

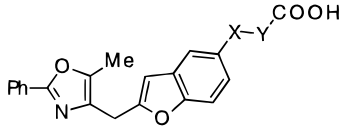
Table 2. Hypoglycemic Activity of α-Thioether Carboxylic Acids



compound		% glucose normalization in db/db mouse (mg/kg)[a]				
no.	R	5	1	0.5	0.25	0.1
11	Me	NT	89*	100*	16	26
12	Et	86*	60*	80*	3	NT
13	*n*-Pr	94*	69*	82*	39	NT
14	*n*-Oct	96*	75*	100*	99*	14
15	Bn	100*	88*	93*	72*	IA
16	Ph	70*	90*	100*	92*	86

[a] *p < 0.05; NT, not tested; IA, inactive.

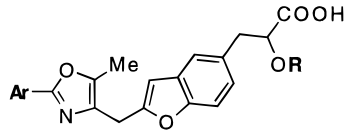
With highly potent compounds in hand it was deemed feasible to start a search for carboxylic acid analogs of **3**, since even a substantial (100×) loss in potency upon replacement of the thiazolidinedione ring would lead to a series of compounds with acceptable activity and, possibly, devoid of associated toxicity. Our first (and obvious) target was the unsubstituted hydrocinnamic acid **9**. This compound and the corresponding cinnamic acid **10** lacked any activity at 5 mg/kg. Although this lack of activity was disappointing, it was possible that it simply reflected the absolute necessity of a substituent at the α-position of the carboxylic acid that could take the place of the sulfur atom of the thiazolidinedione ring.



9 X-Y = CH_2-CH_2
10 X-Y = CH=CH

Accordingly, we set out to prepare carboxylic acids equipped with a thioether substituent at the α-position, starting with the methylthio moiety, a group small enough to fill the space occupied by the thiazolidinedione ring. This compound, **11**, showed remarkable activity at 1 and 0.5 mg/kg. Other compounds with various alkylthio groups were then prepared. The results are shown in Table 2. All the compounds prepared were active at 1 mg/kg or below, indicating that many different sulfur substituents are tolerated. Larger groups appear to be somewhat preferred, as evidenced by the activity at 0.25 mg/kg of **14**, **15**, and **16**.

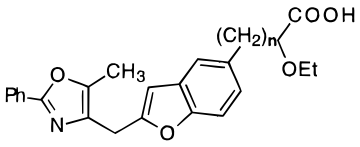
Table 3. Hypoglycemic Activity of α-Alkoxy Carboxylic Acids



compound			% glucose normalization in db/db mouse (mg/kg)[a]				
no.	R	Ar	5	1	0.1	0.05	0.01
17	Me	Ph	94*	100*	83*	82*	44
18	Et	Ph	100*	NT	100*	97*	69*
19	*n*-Pr	Ph	100*	100*	100*	76*	43
20	allyl	Ph	92*	85*	85*	91*	27
21	propargyl	Ph	100*	74	NT	NT	NT
22	Bn	Ph	NT	NT	100*	100*	74*
23	$(CH_2)_3OH$	Ph	NT	NT	91	19	NT
24	Et	*p*-OMePh	NT	100*	100*	IA	46
25	Et	2-thienyl	NT	100*	100*	100*	98*
26	Et	2-furyl	NT	100*	100*	NT	63*

[a] *p < 0.05; NT, not tested; IA, inactive.

Table 4. Hypoglycemic Activity of Alkanoic Acids of Varied Chain Length



compound		% glucose normalization in db/db mouse (mg/kg)[a]					
no.	n	5	1	0.5	0.25	0.1	0.01
27	0	9	NT	NT	NT	NT	NT
18	1	100*	NT	NT	100*	100*	69*
28	2	100*	90*	75*	13	NT	NT

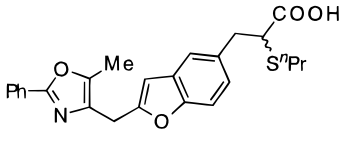
[a] *p < 0.05; NT, not tested.

Because of the potency improvement achieved with the thioether substitution at the α-position, we set out to vary further the α-substituent by changing the *thioether* group into an *ether* group. This variation is analogous to the thiazolidinedione to oxazolidinedione translation seen earlier,[11a] where the activity was retained. Therefore, a series of α-alkoxy carboxylic acids was synthesized and tested (Table 3).

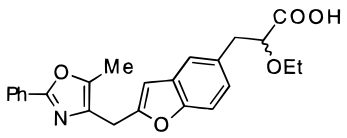
It quickly became apparent that the ether series is more potent than the thioether series. Whether this difference is due to intrinsic activity or to a metabolic liability of the latter series, i.e. rapid oxidation to the sulfoxide or sulfone followed by elimination, was not determined. The most active compounds, **18**, **25**, and **26,** are comparable in potency to the thiazolidinediones **3** and **7**. The nature of the oxygen substituent influences the degree of activity. Among alkyl chains a maximum of activity is observed for the ethyl group. Functionalization of the chain (**21**, **23**) led to a decrease in activity, while the benzyl-substituted compound was also very potent. Standard replacement of the phenyl substituent on the oxazole ring with 2-thienyl or 2-furyl (**25**, **26**) resulted in compounds with similar potency.

The length of the connector between the aromatic ring and the carboxylic acid function is critical for the activity (Table 4). Shortening this chain to one carbon led to the acetic acid **27**, which was devoid of activity even at

Table 5. Hypoglycemic Activity of Individual Enantiomers of **13** and **18**



(+)- and (-)-13



(*R*)-(+)- and (*S*)-(-)-18

compound		% glucose normalization in db/db mouse (mg/kg)[a]		
no.	stereochemistry	2.5	1	0.5
(+)-**13**	ND	69*	91*	52*
(−)-**13**	ND	75*	56*	45

compound		% glucose normalization in db/db mouse (mg/kg)[a]		
no.	stereochemistry	1	0.1	0.01
(−)-**18**	S	NT	100*	78*
(+)-**18**	R	74*	19	16

[a] *$p < 0.05$; ND, not determined; NT, not tested.

5 mg/kg, whereas the butyric acid analog **28** showed significant activity at 0.5 mg/kg.

The effect of the stereochemistry at the α-position to the carboxylic acid group was examined in both series by preparing the individual enantiomers of **13** and **18**. The two enantiomers of **13**, the absolute configuration of which was not established, were equipotent in their ability to lower glucose *in vivo* (Table 5). However it is quite possible that the the inactive antipode readily racemizes either directly or indirectly. The two enantiomers of ciglitazone have equivalent antihyperglycemic potency and have been hypothesized to interconvert,[15] and direct *in vivo* proton exchange has been shown to take place for the thiazolidinedione englitazone[5] and is a well-known process for 2-arylpropionic acids such as ibuprofen.[16] Indirect racemization may proceed *via* the corresponding sulfoxide, since most sulfides readily undergo reversible *in vivo* oxidation,[17] and the resultant α-sulfinyl carboxylic acid would be readily ionized at physiological pH. The intrinsic potency of the two enantiomers was assayed by examining their ability to stimulate glucose uptake in 3T3-L1 adipocytes after 48 h[18] incubation, an effect which had been observed with englitazone at micromolar concentrations[19] and with the oxazolidinedione CP-92768 (EC_{50} = 10 nM).[11b] Both antipodes of **13** increased the uptake in a dose-responsive manner with a maximum 5-fold stimulation. This low dose increase was followed by a second phase of stimulation at higher concentrations (not shown). (−)-**13** was clearly more potent than (+)-**13** in this assay, with EC_{50}'s *ca.* 0.2 and 20 nM, respectively (Figure 1a).[20] This result is consistent with racemization taking place *in vivo*. In the case of the alkoxy carboxylic acid **18**, where *in vivo* racemization would not be expected, the activity was shown to reside entirely within the (*S*) enantiomer *in vivo*, while in the glucose uptake assay, the same (*S*) antipode displayed a 2-fold stimulation with an EC_{50} *ca.* 5 nM. In contrast, the dose−response curve for the (*R*) antipode was shifted to the right about 20-fold, with an EC_{50} *ca.* 100 nM (Figure 1b).

This result is the first example of nonracemizable ciglitazone-like compounds where the stereochemistry α to the acidic moiety has been shown to be critical for the activity. In the case of thiazolidinediones, even if the activity resides in only one of the enantiomers, the other antipode is always present because of the rapid racemization *in vivo*. The alkoxy carboxylic acid series allows one to remove this "isomeric ballast", i.e. a 50% impurity which does not contribute to the desired activity but may impart toxicity. The results presented herein may also have significance with respect to the mechanism of action of this class of compounds: the high *in vivo* and *in vitro* potencies and the concordance of the *in vitro* and *in vivo* enantiospecificities for (+)- and (−)-**18** are consistent with the stimulation of glucose uptake being responsible for the hypoglycemic activity of these compounds.

In summary, we have shown that the thiazolidinedione group of potent ciglitazone-like compounds can be adequately replaced by an appropriately substituted carboxylic acid. The resulting series of α-thioether and α-alkoxy carboxylic acids have been shown to lower blood glucose levels in an animal model of NIDDM at low doses, equivalent to the effective doses for the corresponding thiazolidinediones. Two of these compounds, (−)-**13** and (−)-**18**, were shown to stimulate glucose uptake at low nanomolar concentration in an adipocyte cell line. Both the *in vivo* and *in vitro* effects are stereospecific for the nonracemizable alkoxy carboxylic acid series.

Chemistry

The thiazolidinediones in Table 1 were prepared from intermediate **29**[11a] by a standard sequence: transmetalation and reaction with DMF to form the aldehyde, condensation with 2,4-thiazolidinedione, and sequential reductions of the double bond and the alcohol function (Scheme 1).

The unsubstituted cinnamic and hydrocinnamic acids **10** and **9** were prepared from the known aldehyde **32**[11a] by Knoevenagel condensation followed by reduction. **32** was synthesized by an improved procedure, as detailed in Scheme 2.

The thioether carboxylic acids were prepared from aniline **36** by Meerwein arylation[6a,21] followed by displacement with the appropriate mercaptan and hydrolysis of the ester (Scheme 3).

The series of alkoxy carboxylic acids was obtained from the aldehyde **32** by Wittig reaction to form the homologated vinyl ether followed by acetal formation,

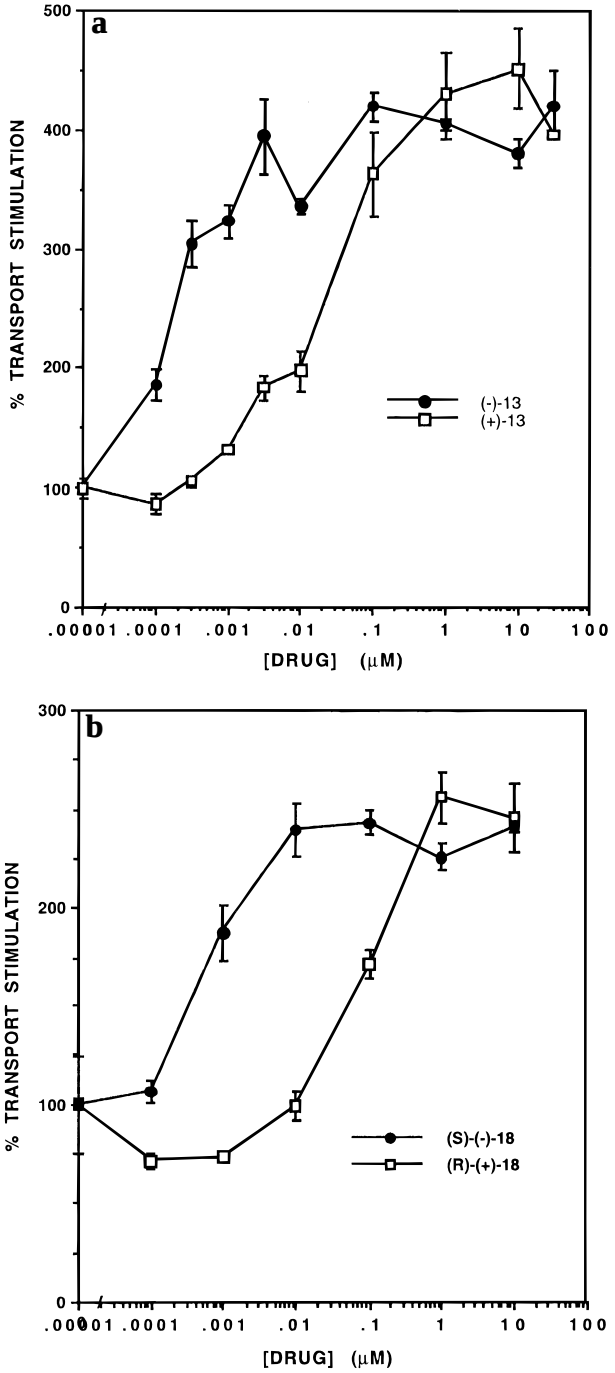


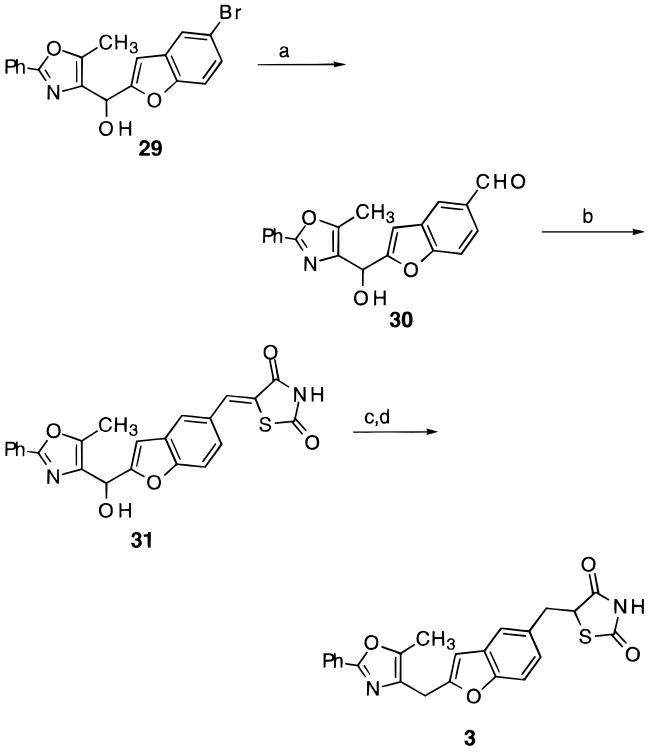
Figure 1. Glucose uptake dose−response curves for individual enantiomers of **13** (a) and **18** (b).

reaction with trimethylsilyl cyanide, and hydrolysis. This versatile sequence allowed the variation of the alkoxy group at a late stage in the synthesis by using the appropriate alcohol to form the acetal (Scheme 4).

The acetic and butyric acid analogs **27** and **28** were obtained following a variation of this sequence (Scheme 5).

Resolution of **13** was accomplished using the method of Helmchen.[22] The amides **47m** (more polar by TLC analysis) and **47l** (less polar) were easily separated by chromatography and recrystallization. Hydrolysis of the amides under acidic conditions proceeded with *ca.* 10% racemization as determined by conversion back to the Helmchen amide under neutral conditions. The acid could be purified by recrystallization to yield material enantiomerically pure (by NMR analysis of the Helmchen amide) (Scheme 6). (+)- and (−)-**18** were synthesized by aldol reaction of **32** with **48**, a derivative of ethoxyacetic acid fitted with an Evans' chiral auxiliary,[23] followed by removal of the hydroxyl group and hydrolysis of the auxiliary (Scheme 7).

Scheme 1[a]



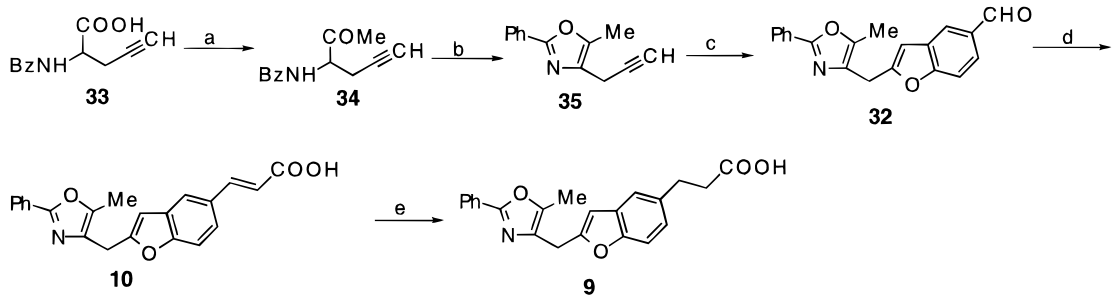
[a] (a) ^{n}BuLi, DMF, THF; (b) 2,4-thiazolidinedione, piperidine, ethanol; (c) 3% sodium amalgam, methanol, THF; (d) Et_3SiH, TFA.

Experimental Section

Biological Procedure. ***Measure of in Vivo Hypoglycemic Activity.*** The method used has been described previously[10,14] and is herein repeated for convenience, the only difference being the use of db/db mice instead of ob/ob mice. Six- to eight-week-old db/db mice (obtained from Jackson Laboratories, Bar Harbor, ME) were housed five per cage under standard animal care practices. After a 1 week acclimation period, the animals were weighed and 25 μL of blood were collected via the retro-orbital sinus prior to any treatment. The blood sample was immediately diluted 1:5 with saline containing 2% sodium heparin and held on ice for glucose analysis. Animals were then dosed daily for 4 days with drug or vehicle. All drugs were administered by oral gavage, once daily, in a vehicle consisting of 0.25% (w/v) methylcellulose in water with no pH adjustment (0.1 mL of solution per 20 g of animal weight). Animals were bled 24 h after the fourth administration of drug or vehicle (via the retro-orbital sinus) for blood glucose levels. The weight of each animal was recorded on days 1 and 5 of the treatment. The freshly collected samples (125 μL in 330 μL tubes) were centrifuged for 2 min at 10000*g* at room temperature. A 50 μL sample was analyzed for glucose by the Abbott VP Super System Analyzer,[24] using the A-gent glucose UV reagent system[25] (hexokinase method using 100, 300, and 500 mg/dL standards). Englitazone was dosed at 100 mg/kg as a positive control, and results are reported in all tables as the percentage of glucose normalization compared to the standard englitazone-treated group (100% at 100 mg/kg) and the vehicle treated group (0%).

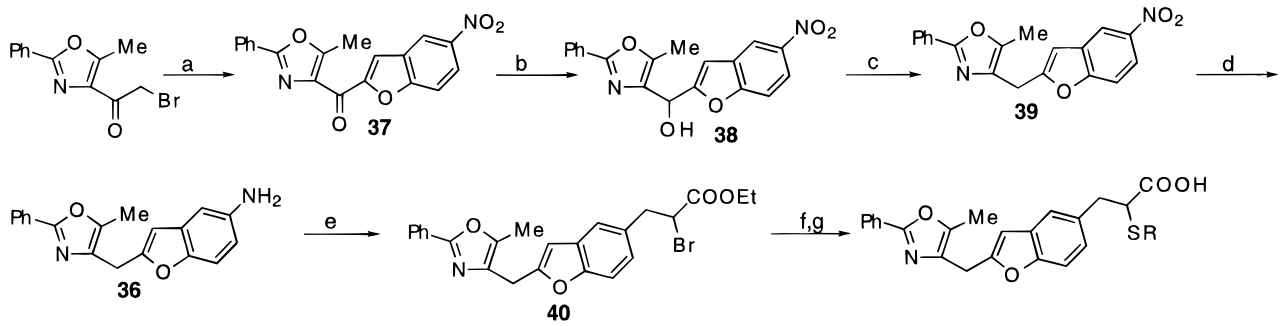
Glucose Uptake Assay. 3T3-L1 cells were grown as described previously[19] and treated by adding drug dissolved in DMSO. After 48 h the cells were incubated with [1-^{14}C]-2-deoxyglucose (0.05 mM) for 10 min. Uptake was terminated by aspirating the media and washing the cells three times with saline. The cells were dissolved in 0.5 mL of 1% Triton X-100, and radioactivity was quantitated by liquid-scintillation counting.

Scheme 2[a]



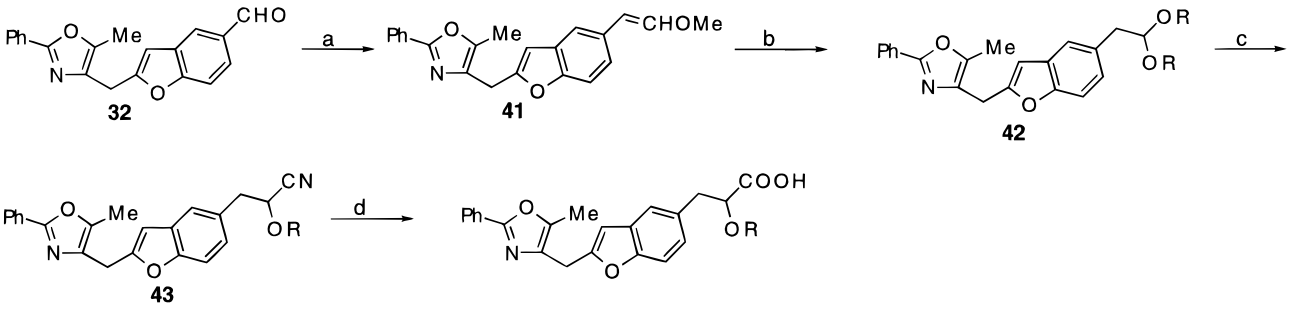
[a] (a) Ac_2O, pyridine, Δ; (b) TFA, TFAA; (c) 4-hydroxy-3-iodobenzaldehyde, Cu_2O, $(PPh_3)_2PdCl_2$, pyridine, Δ; (d) malonic acid, pyridine, Δ; (e) H_2, PtO_2, MeOH.

Scheme 3[a]



[a] (a) 5-Nitrosalicylaldehyde, $^iPr_2NEt$, DMF, Δ; (b) $NaBH_4$, MeOH, THF, 0 °C; (c) Et_3SiH, TFA; (d) H_2, PtO_2, EtOAc; (e) $NaNO_2$, HBr, H_2O, acetone, methanol; ethyl acrylate, Cu_2O; (f) RSH, K_2CO_3, DMF; (g) NaOH, H_2O, MeOH.

Scheme 4[a]



[a] (a) $Ph_3P^+CH_2OMeCl^-$, LDA, THF; (b) ROH, ^{p}TsOH, Δ; (c) TMSCN, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (d) NaOH, H_2O, EtOH, Δ.

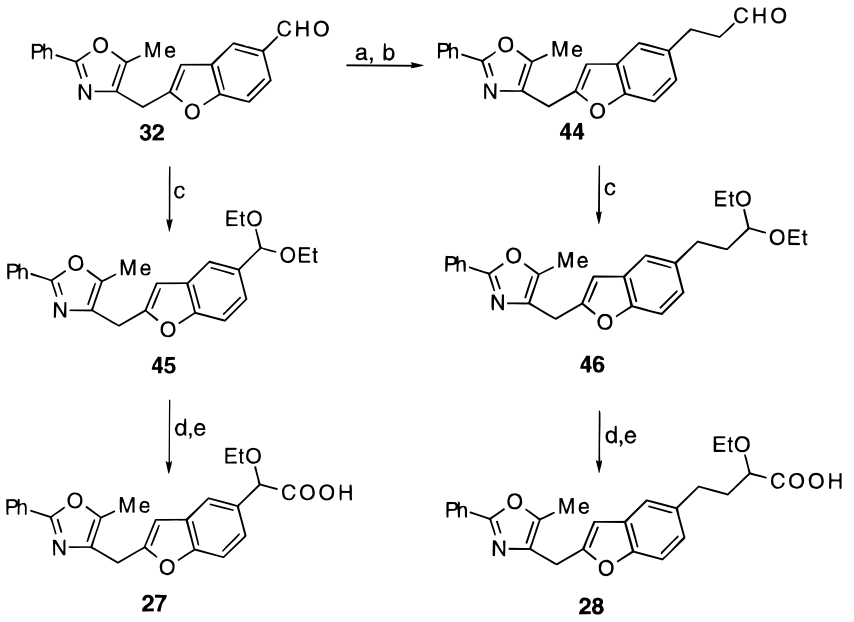
Chemistry. Melting points were taken using a Thomas Hoover apparatus and are uncorrected. Elemental analyses were carried out by the Analytical Department of Pfizer Central Research or Schwartzkopf Analytical Laboratory and results obtained for specified elements are within ±0.4% of the theoretical values unless otherwise denoted. ^1H and ^{13}C NMR spectra of deuteriochloroform or DMSO-d_6 solutions were recorded on Bruker AM-300 or Varian XL-300 spectrometers. Low- and high-resolution mass spectra were obtained on a Finnigan 4510 and AEI MS-30 instruments, respectively. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer.

Synthesis of 5-{[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]-5-benzofuranyl]methyl}-2,4-thiazolidinedione (3): 2-[Hydroxy(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-carbaldehyde (30). To a solution of 5-bromo-α-(5-methyl-2-phenyloxazol-4-yl)-2-benzofuranmethanol (**29**)[11a] (10 g, 26 mmol) in dry THF (425 mL) was added at −78 °C a 1.6 M solution of *n*-butyllithium in hexane (65 mL, 0.10 mol) over 30 min. The red-purple solution was stirred for 30 min at −78 °C, and then a solution of DMF (10 mL, 0.13 mol) in THF (25 mL) was added. The mixture was warmed to room temperature, diluted with saturated aqueous ammonium chloride (500 mL), and extracted with ethyl acetate (2 × 200 mL). The combined extracts were washed with water (150 mL) and brine (200 mL), dried over sodium sulfate, and concentrated. The residue was recrystallized from ethyl acetate (240 mL) to give an off-white solid (4.2 g, 48%, mp 175−176 °C): ^1H NMR (300 MHz, DMSO-d_6) ∂ 2.46 (s, 3 H), 5.97 (d, J = 4.9 Hz, 1 H), 6.40 (d, J = 5.3 Hz, 1 H), 7.05 (s, 1 H), 7.46−7.51 (m, 3 H), 7.74 (d, J = 8.5 Hz, 1 H), 7.84 (dd, J = 8.5 Hz, 1.6 Hz, 1 H), 7.89−7.92 (m, 2 H), 8.23 (d, J = 1.3 Hz, 1 H), 10.06 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 10.45, 62.51, 62.59, 104.16, 111.98, 124.28, 125.42, 125.62, 126.94, 128.65, 129.10, 130.30, 132.12, 136.75, 146.07, 157.59, 158.56, 160.84, 192.47; IR (KBR) ν 1045, 1260, 1695 (s). Anal. ($C_{20}H_{15}NO_4$) C, H, N.

5-{[2-[Hydroxy(5-methyl-2-phenyloxazol-4-yl)methyl]-benzofuran-5-yl]methylene}thiazolidine-2,4-dione (31). A solution 2-[hydroxy(5-methyl-2-phenyloxazol-4-yl)methyl]-benzofuran-5-carbaldehyde **30** (1.0 g, 3.0 mmol), 2,4-thiazolidinedione (0.53 g, 4.5 mmol), and piperidine (5 drops) in ethanol (25 mL) was heated to reflux overnight. The solution was cooled, and the precipitated solid was filtered (0.75 g, 58%, mp > 250 °C): ^1H NMR (300 MHz, DMSO-d_6) ∂ 2.35 (s, 3 H), 5.90 (d, J = 4 Hz, 1 H), 6.3 (d, J = 4 Hz, 1 H), 7.0 (s, 1 H), 7.4−7.6 (m, 4 H), 7.7 (d, J = 8 Hz, 1 H), 7.9−7.95 (m, 4 H), 12.5 (s, 1 H); MS (CI, NH_3) *m/e* 433 ($M^+ + 1$), 194, 178, 153; IR (KBr) ν (cm^{-1}) 1275, 1589, 1654, 1690 (s), 1747. Anal. ($C_{23}H_{16}N_2O_5S$) C, H, N.

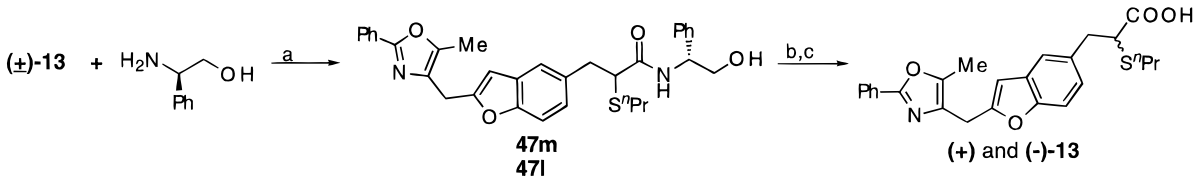
5-{[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]-5-benzofuranyl]methyl}-2,4-thiazolidinedione (3). To a slurry of 5-{[2-[hydroxy(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]methylene}thiazolidine-2,4-dione (**31**) (0.75 g, 1.7 mmol) in methanol (15 mL) and THF (15 mL) was added 3% sodium amalgam (5 g). The mixture was stirred for 1 h and then decanted. The residue was rinsed with methanol, and

Scheme 5[a]



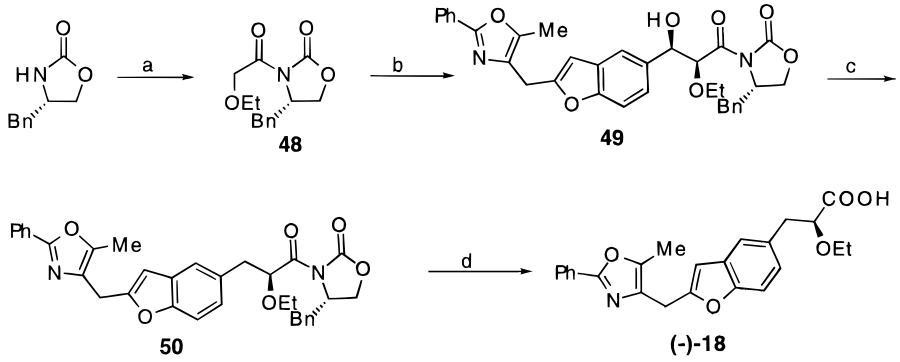
[a] (a) $Ph_3P{=}CHCHO$, toluene, Δ; (b) H_2, Pd−C, EtOAc; (c) EtOH, Amberlyst-15, Δ; (d) TMSCN, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (e) NaOH, H_2O, EtOH, Δ.

Scheme 6[a]



[a] (a) $(COCl)_2$, (*R*)-(−)-D-phenylglycinol, benzene; (b) separation; (c) ^{p}TsOH, ^{i}PrOH, H_2O.

Scheme 7[a]



[a] (a) ^{n}BuLi, $EtOCH_2COCl$, THF, −78 °C; (b) Bu_2BOTf, Et_3N, **32**, CH_2Cl_2, 0 °C; (c) Et_3SiH, TFA; (d) LiOH, THF, H_2O.

the combined solutions were concentrated. The residue was slurried in 0.1 N hydrochloric acid (60 mL) and extracted with chloroform (2 × 70 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over sodium sulfate, and concentrated. The product was purified by flash chromatography (hexane/ethyl acetate, 1:1) and obtained as a white solid (0.46 g): mp 182 °C dec. To a solution of this product (0.23 g, 0.53 mmol) in trifluoroacetic acid (3 mL) was added triethylsilane (0.21 mL, 1.3 mmol). The solution was heated to reflux for 1 h, then diluted with ethyl acetate (50 mL), washed with water (2 × 30 mL) and carefully with saturated sodium bicarbonate (2 × 30 mL), water (30 mL), and brine (30 mL), dried over sodium sulfate, and concentrated. The tacky solid was recrystallized from ethanol (8−10 mL) and water (a few drops) to give white crystals (110 mg, 15%, mp 160−161 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 2.39 (s, 3 H), 3.17 (dd, J = 14.2 Hz, 9.2 Hz, 1 H), 3.44 (dd, J = 14.0 Hz, 4.5 Hz, 1 H), 4.06 (s, 2 H), 4.92 (dd, J = 9.2 Hz, 4.3 Hz, 1 H), 6.62 (s, 1 H), 7.10 (dd, J = 8.1 Hz, 1.7 Hz, 1 H), 7.39−7.50 (m, 5 H), 7.88−7.92 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.9, 25.1, 37.1, 53.3, 103.3, 110.7, 121.2. 124.9, 125.5, 127.0, 128.6, 129.1, 130.2, 131.3, 131.8, 145.3, 153.4, 156.7, 158.6, 171.7, 175.7; HRMS calcd 418.0987, found 418.0925; IR (KBr) ν 707, 1708, 1751. Anal. ($C_{23}H_{18}N_2O_4S{\cdot}^{1}/_{2}H_2O$) C, H, N.

Synthesis of (*E*)-3-[2-[(5-Methyl-2-phenyloxazol-4-yl)-methyl]benzofuran-5-yl]acrylic Acid (10) and 3-[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionic Acid (9): *N*-(1-Acetylbut-3-ynyl)benzamide 34. Acetic anhydride (150 mL) was added to a solution of 2-(benzoylamino)-4-pentynoic acid[26] (**33**) (73 g, 0.34 mol) in pyridine (200 mL), and the solution was heated to 90 °C for 1 h and then allowed to cool to 60 °C, and water (150 mL) was added. The mixture was heated to 85−90 °C for 20 min, then cooled, diluted with water (300 mL), and extracted with chloroform (2 × 400 mL). The combined extracts were washed with water, 1 N hydrochloric acid (3 × 500 mL), sodium bicarbonate, and brine and dried over magnesium sulfate. The chloroform solution was decolorized with charcoal, filtered, and concentrated. The residue was recrystallized from butyl chloride to yield a tan solid (51 g, 70%, mp 101−103 °C): ^{1}H NMR (300

MHz, DMSO-d_6) ∂ 2.16 (s, 3 H), 2.61 (ddd, J = 17.0 Hz, 8.9 Hz, 2.6 Hz, 1 H), 2.74 (ddd, J = 17.0 Hz, 5.4 Hz, 2.7 Hz, 1 H), 2.86 (t, J = 2.6 Hz, 1 H), 4.55 (m, 1 H), 7.47−7.58 (m, 3 H), 7.90 (dd, J = 7.7 Hz, 1,6 Hz, 2 H), 8.95 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 19.23, 26.81, 57.78, 72.77, 81.08, 127.44, 128.42, 131.65, 133.68, 133.72, 166.54, 205.39; MS (EI) *m/e* 172, 105, 77; IR (KBr) ν (cm^{-1}) 720, 1486, 1517, 1645, 1725, 3215, 3400. Anal. ($C_{13}H_{13}NO_2$) C, H, N.

5-Methyl-2-phenyl-4-prop-2-ynyloxazole (35). A solution of *N*-(1-acetylbut-3-ynyl)benzamide (**34**) (30 g, 0.14 mol) in trifluoroacetic anhydride (100 mL) and trifluoroacetic acid (200 mL) was heated to 35−40 °C for 6 h. The solution was concentrated and the residue taken up in ethyl acetate (400 mL). To this solution was added saturated sodium bicarbonate solution (400 mL) followed by solid sodium bicarbonate until the water layer became neutral. The layers were separated, the organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give a brown oil (28 g, 100%) which was used as such: ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 2.12 (t, J = 2.8 Hz, 1 H), 2.41 (d, J = 0.6 Hz, 3 H), 3.50 (dd, J = 2.8 Hz, 0.7 Hz, 2 H), 7.39−7.43 (m, 3 H), 7.96−7.99 (m, 2 H).

2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]-5-benzofurancarboxaldehyde (32). To a slurry of cuprous oxide (12 g, 84 mmol) in pyridine (150 mL) was added a solution of 5-methyl-2-phenyl-4-prop-2-ynyloxazole (**35**) in pyridine (150 mL) followed by a solution of 4-hydroxy-3-iodobenzaldehyde (35 g, 0.14 mol) in pyridine (100 mL). Bis(triphenylphosphine)palladium-(II) chloride (0.50 g, 0.7 mmol) was then added as a solid, and the mixture was heated to reflux overnight. The mixture was cooled and concentrated. The residue was taken up in ethyl acetate (250 mL + 3 × 50 mL). The ethyl acetate solution was concentrated, and the residue was extracted with hot cyclohexane. The hot solution was filtered and cooled, and the solid was collected (29 g, 65%). Physical and spectroscopic properties were identical to those reported previously.[11a]

***(E)*-3-[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]acrylic Acid (10).** A solution of 2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-5-benzofurancarboxaldehyde (**32**) (1.0 g, 3.2 mmol), malonic acid (0.36 g, 3.5 mmol), and pyridine (0.5 mL, 6.4 mmol) in ethanol (5 mL) was heated to reflux for 24 h, then diluted with water, and acidified with 6 N HCl. The yellow precipitate was collected, washed with water, and dried (0.94 g, 82%, mp 233−234 °C (acetic acid)): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 2.39 (s, 3 H), 4.09 (s, 2 H), 6.47 (d, J = 16.2 Hz, 1 H), 6.68 (s, 1 H), 7.46−7.60 (m, 6 H), 7.66 (d, J = 16.2 Hz, 1 H), 7.86−7.91 (m, 2 H), 12.3 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.83, 25.03, 103.61, 111.34, 121.07, 123.99, 125.53, 127.02, 129.07, 129.34, 130.19, 131.66, 144.63, 145.34, 155.29, 157.41, 158.63; MS (CI, NH_3) *m/e* 388 (M^+ + 18), 360 (M^+ + 1), 319, 318, 316, 194, 153; IR (KBr) ν (cm^{-1}) 1294, 1311, 1319, 1632 (s), 1675 (s). Anal. ($C_{22}H_{17}NO_4$) C, H, N.

3-[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionic Acid (9). A solution of (*E*)-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]acrylic acid (**10**) (115 mg, 0.32 mmol) in methanol (10 mL) containing platinum oxide (23 mg) was placed in a Parr apparatus, and the mixture was hydrogenated at 50 psi for 3 h. The catalyst was filtered over diatomaceous earth, and the solution was concentrated to a yellow oil. The product was purified by flash chromatography (hexane/ethyl acetate, 1:1, 1% acetic acid) and obtained as a yellow solid (106 mg, 92%, mp 122−124 °C): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 2.33 (s, 3 H), 2.66 (t, J = 7.7 Hz, 2 H), 2.99 (t, J = 7.7 Hz, 2 H), 4.01 (s, 2 H), 6.40 (s, 1 H), 7.03 (dd, J = 8.4, 1.6 Hz, 1 H), 7.29 (s, 1 H), 7.30 (d, J = 9.2 Hz, 1 H), 7.39−7.44 (m, 3 H), 7.96−7.99 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ∂ 10.2, 25.8, 30.6, 36.3, 103.3, 110.8, 119.9, 123.9, 126.1, 127.4, 128.7, 129.0, 130.0, 131.7, 134.6, 145.1, 153.7, 156.0, 159.7, 178.1; MS (CI, NH_3) *m/e* 390 (M^+ + 18), 362 (M^+ + 1), 320, 318, 181, 164; IR (KBr) ν (cm^{-1}) 1193, 1254, 1441, 1641, 1695 (s), 1720 (s). Anal. ($C_{22}H_{19}NO_4 \cdot {}^1/_2H_2O$) C, H, N.

Synthesis of 3-[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]-2-(propylsulfanyl)propionic Acid (13). (5-Methyl-2-phenyloxazol-4-yl)(5-nitrobenzofuran-2-yl)-methanone 37. A solution of 4-(bromoacetyl)-5-methyl-2-phenyloxazole[27] (53 g, 0.19 mol), 5-nitrosalicylaldehyde (32 g, 0.19 mol), and diisopropylethylamine (66 mL, 0.38 mol) in DMF (250 mL) was heated to 91−94 °C for 3 h. The mixture was cooled and diluted with ethyl acetate (300 mL), and the solid was collected, washed with chloroform (2 × 100 mL), and dried (56 g, 85%, mp 233−234 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 2.75 (s, 3 H), 7.5−7.6 (m, 3 H), 7.96 (d, J = 9.3 Hz, 1 H), 8.1 (m, 2 H), 8.35 (dd, J = 8.7 Hz, 1.5 Hz, 1 H), 8.85 (s, 1 H), 8.89 (d, J = 1.1 Hz, 1 H); HRMS calcd 348.0747, found 348.0767; IR (KBr) ν (cm^{-1}) 710, 960, 1350, 1520, 1650. Anal. ($C_{19}H_{12}N_2O_5$) C, H, N.

(5-Methyl-2-phenyloxazol-4-yl)(5-nitrobenzofuran-2-yl)methanol (38). (5-Methyl-2-phenyloxazol-4-yl)(5-nitrobenzofuran-2-yl)methanone (**37**) (56 g, 0.16 mol) was placed in THF (600 mL), and methanol (300 mL) and the slurry was cooled to 0 °C. Sodium borohydride (9.1 g, 0.24 mol) was added portionwise over 1 h, and the cloudy solution was stirred at 0 °C for 2 h. The bulk of the solvent was removed *in vacuo*, and water (700 mL) was added. The mixture was acidified with 6 N hydrochloric acid and stirred for 30 min. The yellow-tan solid was collected, washed with water, and dried (57 g, 100%, mp 196−197 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 2.45 (s, 3 H), 5.96 (d, J = 4.3 Hz, 1 H), 6.42 (d, J = 5.2 Hz, 1 H), 7.08 (s, 1 H), 7.47−7.50 (m, 3 H), 7.78 (d, J = 9.2 Hz, 1 H), 7.88−7.91, (m, 2 H), 8.16 (dd, J = 8.8 Hz, 2.8 Hz, 1 H), 8.60 (d, J = 2.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 10.2, 62.5, 104.6, 112.0, 117.7, 119.9, 125.6, 126.9, 128.7, 129.1, 130.3, 135.6, 143.7, 146.2, 157.2, 158.6, 162.2; HRMS calcd 350.0902, found 350.1106; IR (KBr) ν (cm^{-1}) 1263, 1346, 1449, 3202.

5-Methyl-4-[(5-nitrobenzofuran-2-yl)methyl]-2-phenyloxazole (39). (5-Methyl-2-phenyloxazol-4-yl)(5-nitrobenzofuran-2-yl)methanol (**38**) (57 g, 0.16 mol) was dissolved in trifluoroacetic acid (350 mL), while cooling to 0 °C. Triethylsilane (64 mL, 0.40 mol) was added. The solution was stirred 1.5 h at 0 °C and overnight at room temperature. The solution was concentrated to near dryness and the residue dissolved in ethyl acetate (750 mL). This solution was washed with water. The precipitate formed during the wash was collected. The organic solution was washed with saturated sodium bicarbonate, during which more precipitate formed and was collected. The ethyl acetate phase of the filtrate was washed again with saturated sodium bicarbonate and then with brine, dried over sodium sulfate, and concentrated. The residue was triturated with isopropyl ether, and the collected solids were combined (51 g, 95%, mp 132−133 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 2.41 (s, 3 H), 4.16 (s, 2 H), 6.90 (s, 1 H), 7.47−7.51 (m, 3 H), 7.76 (d, J = 8.9 Hz, 1 H), 7.88−7.91 (m, 2 H), 8.14 (dd, J = 9.1 Hz, 2.5 Hz, 1 H), 8.52 (d, J = 2.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.8, 25.0, 104.5, 111.7, 117.1, 119.5, 126.5, 127.0, 129.1, 130.3, 131.2, 143.7, 145.6, 157.2, 158.7, 159.9; HRMS calcd 334.0953, found 334.0890; IR (KBr) ν (cm^{-1}) 705, 1347, 1451, 1514.

2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-ylamine (36). 5-Methyl-4-[(5-nitrobenzofuran-2-yl)methyl]-2-phenyloxazole (**39**) (51 g, 0.15 mol) was placed in a Parr bottle together with platinum oxide (3 g) and ethyl acetate (1.5 L), and the mixture was hydrogenated at 40 psi for 1.25 h. The catalyst was filtered through diatomaceous earth, and after washing the filtering pad with more ethyl acetate, the solvent was removed *in vacuo* to give a yellow residue which was triturated with isopropyl ether (200 mL). The pale yellow solid was collected (37.1 g, 80%, mp 161.5−162.5 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 2.36 (s, 3 H), 3.97 (s, 2 H), 4.75 (s, 2 H), 6.38 (s, 1 H), 6.48 (dd, J = 8.5 Hz, 2.4 Hz, 1 H), 6.63 (d, J = 1.9 Hz, 1 H), 7.13 (d, J = 8.3 Hz, 1 H), 7.47−7.49 (m, 3 H), 7.88−7.91 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.84, 25.2, 103.0, 103.9, 110.6, 111.8, 125.5, 127.1, 129.1, 130.2, 132.1, 144.4, 145.1, 147.6, 155.6, 158.5; HRMS calcd 304.1211, found 304.1232; IR (KBr) ν (cm^{-1}) 707, 784, 1208, 1481, 3310, 3436. Anal. ($C_{19}H_{16}N_2O_2$) C, H, N.

2-Bromo-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-benzofuran-5-yl]propionic Acid Ethyl Ester (40). To a slurry of 2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-ylamine (**36**) (4.0 g, 13 mmol) in methanol (30 mL) and acetone (30 mL), cooled to −10 °C, was added 48% aqueous HBr (5.95 mL, 53 mmol). The mixture was stirred at 0 °C for 5 min, and a solution of sodium nitrite (0.985 g, 14 mmol) in water (3 mL) was added dropwise so as to keep the reaction temperature below 5 °C. The mixture was stirred at 0−5 °C

for 15 min, and then ethyl acrylate (8.3 mL, 77 mmol) was added dropwise. The mixture was warmed to 38 °C, powdered copper(I) oxide (0.405 g, 2.8 mmol) was added, and the mixture was stirred for 1 h, then made basic with concentrated aqueous ammonia, and extracted with ethyl acetate (2×). The combined extracts were washed with water (2X) and brine, dried over magnesium sulfate, and concentrated. The product was isolated by flash chromatography (hexane/ethyl acetate, 7:1) as a yellow solid (1.78 g, 29%, mp 129−130 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 1.10 (t, J = 7.1 Hz), 2.38 (s, 3 H), 3.23 (dd, J = 13.8 Hz, 7.2 Hz, 1 H), 3.42 (dd, J = 14.0 Hz, 8.1 Hz, 1 H), 4.06 (s, 2 H), 4.08 (m, 2 H), 6.61 (s, 1 H), 7.14 (dd, J = 8.6 Hz, 1.6 Hz, 1 H), 7.41−7.50 (m, 5 H), 7.88−7.91, (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.9, 13.7, 25.1, 46.7, 61.5, 103.3, 110.6, 121.2, 124.9, 125.5, 127.0, 128.6, 129.1, 130.2, 131.3, 131.8, 145.3, 153.4, 156.6, 158.6, 169.0; HRMS calcd 469.0699, found 469.0618; IR (KBr) ν 704, 1023, 1261, 1719. Anal. ($C_{24}H_{22}BrNO_4$) C, H, N.

3-[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]-2-(propylsulfanyl)propionic Acid Ethyl Ester. To a solution of 2-bromo-3-[2-[(5-methyl-2-phenyloxazol-4-yl)-methyl]benzofuran-5-yl]propionic acid ethyl ester (**40**) (5 g, 12 mmol) in DMF (100 mL) was added propyl mercaptan (3.0 mL, 33 mmol), followed by potassium carbonate (4.6 g, 33 mmol). The slurry was stirred at room temperature overnight, then poured into water (400 mL), acidified with 6 N hydrochloric acid, and extracted with ethyl acetate (2 × 300 mL). The combined extracts were washed with water (3 × 200 mL) and brine, dried over sodium sulfate, and concentrated, leaving a yellow oil (4.3 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 0.93 (t, J = 7.5 Hz, 3 H), 1.15 (t, J = 7.0 Hz, 3 H), 1.56 (m, 2 H), 2.32 (s, 3 H), 2.57 (m, 2 H), 2.99 (dd, J = 6.4 Hz, 13.9 Hz, 1 H), 3.22 (dd, J = 9.4 Hz, 13.6 Hz, 1 H), 3.48 (dd, J = 6.4 Hz, 9.1 Hz, 1 H), 3.99 (s, 2 H), 4.08 (m, 2 H), 6.40 (d, J = 1.1 Hz, 1 H), 7.03 (dd, J = 1.6 Hz, 8.6 Hz, 1 H), 7.29 (s, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 7.37−7.42 (m, 3 H), 7.96−7.99 (m, 2 H).

3-[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]-2-(propylsulfanyl)propionic Acid (13). To a solution of 3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]-2-(propylsulfanyl)propionic acid ethyl ester (3.8 g, 8.2 mmol) in methanol (100 mL) was added 1 N sodium hydroxide (100 mL). The mixture was heated to reflux for 2 h, cooled, poured onto ice (300 mL), acidified with 6 N hydrochloric acid, and then extracted with ethyl acetate (500 mL), during which some precipitated solid was collected. The aqueous phase was extracted again with ethyl acetate (200 mL), and the combined extracts were washed with water (300 mL) and brine (300 mL), dried over sodium sulfate, and concentrated, leaving a yellow-orange solid. The solids were combined and recrystallized from ethyl acetate (150 mL) to give the title compound as an off-white solid (2.5 g, 70%, mp 169−170 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 0.87 (t, J = 7.5 Hz, 3 H), 1.50 (m, 2 H), 2.38 (s, 3 H), 2.57 (t, J = 7.3 Hz, 2 H), 2.91 (dd, J = 14 Hz, 6.2 Hz, 1 H), 3.11 (dd, J = 14 Hz, 9.2 Hz, 1 H), 3.48 (dd, J = 9.3 Hz, 6.2 Hz, 1 H), 4.05 (s, 2 H), 6.59 (s, 1 H), 7.10 (dd, J = 8.6 Hz, 1.7 Hz, 1 H), 7.37−7.40 (m, 2 H), 7.46−7.49 (m, 3 H), 7.88−7.92 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.9, 13.2, 22.3, 25.1, 32.9, 37.4, 48.0, 103.3, 110.4, 120.8, 124.7, 125.5, 127.1, 128.4, 129.1, 130.2, 131.9, 132.9, 145.2, 153.2, 156.4, 158.6, 173.1; MS (EI) m/e 435 (M^+), 302, 260, 259, 186, 172, 104; IR (KBr) ν 1160, 1225, 1470, 1550, 1710 (s). Anal. ($C_{25}H_{25}NO_4S$) C, H, N.

Synthesis of 2-Methoxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionic Acid (17): 4-[5-[(2-Methoxyvinyl)benzofuran-2-yl)methyl]-5-methyl-2-phenyloxazole (41). To a slurry of (methoxymethyl)triphenylphosphonium chloride (34 g, 0.10 mol) and diisopropylamine (9.9 mL, 75 mmol) in THF (500 mL) was added a 2.5 M n-butyllithium solution in hexane (30 mL, 75 mmol), at −10 °C. After 1 h at −10 °C a solution of 2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-5-benzofurancarbaldehyde (**32**) (16 g, 50 mmol) in THF (200 mL) was added. The mixture was allowed to warm to room temperature over 2 h, then poured into water (600 mL), and extracted with ether (3×). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated. The product (1:1 mixture of geometrical isomers) was isolated by flash chromatography (hexane/ethyl acetate, 4:1) as a solid (14 g, 41%, mp 86−90 °C): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 2.32 (s, $^3/_2$ H), 2.34 (s, $^3/_2$ H), 3.67 (s, $^3/_2$ H), 3.76 (s, $^3/_2$ H), 4.01 (s, 2 H), 5.27 (d, J = 7.1 Hz, $^1/_2$ H), 5.88 (d, J = 12.9 Hz, $^1/_2$ H), 6.09 (d, J = 7.0 Hz, $^1/_2$ H), 6.42 (d, J = 6.6 Hz, 1 H), 6.98 (d, J = 12.9 Hz, $^1/_2$ H), 7.09 (dd, J = 8.6 Hz, 1.7 Hz, $^1/_2$ H), 7.28−7.32 (m, 2 H), 7.39−7.44 (m, 3 H), 7.73 (d, J = 1.7 Hz, $^1/_2$ H), 7.96−8.00 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ∂ 10.26, 26.01, 26.04, 56.49, 60.53, 103.34, 103.59, 105.41, 105.96, 110.39, 110.88, 116.80, 120.04, 121.16, 124.39, 126.01, 127.70, 128.66, 128.86, 129.26, 129.86, 129.89, 130.67, 131.01, 131.80, 13.87, 145.00, 146.62, 147.97, 153.33, 153.63, 155.79, 156.12, 159.55, 159.59; MS (CI, NH_3) m/e 347, 346 (M^+ + 1); IR (KBr) ν (cm^{-1}) 1087, 1149, 1643 (s).

4-[5-[(2,2-Dimethoxyethyl)benzofuran-2-yl]methyl]-5-methyl-2-phenyloxazole (42, R = Me). A solution of 4-[[5-(2-methoxyvinyl)benzofuran-2-yl]methyl]-5-methyl-2-phenyloxazole (**41**) (0.69 g, 2.0 mmol) and p-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol) in methanol (30 mL) was heated to reflux overnight. The solvent was removed, the residue was taken up in ethyl acetate, and the solution was washed with 5% sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated to an oil which slowly solidified on standing (0.75 g, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) ∂ 2.35 (s, 3 H), 2.96 (d, J = 5.6 Hz, 2 H), 3.32 (s, 6 H), 4.01 (s, 2 H), 4.53 (t, J = 5.6 Hz, 1 H), 6.43 (d, J = 0.8 Hz, 1 H), 7.08 (dd, J = 8.5 Hz, 1.7 Hz, 1 H), 7.31−7.34 (m, 2 H), 7.40−7.44 (m, 3 H), 7.97−8.00 (m, 2 H).

2-Methoxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-benzofuran-5-yl]propionitrile (43, R = Me). To a solution of 4-[[5-(2,2-dimethoxyethyl)benzofuran-2-yl]methyl]-5-methyl-2-phenyloxazole (**42**, R = Me) (0.75 g, 2.0 mmol) in dichloromethane (15 mL) were added trimethylsilyl cyanide (0.80 mL, 6.0 mmol) and boron trifluoride etherate (50 μL, 0.5 mmol). After 1 h the solution was diluted with dichloromethane, washed with 5% sodium bicarbonate, water, and brine, dried over magnesium sulfate, and concentrated. The product was purified by flash chromatography (hexane/ethyl acetate, 2:1) and isolated as a solid (0.64 g, 86%, mp 107−109 °C): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 2.35 (s, 3 H), 3.16 (d, J = 6.9 Hz, 1 H), 3.16 (d, J = 6.7 Hz, 1 H), 3.46 (s, 3 H), 4.02 (s, 2 H), 4.19 (t, J = 6.8 Hz, 1 H), 6.45 (d, J = 0.7 Hz, 1 H), 7.10 (dd, J = 8.4 Hz, 1.8 Hz, 1 H), 7.34−7.44 (m, 5 H), 7.97−8.00 (m, 2 H); MS (EI) m/z 372 (M^+), 302, 104, 43.

2-Methoxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-benzofuran-5-yl]propionic Acid (17). A mixture of 2-methoxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionitrile (**43**, R = Me) (0.64 g, 1.7 mmol), ethanol (30 mL), and 6 N sodium hydroxide (10 mL) was heated to reflux for 3 h. Water (30 mL) was added, and the solution was acidified with concentrated hydrochloric acid (6 mL) and then extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The product was recrystallized from ethyl acetate/hexane and obtained as a white solid (0.47 g, 71%, mp 159−160.5 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 2.40 (s, 3 H), 2.93 (dd, J = 14.0 Hz, 7.8 Hz, 1 H), 3.03 (dd, J = 14.0 Hz, 4.9 Hz, 1 H), 3.22 (s, 3 H), 3.93 (dd, J = 7.8 Hz, 5.0 Hz, 1 H), 4.07 (s, 2 H), 6.61 (s, 1 H), 7.09 (dd, J = 8.4 Hz, 1.7 Hz, 1 H), 7.38 (s, 1 H),7.39 (d, J = 8.7 Hz, 1 H), 7.48−7.52 (m, 3 H), 7.90−7.93 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.9, 25.1, 38.2, 57.3, 81.1, 103.3, 110.3, 121.0, 125.0, 127.0, 128.4, 129.1, 130.2, 131.8, 131.9, 145.3, 153.2, 156.3, 158.6, 172.9; MS (EI) m/e 391 (M^+), 302, 172, 128, 105, 104; IR (KBr) ν (cm^{-1}) 690, 715, 1060, 1200, 1735 (s). Anal. ($C_{23}H_{21}NO_5 \cdot {}^1/_2H_2O$) C, H, N.

Synthesis of 2-Ethoxy-4-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]butyric Acid (28): 3-[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionaldehyde (44). A solution of 2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-5-benzofurancarbaldehyde (**32**) (3.2 g, 10 mmol) and (formylmethylene)triphenylphosphorane (4.6 g, 15 mmol) in toluene (70 mL) was heated to reflux for 48 h. The solvent was removed, and the product was purified by flash chromatography (hexane/ethyl acetate, 2:1). The product (1.2 g) was placed in a Parr shaker together with 10% palladium on carbon (0.12 g) and ethyl acetate (100 mL) and hydrogenated at 40 psi. After 2 h, the catalyst was filtered over Diatomaceous earth, the filtrate was concentrated, and the products were

separated by flash chromatography (hexane/ethyl acetate, 3:1). The expected product was obtained as a solid (0.28 g, 8%): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 2.35 (s, 3 H), 2.78 (td J = 8 Hz, 1 Hz, 2 H), 3.05 (t, J = 8 Hz, 2 H), 4.05 (s, 2 H), 6.42 (s, 1 H), 7.00 (dd, J = 8 Hz, 2 Hz, 1 H), 7.28 (d, J = 2 Hz, 1 H), 7.32 (d, J = 8 Hz, 1 H), 7.38−7.44 (m, 3 H), 7.95−8.01 (m, 2 H), 9.70 (t, J = 1 Hz, 1 H); MS (EI) *m/e* 345 (M^+), 302, 172, 151, 115, 105, 104, 77.

4-[[5-(3,3-Diethoxypropyl)benzofuran-2-yl]methyl]-5-methyl-2-phenyloxazole (46). A solution 3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionaldehyde (**44**) (0.27 g, 0.78 mmol) in ethanol (20 mL) containing Amberlyst-15 resin beads (20 mg) was heated to reflux for 2.5 h and then stirred at room temperature overnight. The solution was filtered and concentrated to an oil (0.29 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 1.21 (t, J = 9 Hz, 3 H), 1.95 (m, 2 H), 2.35 (s, 3 H), 2.74 (t, J = 8 Hz, 2 H), 3.45 (m, 2 H), 3.62 (m, 2 H), 4.02 (s, 2 H), 4.48 (t, J = 5 Hz, 1 H), 6.42 (s, 1 H), 7.00 (dd, J = 8 Hz, 2 Hz, 1 H), 7.28−7.35 (m, 2 H), 7.38−7.44 (m, 3 H), 7.95−8.01 (m, 2 H).

2-Ethoxy-4-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-benzofuran-5-yl]butyronitrile. This intermediate was prepared from 4-[5-[(3,3-diethoxypropyl)benzofuran-2-yl]methyl]-5-methyl-2-phenyloxazole (**46**) with TMSCN in an analogous manner to that of **43**: ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 1.25 (t, J = 7.0 Hz, 3 H), 2.13 (m, 2 H), 2.36 (s, 3 H), 2.87 (t, J = 7.0 Hz, 2 H), 3.44 (m, 2 H), 3.79 (m, 2 H), 3.99 (t, J = 7.2 Hz, 1 H), 4.02 (s, 2 H), 6.43 (d, J = 0.9 Hz, 1 H), 7.02 (dd, J = 8.4 Hz, 1.8 Hz, 1 H), 7.27 (d, J = 1.5 Hz, 1 H), 7.33 (d, J = 8.3 Hz, 1 H), 7.40−7.44 (m, 3 H), 7.97−8.00 (m, 2 H).

2-Ethoxy-4-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-benzofuran-5-yl]butyric Acid (28). A solution of 2-ethoxy-4-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]-butyronitrile (0.22 g, 0.55 mmol) in ethanol (5 mL) and sodium hydroxide (15 mL) was heated to reflux for 7 h, then cooled, diluted with water, acidified with concentrated hydrochloric acid, and extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated. The solid was recrystallized in ethyl acetate/hexane (87 mg, 38%, mp 137−138 °C): ^{1}H NMR (DMSO-d_6, 300 MHz) ∂ 1.13 (t, J = 6.9 Hz, 3 H), 1.90 (m, 2 H), 2.39 (s, 3 H), 2.71 (t, J = 7.2 Hz, 2 H), 3.33 (m, 2 H), 3.55 (m, 2 H), 3.68 (dd, J = 7.8 Hz, 4.6 Hz, 1 H), 4.06 (s, 2 H), 6.59 (s, 1 H), 7.05 (d, J = 8.4 Hz, 1 H), 7.34 (s, 1 H), 7.40 (d, J = 8.4 Hz, 1 H), 7.48−7.50 (m, 3 H), 7.90−7.92 (m, 2 H), 12.65 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.9, 15.2, 25.1, 64.9, 77.0, 103.3, 110.5, 120.0, 124.2, 125.5, 127.0, 128.6, 129.1, 130.2, 131.9, 135.6, 145.3, 152.9, 156.3, 174.0; MS (EI) *m/e* 419 (M^+), 303, 172, 151, 105, 104; IR (KBr) ν 715, 795, 1120, 1130, 1725 (s). Anal. ($C_{25}H_{25}NO_5 \cdot 0.5H_2O$) C, H, N.

Synthesis of Ethoxy[2-[(5-methyl-2-phenyloxazol-4-yl)-methyl]benzofuran-5-yl]acetic Acid (27): 4-[[5-(Diethoxymethyl)benzofuran-2-yl]methyl]-5-methyl-2-phenyloxazole (45). To a solution of 2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-5-benzofurancarbaldehyde (**32**) (0.63 g, 2.0 mmol) and ethyl orthoformate (1.7 mL, 10 mmol) in methylene chloride (5 mL) was added Amberlyst 15 resin (55 mg). The mixture was heated to reflux for 2 h, filtered, and concentrated to give a yellow oil. The product was purified by flash chromatography (hexane/ethyl acetate, 4:1) and obtained as a low-melting solid (0.54 g, 69%): ^{1}H NMR ($CDCl_3$, 300 MHz) ∂ 1.22 (t, J = 7.0 Hz, 3 H), 2.34 (s, 3 H), 3.46−3.59 (m, 4 H), 4.02 (s, 2 H), 5.55 (s, 1 H), 6.47 (d, J = 0.8 Hz, 1 H), 7.32 (dd, J = 8.5 Hz, 1.6 Hz, 1 H), 7.37−7.44 (m, 4 H), 7.59 (d, J = 1.6 Hz, 1 H), 7.97−8.00 (m, 2 H).

Ethoxy[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]acetonitrile. To a mixture of 4-[(5-(diethoxymethyl)benzofuran-2-yl)methyl]-5-methyl-2-phenyloxazole (**45**) (0.54 g, 1.4 mmol) and trimethylsilyl cyanide (3 mL, 22.5 mmol) was added boron trifluoride etherate (20 μL, 0.16 mmol). After 15 min the reaction was quenched with saturated $NaHCO_3$, and ethyl acetate was added. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated. The product was purified by flash chromatography (hexane/ethyl acetate, 4:1) and obtained as an oil (0.38 g, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 1.28 (t, J = 7.0 Hz, 3 H), 2.35 (s, 3 H), 3.64 (m, 2 H), 3.81 (m, 2 H), 4.04 (s, 2 H), 5.30 (s, 1 H), 6.51 (d, J = 0.9 Hz, 1 H), 7.33 (dd, J = 8.5 Hz, 1.9 Hz, 1 H), 7.40−7.46 (m, 4 H), 7.62 (d, J = 1.8 Hz, 1 H), 7.97−8.00 (m, 2 H).

Ethoxy[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]acetic Acid (27). A solution of ethoxy[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]acetonitrile (0.38 g, 1.0 mmol) in ethanol (15 mL) and 6 N NaOH (5 mL) was heated to reflux for 3 h, diluted with ethyl acetate (50 mL) and water (30 mL), and acidified with concentrated HCl (3 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated. The product was recrystallized from ethyl acetate/hexane and obtained as a white solid (0.28 g, 69%, mp 167−169 °C): ^{1}H NMR (300 MHz, DMSO-d_6) ∂ 1.15 (t, J = 7.0 Hz, 3 H), 2.40 (s, 3 H), 3.42 (m, 2 H), 3.56 (m, 2 H), 4.02 (s, 2 H), 4.91 (s, 1 H), 6.69 (s, 1 H), 7.27 (dd, J = 8.5 Hz, 1.6 Hz, 1 H), 7.48−7.50 (m, 4 H), 7.59 (s, 1 H), 7.90−7.93 (m, 2 H), 12.75 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) ∂ 9.9, 15.1, 25.1, 64.2, 80.1, 103.5, 110.6, 119.5, 122.9, 125.5, 127.0, 128.5, 129.1, 130.2, 131.8, 132.2, 145.3, 154.0, 156.8, 158.6, 172.3; MS (EI) *m/e* 391 (M^+), 346, 172, 159, 104; IR (KBr) ν 720, 795, 1120, 1185, 1730 (s). Anal. ($C_{23}H_{21}NO_5 \cdot 0.5H_2O$) Calcd: C, 68.98; H, 5.54; N, 3.50. Found: C, 69.80; H, 5.45; N, 3.54.

Optical Resolution of 3-[2-[(5-Methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]-2-(propylsulfanyl)propionic Acid (13). To a slurry of 3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]-2-(propylsulfanyl)propionic acid (**13**) (1.6 g, 3.8 mmol) in benzene (35 mL) was added oxalyl chloride (1.8 mL, 21 mmol). Gas was evolved and the slurry turned into a clear yellow solution within 10 min. After 2 h the solvent was removed, and the residue was dissolved in dioxane (25 mL) and added dropwise to a solution of (*S*)-(+)-2-phenylglycinol (0.52 g, 3.8 mmol) and triethylamine (0.53 mL) in dioxane (10 mL). After 2 h, the solvent was removed, water was added to the residue, and the mixture was acidified with 6 N hydrochloric acid. The solid was collected, dried, and recrystallized from ethyl acetate/hexane then from ethyl acetate to give the less polar isomer **47l** (on silica gel thin-layer chromatography, hexane/ethyl acetate, 1:2) as a pale yellow solid (0.41 g). The combined mother liquors were concentrated and the products separated by flash chromatography (hexane/ethyl acetate, 1:1). More of **47l** was thus obtained (total yield 0.55 g, 26%) as well as the more polar isomer **47m** (0.39 g, 19%).

The less polar amide **47l** (0.54 g, 0.97 mmol) and *p*-toluenesulfonic acid (2.8 g, 15 mmol) were placed in water (20 mL) and 2-propanol (20 mL) and heated to reflux for 3 days. The solution was cooled, diluted with water (75 mL), and extracted with ethyl acetate (2 × 75 mL). The combined extracts were washed with water (2 × 75 mL) and brine (75 mL), dried over sodium sulfate, and concentrated. The product was purified by flash chromatography (hexane/ethyl acetate/acetic acid, 16:4:1), then recrystallized from ethyl acetate (15 mL)/hexane (5 mL). The mother liquor was concentrated to give a white solid (+)-**13** (83 mg, $[\alpha]_D$ = +8.8° (*c* 1.08, $CDCl_3$)). This material was subsequently found to be >95% optically pure by conversion back to the amide under neutral conditions (EEDQ), and its NMR spectrum was identical to the one of the racemic material.

In the same manner the more polar amide **47m** (0.39 g, 0.71 mmol) was converted into the levorotatory acid (−)-**13** (81 mg, $[\alpha]_D$ = −9.4° (*c* 1.06, $CDCl_3$)).

Synthesis of (*S*)-2-Ethoxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionic Acid [(−)-18]: (*S*)-4-Benzyl-3-(ethoxyacetyl)oxazolidin-2-one (48). To a solution of (*S*)-4-benzyloxazolidin-2-one (4.4 g, 25 mmol) in dry THF (20 mL), cooled to −78 °C, was added *n*-butyllithium (2.5 M solution in hexane, 10 mL, 25 mmol) dropwise. Another 20 mL of THF was added to facilitate stirring. A solution of ethoxyacetyl chloride (3.0 g, 25 mmol) in THF (5 mL) was added, and the mixture was stirred at −78 °C for 30 min, then warmed to room temperature, poured into water, and extracted with ethyl acetate (3×). The combined extracts were washed with water and brine, dried over sodium sulfate, and concentrated to a yellow oil (4.3 g, 65%, $[\alpha]_D$ = +56.7° (*c* 0.095, $CHCl_3$)): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 1.28 (t, J = 6.9

Hz, 1 H), 2.79 (dd, J = 13.3 Hz, 9.3 Hz, 1 H), 3.31 (dd, J = 13.3 Hz, 3.1 Hz, 1 H), 3.63 (q, J = 7.1 Hz, 1 H), 3.64 (q, J = 7.2 Hz, 1 H), 4.19−4.30 (m, 2 H), 4.63−4.67 (m, 3 H), 7.17−7.34 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ∂ 15.1, 37.8, 54.8, 67.3, 67.3, 70.4, 127.4, 129.0, 129.4, 135.0, 153.4, 170.4; MS (EI) *m/e* 263 (M^+), 218, 134, 117, 91, 85, 65, 58; IR (KBr) ν (cm^{-1}) 1072, 1203, 1352, 1388, 1716, 1784 (s).

4(*S*)-Benzyl-3-{(2*S*,3*R*)-2-ethoxy-3-hydroxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]-propionyl}oxazolidin-2-one (49). To a solution of (*S*)-4-benzyl-3-(ethoxyacetyl)oxazolidin-2-one (**48**) (1.0 g, 3.8 mmol) in dichloromethane (10 mL), cooled to 0 °C, was added freshly distilled dibutylboron triflate (1.1 mL, 4.6 mmol) dropwise, followed by triethylamine (0.69 mL, 4.9 mmol). After 5 min the solution was cooled to −78 °C, and a precooled solution of 2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-5-benzofurancarboxaldehyde (**32**) (1.33 g, 4.2 mmol) in dichloromethane (5 mL) was added. After 20 min the mixture was warmed to 0 °C, stirred at that temperature for 1 h, then quenched with a solution of pH 7 buffer (10 mL) in methanol (30 mL), followed by a solution of 30% hydrogen peroxide (10 mL) in methanol (30 mL), and stirred at 0 °C for 1 h. The mixture was then diluted with water and extracted with ethyl acetate (3). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The product was purified by flash chromatography (hexane/ethyl acetate, 1:1) and obtained as a yellow solid (1.16 g, 53%, mp 66−70 °C, $[\alpha]_D$ = +70° (*c* 0.093, $CHCl_3$)): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 1.19 (t, J = 7.0 Hz, 1 H), 2.32 (s, 3 H), 2.73 (dd, J = 13.3 Hz, 9.6 Hz, 1 H), 3.22 (dd, J = 13.3 Hz, 3.2 Hz, 1 H), 3.46−3.70 (m, 3 H), 3.95 (dd, J = 9.1 Hz, 1.8 Hz, 1 H), 3.99 (s, 2 H), 4.37 (m, 1 H), 4.97 (d, J = 5.2 Hz, 1 H), 5.39 (d, J = 5.2 Hz, 1 H), 6.46 (s, 1 H), 7.13 (dd, J = 6.0 Hz, 1.8 Hz, 2 H), 7.25−7.34 (m, 5 H), 7.36−7.43 (m, 3 H), 7.52 (s, 1 H), 7.93−7.98 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ∂ 10.2, 15.1, 25.9, 37.8, 55.8, 66.6, 66.9, 75.5, 81.7, 103.5, 110.5, 118.8, 122.3, 126.0, 127.4, 127.6, 128.7, 1128.9, 129.4, 129.9, 131.6, 133.3, 135.0, 145.0, 153.0, 154.7, 156.5, 159.6, 171.3; MS (EI) *m/e* 263, 172, 117, 105, 92, 91, 86, 85, 83; IR (KBr) ν (cm^{-1}) 715, 1120, 1705, 1780 (s). Anal. ($C_{34}H_{32}N_2O_7 \cdot {}^1/_2H_2O$) C, H, N.

4(*S*)-Benzyl-3-{2(*R*)-ethoxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionyl}oxazolidin-2-one (50). To a solution of 4(*S*)-benzyl-3-{(2*S*,3*R*)-2-ethoxy-3-hydroxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]-benzofuran-5-yl]propionyl}oxazolidin-2-one (**49**) (1.0 g, 1.72 mmol) in trifluoroacetic acid (20 mL) was added triethylsilane (3.0 mL, 19 mmol). The solution was stirred for 4 days at room temperature, then diluted with ethyl acetate, washed with water and saturated sodium bicarbonate solution (3×), dried over sodium sulfate, and concentrated. The product was isolated by flash chromatography (hexane/ethyl acetate, 5:1) as a pale yellow solid (0.44 g, 45%, mp 116−117 °C, $[\alpha]_D$ = +53.8° (*c* 0.12, $CHCl_3$)): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 1.14 (t, J = 6.9 Hz, 1 H), 2.32 (s, 3 H), 2.78 (dd, J = 13.3 Hz, 9.4 Hz, 1 H), 3.02−3.05 (m, 2 H), 3.23 (dd, J = 13.5 Hz, 3.3 Hz, 1 H), 3.37 (m, 1 H), 3.55 (m, 1 H), 3.88 (t, J = 8.4 Hz, 1 H), 3.98 (s, 2 H), 4.06 (dd, J = 8.7 Hz, 2.4 Hz, 1 H), 4.48 (m, 1 H), 5.29 (dd, J = 7.5 Hz, 5.6 Hz, 1 H), 6.41 (s, 1 H), 7.13−7.18 (m, 4 H), 7.26−7.32 (m, 4 H), 7.38−7.42 (m, 3 H), 7.95−7.98 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ∂ 10.3, 15.2, 26.0, 37.8, 39.5, 55.5, 66.3, 66.5, 79.0, 103.3, 110.4, 121.4, 125.2, 126.0, 127.4, 127.6, 128.7, 128.8, 128.9, 129.4, 129.9, 131.1, 131.8, 135.1, 145.0, 153.1, 154.0, 156.0, 159.6, 173.1; MS (EI) *m/e* 564 (M^+), 518, 360, 342, 302, 172, 166; IR (KBr) ν (cm^{-1}) 700, 710, 720, 750, 780, 810, 1125, 1200, 1240, 1260, 1295, 1355, 1380, 1480, 1705, 1790. Anal. ($C_{34}H_{32}N_2O_6$) C, H, N.

(*S*)-2-Ethoxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionic Acid ((−)-18). 4(*S*)-Benzyl-3-{2(*R*)-ethoxy-3-[2-[(5-methyl-2-phenyloxazol-4-yl)methyl]benzofuran-5-yl]propionyl}oxazolidin-2-one (**50**) (0.15 g, 0.26 mmol) was dissolved in THF (5 mL). The solution was cooled to 0 °C, and 0.5 N lithium hydroxide (1.1 mL, 0.52 mmol) was added. After 15 min the bulk of the THF was removed, and the residue was acidified with 1 N HCl, diluted with water, and extracted with ethyl acetate (3×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The product was purified by flash chromatography (hexane/ethyl acetate/acetic acid, 10:10:1) and then recrystallized from hexane/ethyl acetate and obtained as a white solid (48 mg, 46%, mp 129−129.5 °C, $[\alpha]_D$ = −12.5° (*c* 0.99, $CDCl_3$)): ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 1.13 (t, J = 7.1 Hz, 1 H), 2.33 (s, 3 H), 3.05 (dd, J = 14.2 Hz, 7.6 Hz, 1 H), 3.18 (dd, J = 14.2 Hz, 4.3 Hz, 1 H), 3.40 (m, 1 H), 3.54 (m, 1 H), 3.99 (s, 2 H), 4.07 (dd, J = 7.6 Hz, 4.3 Hz, 1 H), 6.40 (d, J = 1.3 Hz, 1 H), 7.07 (dd, J = 8.4 Hz, 1.9 Hz, 1 H), 7.31 (d, J = 8.5 Hz, 1 H), 7.32 (s, 1 H), 7.39−7.43 (m, 3 H), 7.96−7.99 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ∂ 9.87, 20.52, 33.61, 48.72, 61.47, 74.97, 98.21, 105.38, 116.08, 119.89, 120.94, 122.17, 123.53, 123.74, 123.81, 124.90, 125.95, 126.45, 139.95, 148.81, 150.70, 154.55, 170.05; MS (CI, NH_3) *m/e* 407, 406 (M^+ + 1), 362, 195; IR (KBr) ν (cm^{-1}) 709, 1110, 1124, 1197, 1723 (s). Anal. ($C_{24}H_{23}NO_5$) C, H, N.

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