Glucose Transport-Enhancing and Hypoglycemic Activity of 2-Methyl-2-phenoxy-3-phenylpropanoic Acids

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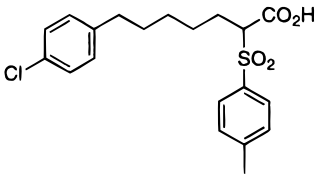
A series of 2-phenoxy-3-phenylpropanoic acids has been prepared which contains many potent hypoglycemic agents as demonstrated by assessing glucose lowering in *ob/ob* mice. Some compounds (**32**, **33**, **59**) normalize plasma glucose in this diabetic model at doses of approximately 1 mg/kg. The mechanism of action of these drugs may involve enhanced glucose transport, especially in fat cells, but the compounds do not stimulate GLUT4 translocation and do not increase the levels of GLUT1 or GLUT4 in vivo. Thus, these compounds may enhance the intrinsic activity of the glucose transporter GLUT1 or GLUT4. Some compounds also modestly decrease hepatocyte gluconeogenesis in vitro, but this is not likely to be a major contributor to the hypoglycemic effect observed in vivo. Likewise, a modest decrease in food consumption observed with some of these compounds was shown by a pair-feeding experiment not to be the primary cause of the hypoglycemia observed.

Introduction

The search for antidiabetic agents has not been rewarded with marketable novel agents in the last 20 years, and efforts to find such drugs continue. Of particular interest have been hypoglycemic agents with novel mechanisms, such as thiazolidinediones, typified by englitazone,[1,2] pioglitazone,[3] and troglitazone,[4] which may act by sensitizing peripheral tissues to insulin and increasing the level of glucose transporter protein expression,[2,5] and α-tosylated carboxylic acids such as BM 13.0795 (Table 1) which are reported to acutely

BM 13.0795



stimulate the translocation of GLUT4 to the plasma membrane.[6] The relevance of targeting glucose transport as a site for pharmacological intervention for the treatment of non-insulin-dependent diabetes mellitus was strongly supported by a recent study that demonstrated that increasing GLUT4 expression in genetically diabetic *db*/*db* mice markedly improved glycemic control.[7] Furthermore, in the diabetic *ob*/*ob* mouse, which is characterized by severe insulin resistance and impaired peripheral glucose utilization, enhancement of muscle and adipose tissue glucose uptake and metabolism due to pharmacological treatment with glitazone agents is associated with glucose normalization.[8,9] Therefore, upregulation of glucose transporter protein expression or activity appears to be an efficacious means of restoring glycemic control in non-insulin-dependent diabetes mellitus.

In attempts to discover improved antidiabetic agents that enhance glucose uptake, we conducted empirical structure−activity relationship (SAR) explorations around BM 13.0795 and found that α-phenoxycarboxylic acids, particularly those with a 4-isopropyl group, shared some of the in vitro and in vivo characteristics of BM 13.0795, namely, enhanced 2-deoxyglucose uptake in adipocytes and hypoglycemic activity in genetically diabetic *ob/ob* mice after acute or chronic administration. In particular, α-phenoxy-substituted 3-phenylpropanoic acids distinguished themselves with potent oral hypoglycemic activity in *ob/ob* mice. This interesting finding prompted us to carry out a systematic SAR study in this subset of compounds. The only structurally related compounds described in the literature are α-phenoxy-3-phenylpropanoic acids with halogen substituents in the phenoxy ring, which are claimed in a Lilly patent to be hypoglycemic in rats at doses of 50−100 mg/kg, but no mechanism of action was reported.[10]

Chemistry

The α-phenoxy-substituted 3-phenylpropanoic acids with hydrogen in the α-position (Table 1) were prepared by several routes. Conversion of α-haloacetic esters to α-phenoxyacetic esters followed by proton abstraction with lithium bis(trimethylsilyl)amide and alkylation with benzyl halides (general method A) or conversion of the α-phenoxyacetic esters to the acids followed by dianion formation with 2 equiv of LDA and alkylation with benzyl halides (general method D), as shown in Scheme 1, proved to be convenient. Some compounds were prepared by conversion of α-phenoxyacetic acids to 4,5-dihydro-4,4-dimethyl-2-(phenoxymethyl)oxazoles followed by proton abstraction with butyllithium, alkylation with benzyl halides, and hydrolysis to the acids (general method B), as shown in Scheme 2. Yet another route involved conversion of diethyl chloromalonate to diethyl 2-phenoxymalonates, proton abstraction with NaH, and alkylation with benzyl halides to give the desired acids after saponification and decarboxylation (general method C, Scheme 3). In the syntheses of α-methyl-α-phenoxycarboxylic acids (Table 2), we found

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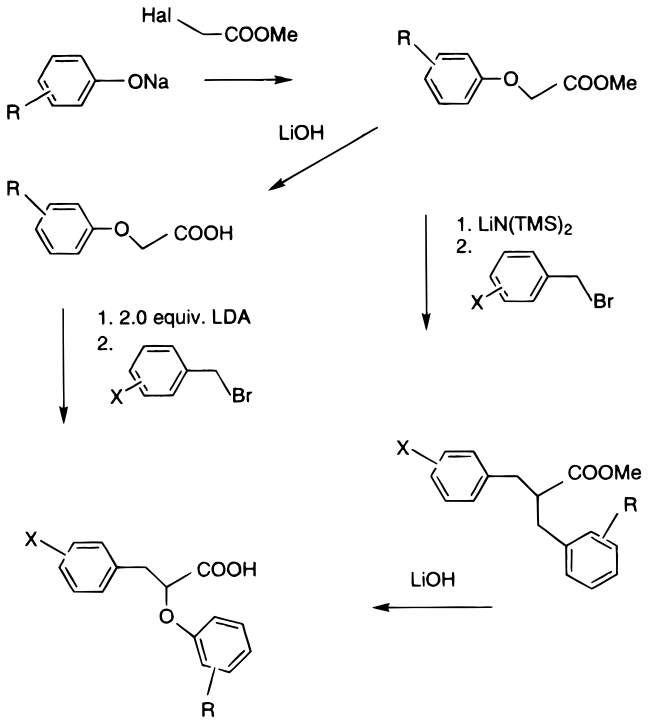
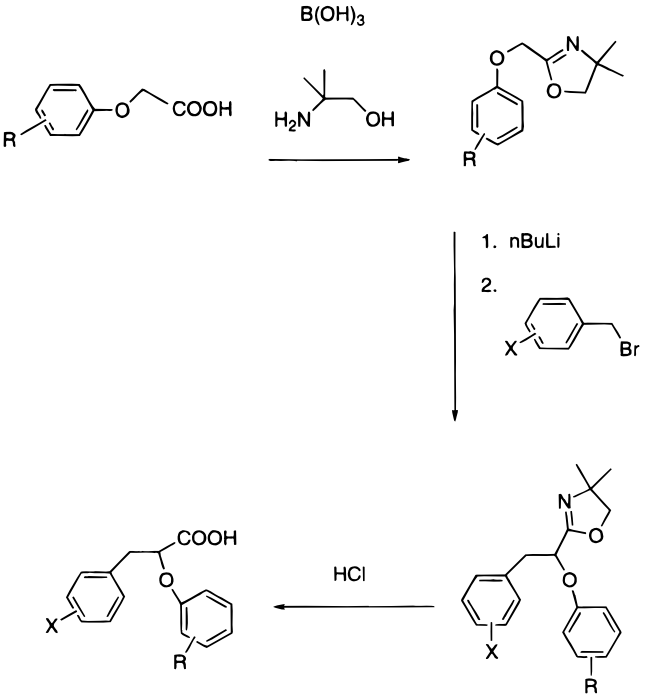
Scheme 1. General Methods A and D



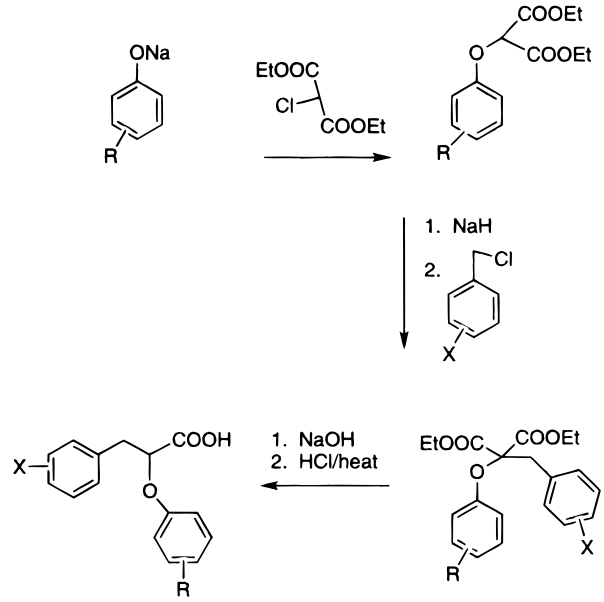
Scheme 2. General Method B



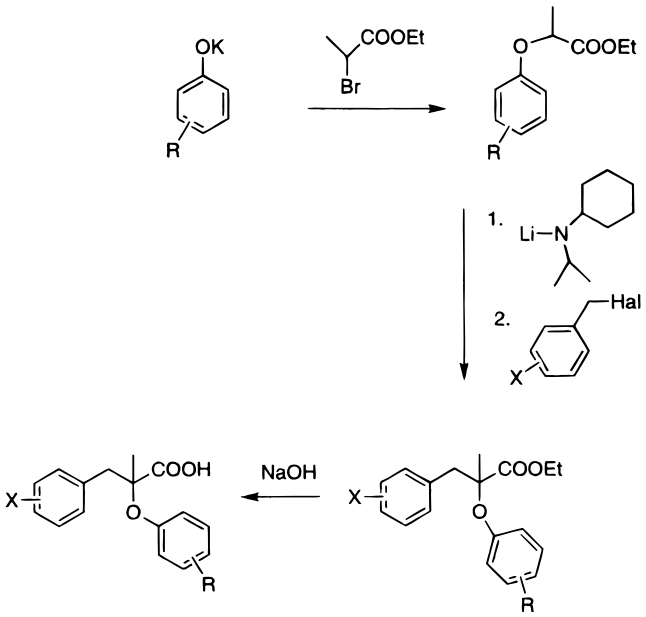
it advantageous to treat the ethyl esters of α-phenoxypropanoic acids with LICA (lithium cyclohexylisopropylamide)[11] and to treat the intermediate anion with the desired benzyl halide (general method E), as shown in Scheme 4. Use of LDA (lithium diisopropylamide) in place of LICA led in this case to considerable formation of Claisen condensation products.

The compounds in which the carboxylic acid function was modified are listed in Table 3. The sulfonimides in this series were prepared by reaction of the parent acid (e.g., **26**) with sulfonamides and a water-soluble carbodiimide in the presence of 4-(dimethylamino)-pyridine (general method F). Using general method E

Scheme 3. General Method C



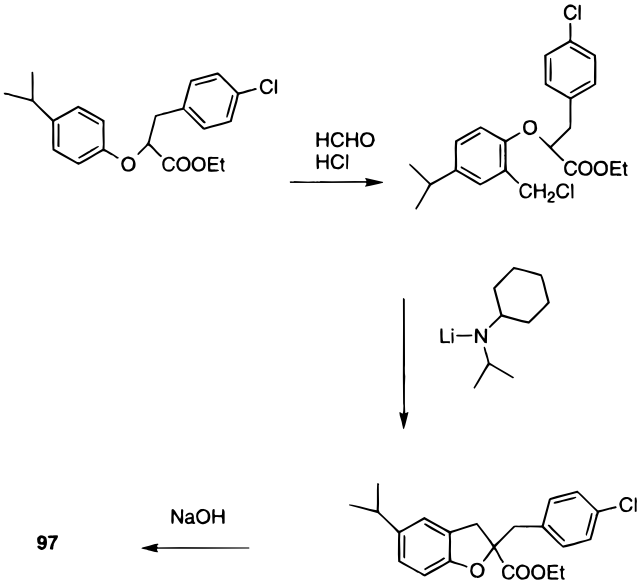
Scheme 4. General Method E



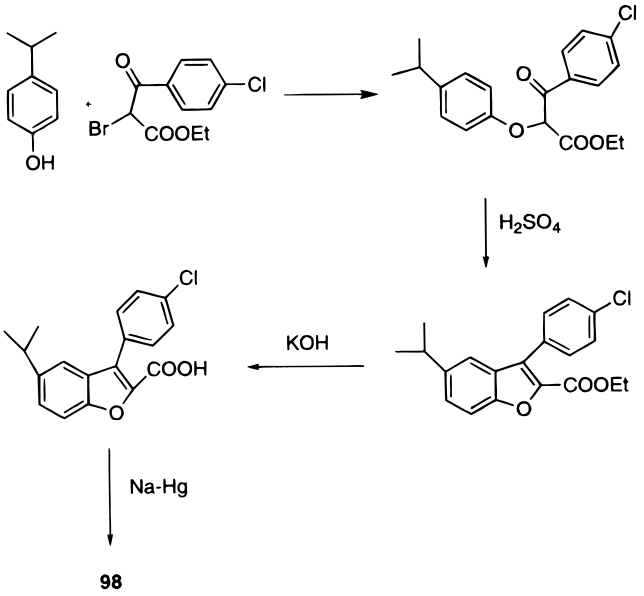
with α-bromopropionitrile instead of ethyl α-bromopropionate, we obtained the nitrile of **26**, which was reduced with borane to the amine and then sulfonylated to give sulfonamides **71** and **72** (general method F). Treatment of the nitrile intermediate with HN_3 gave tetrazole **73**; treatment with hydroxylamine gave amidoxime **76**. Reduction of the acid **26** with borane gave the alcohol **70**, which was converted to the monophosphate ester **75** with $POCl_3$. The acylguanidine **74** was obtained from the ester of **26** by treatment with guanidine. The hydroxymethyl ketone **77** proved to be sensitive to aqueous acid and base and was prepared by mild hydrolysis of the acetoxymethyl ketone with KCN; the acetoxymethyl ketone was obtained from acid **26** via the acid chloride, diazo ketone, and bromomethyl ketone.

The compounds which probed the manipulation of the α-methyl group of **26** and methyl substitution in the *β*-position (Table 4) were synthesized by adaption of general method E, as were the analogs of **26** in which

Scheme 5. Synthesis of Compound **97**



Scheme 6. Synthesis of Compound **98**

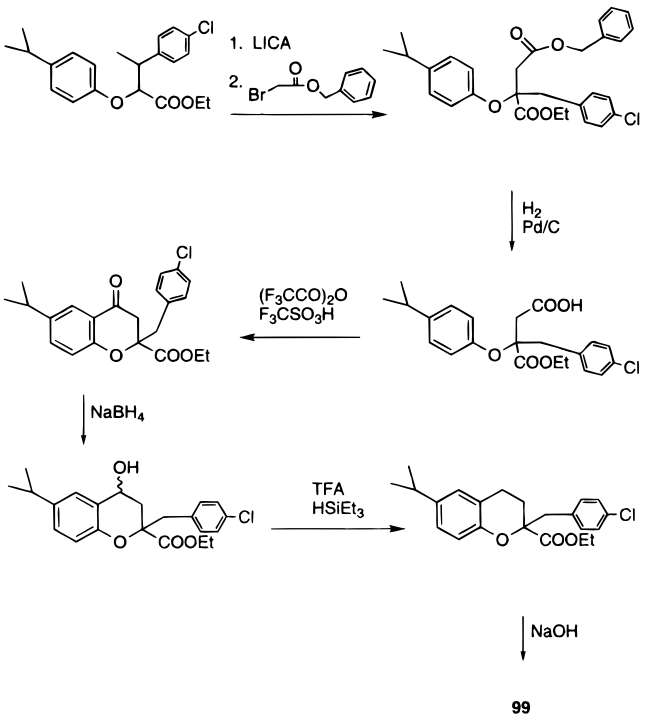


the phenoxy group was replaced by isosteres (Table 5). The synthesis of the ring-constrained derivatives of **26** (**97**−**101**; Table 6) is shown in Schemes 5−8.

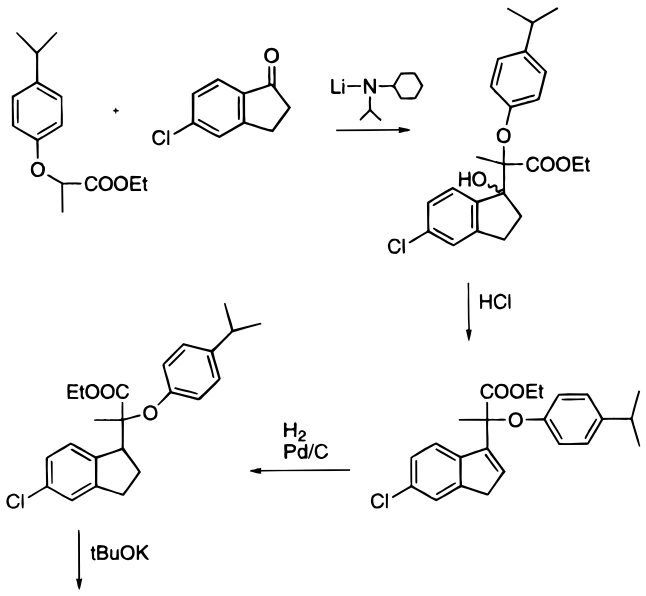
Biology

For in vitro characterization, compounds were evaluated for their acute effects on glucose transport by measuring 2-deoxyglucose uptake in 3T3-L1 adipocytes or L6 myocytes after 1 h pretreatment with the agents, which may reflect glucose transporter translocation to the plasma membrane from an intracellular storage pool or an increase in the intrinsic activity of the transporter.[12] Glucose transporter translocation was assessed by measuring cell surface glucose transporter levels by immunocytochemistry[13] following pretreatment with the compounds. Chronic effects on glucose transport activity were assessed by measuring 2-deoxyglucose transport in 3T3-L1 adipocytes after 48 h of exposure to the experimental compounds. Chronic effects on glucose transporter expression were assessed by quantitative immunoblotting using isoform-specific

Scheme 7. Synthesis of Compound **99**



Scheme 8. Synthesis of Compounds **100** and **101**



antibodies.[14] Inhibition of gluconeogenesis was measured in hepatocytes which were isolated by collagenase digestion from livers of fed male Sprague−Dawley rats.[15]

In vivo testing for hypoglycemic activity was carried out in 6−8 week old C57BL/6J-*ob*/*ob* mice (obtained from Jackson Laboratories, Bar Harbor, ME). The compounds were dosed orally for 4 days, and plasma glucose was measured on the fifth day 20−24 h after the last dose to determine their effect after chronic administration.[16] To determine acute hypoglycemic activity following a single oral dose of compound **26** or **84**, *ob*/*ob* mice were treated with vehicle alone on days 1−4 using the protocol above followed by administration of the test compound on the morning of day 5 and

plasma glucose determination 3 h later. Resulting plasma glucose values were compared to those of vehicle-treated mice and analyzed by two-tailed unpaired Student's *t*-test. Values are expressed as percent of plasma glucose lowering produced by racemic englitazone given at 50 mg/kg in the same experiment; this dose typically normalizes plasma glucose.

Results and Discussion

As shown in Table 1, several compounds with different substituents in the phenyl ring of the phenylpropanoic acids retained hypoglycemic activity in *ob/ob* mice. The parent compound **1** exhibited blood glucose-lowering activity at 50 mg/kg. Halogen and alkyl substitutions, particularly in the 4-position, produced agents with hypoglycemic activity comparable to or better than the parent compound. The 4-Cl (**7**) derivative demonstrated glucose-lowering activity at 10 mg/kg. Modification of the 4-isopropyl group in the phenoxy part of **7** led to analogs (**15**−**18**) that generally did not exhibit hypoglycemic activity at 25 mg/kg. Similarly, shortening (**19**) the distance between the α-carbon and the phenyl ring of the 3-phenylpropanoic acids by one C atom decreased the hypoglycemic activity, while increasing this distance by four (**21**), but not one (**20**), C atoms retained hypoglycemic activity. Although there was some correlation between the ability of these compounds to acutely enhance 2-deoxyglucose uptake in 3T3-L1 adipocytes in vitro, we surprisingly found several compounds which showed activity in one of, but not both, the in vitro and in vivo screens (**1, 2, 5, 11, 19**).

Replacing the hydrogen on the α-carbon of compounds **3, 4, 6,** and **7** with methyl led to compounds **23**−**26** in Table 2, which showed in vivo glucose-lowering activity ($ED_{50} \leq 10$ mg/kg), although this was not accompanied by an increase in acute glucose transport activity in 3T3-L1 adipocytes in vitro. The marked hypoglycemic activity displayed by **26** ($ED_{50} = 1-5$ mg/kg) caused us to examine SAR around this structure more thoroughly. Resolution of **26** showed that both isomers (**27, 28**) were active at doses of 2.5 and 5 mg/kg in lowering blood glucose and had equivalent effects to acutely stimulate 2-deoxyglucose transport in 3T3-L1 adipocytes.

Replacement of chlorine in compound **26** with a variety of alkyl groups (**29**−**39**) gave many agents with hypoglycemic activity at doses of ≤1 mg/kg (as exemplified by the 4-ethyl derivative **33**). Replacement of chlorine with methoxy (**40, 41**) gave compounds that exhibited little or no glucose-lowering activity at 10 mg/kg and therefore appeared to be less potent than **26**, but replacement with phenyl (**42**−**44**), especially in the 3- and 4-positions, gave hypoglycemic agents with activity comparable to **26**. Addition of a chlorine to the 3-position of **26** (**45**) or substitution of chlorine with three methyls (**46**) gave analogs that maintained hypoglycemic activity at ≤10 mg/kg. Replacement of chlorine in **26** with the tail of gliburide (**47**) resulted in diminished hypoglycemic activity. Substitution of chlorine with a fused ring resulted in decreased activity in the naphthyl derivative (**48**) and retained activity in the indan (**49**) and tetralin (**50**) derivatives.

Replacement of the 4-isopropyl group in **26** with other groups (**51**−**58**) gave compounds that produced hypoglycemic activity at ≤10 mg/kg (the 4-benzyl derivatives **51, 52, 54**; the 4-phenoxy derivative **57**) and several compounds that exhibited no hypoglycemic activity at 10 mg/kg (**53, 56, 58**). Exploring the simultaneous substitution of the 4-chloro group and the 4-isopropyl group of **26,** we prepared compounds **59**−**65**. Of these, **59, 62**, and **65** showed notable hypoglycemic potency ($ED_{50} \leq 1$ mg/kg).

The effects of the compounds in Table 2 on the acute stimulation of 2-deoxyglucose uptake in 3T3-L1 adipocytes or L6 myocytes was not measured for all compounds. However, there are several examples of compounds with an increased effect on uptake relative to **26** but without a concomitant increase in hypoglycemic activity (e.g., **22, 39, 42, 56**), and conversely there are several agents (e.g., **33, 44**) that induced glucose lowering at low doses (~1 mg/kg) which did not enhance acute 2-deoxyglucose uptake at the concentrations tested.

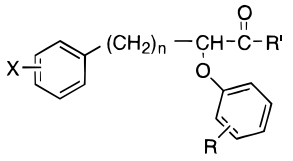
Compounds resulting from replacement of the carboxyl group of **26** with other groups or acidic bioisosteres are listed in Table 3. It is apparent that certain sulfonimides (e.g., **66**−**69**) showed enhanced effects on acute 2-deoxyglucose uptake in vitro, but these compounds did not produce significant glucose lowering at 5 mg/kg and thus appeared to be less potent than **26**. These findings support the unexpected conclusion that enhanced acute glucose uptake in 3T3-L1 adipocytes does not necessarily translate to hypoglycemic activity in *ob/ob* mice. However, poor bioavailability cannot be excluded as an explanation for the discordance between potency in vitro and poor in vivo activity. Furthermore, the carboxylic acid group of **26** seems to be an essential ingredient for the hypoglycemic activity of this series in the *ob/ob* mouse.

To explore the importance of the α-methyl group of **26** and the tolerance for substituents in the *β*-position of the α-phenoxy substituted 3-phenylpropanoic acids, we prepared the compounds shown in Table 4. Changing the α-methyl group to ethyl (**81**) or shifting the methyl group from the α- to the *β*-position (**82, 83**) resulted in decreased hypoglycemic potency. Addition of a methyl to the *β*-position of **26** gave one diastereomer (**84**, shown by X-ray analysis to be the 2*R*,3*S*/2*S*,3*R* isomer) with enhanced effects on acute 2-deoxyglucose uptake and comparable hypoglycemic activity. Its diastereomer **85** was less active in the *ob/ob* mouse. Changing the *β*-methyls in **84** and **85** to *β*-ethyls gave the diastereomers **86** and **87**, respectively, with hypoglycemic activity in **86** but not in **87**. Replacing the carboxyl group in **84** with sulfonimides (**88, 89**) again diminished hypoglycemic potency ($ED_{50} > 10$ mg/kg).

The effects of modifying the α-4-isopropylphenoxy group in compounds **7** and **26** are summarized in Table 5. The α-tosyl derivative (**90**) of compound **7** did not exhibit hypoglycemic activity at 50 mg/kg and, therefore, appeared to be less potent than **7**, while the thiophenoxy analog **91** was active at 50 mg/kg. Among the analogs of **26,** the thiophenoxy congener **92** showed some effect in stimulating acute 2-deoxyglucose uptake, but none of the modified derivatives had superior hypoglycemic activity.

Attempts to constrain the conformations of compound **26** in cyclic derivatives are summarized in Table 6. Interestingly, only compound **100** showed hypoglycemic activity comparable to **26**. Since compound **101** was

Table 1



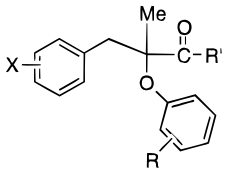
no.	X	R	R′	*n*	formula	method	mp (°C)	2DG uptake stim[a] [drug] (μM): % basal uptake	glucose-lowering *ob*/*ob* mouse[b] dose (mg/kg) (no. of experiments):% glucose lowering relative to positive control	ED_{50}[c]
1	H	4-iPr	OH	1	$C_{18}H_{20}O_3$	A	91−2	100: 79	50: 50*	50
2	2-CF_3	4-iPr	O-DCA[d]	1	$C_{19}H_{19}F_3O_3 \cdot C_{12}H_{23}N$	B	164−5	100: 191**	50: ≤0	>50
3	3-CF_3	4-iPr	O-DCA[d]	1	$C_{19}H_{19}F_3O_3 \cdot C_{12}H_{23}N$	C, D	165−7	100: 284*** 50: 76** 25: 64 10: ≤0		~25
4	4-CF_3	4-iPr	OH	1	$C_{19}H_{19}F_3O_3$	B	134−8	100: 605*** *60*: *104* 50: 74*** 10: 42 5: 30*		~10
5	3-F	4-iPr	O-DCA[d]	1	$C_{18}H_{19}FO_3 \cdot C_{12}H_{23}N$	B	165−7	100: 111	50: 100** 25: 65	<25
6	3-Cl	4-iPr	O-DCA[d]	1	$C_{18}H_{19}ClO_3 \cdot C_{12}H_{23}N$	D	166−8	100: 160**	50: 32	>50
7	4-Cl	4-iPr	OH	1	$C_{18}H_{19}ClO_3$	D	148−9	100: 150*	50: 82*** 10: 58** 5: 26*	~10
8	4-Br	4-iPr	OH	1	$C_{18}H_{19}BrO_3$	D	171−3	100: 203**	50: 122** 10: ≤0	10−50
9	4-Me	4-iPr	OH	1	$C_{19}H_{22}O_3$	D	142−5	100: 147*	50: 113*	<50
10	2-OMe	4-iPr	OH	1	$C_{19}H_{22}O_4$	E	101−3	60: 78	10: <0	>10
11	4-OMe	4-iPr	OH	1	$C_{19}H_{22}O_4$	D	111−4	100: 127**	50: ≤0	>50
12	2,4-Cl_2	4-iPr	OH	1	$C_{18}H_{18}Cl_2O_3$	D	89−90	100: 222**	50: 70*** 10: 30 5: 45	10−50
13	3,4-Cl_2	4-iPr	O-DCA[d]	1	$C_{18}H_{18}Cl_2O_3 \cdot C_{12}H_{23}N$	D	172−3.5	100: 225***	50: 65	<50
14	3,4-$(CH)_4$ (β-naphthyl)	4-iPr	OH	1	$C_{22}H_{22}O_3$	D	140−2	100: 143***	50: 45*	50
15	4-Cl	H	OH	1	$C_{15}H_{13}ClO_3$	D	157−8.5	60: 100 *60*: *86*	25: ≤0	>25
16	4-Cl	4-Me	OH	1	$C_{16}H_{15}ClO_3$	D	128−31	60: ≤100 *60*: *93* *30*: *88* *10*: *82*	25: 33	>25
17	4-Cl	4-OMe	OH	1	$C_{16}H_{15}ClO_4$	D	117.5−20	*60*: *98*	25: 23	>25
18	4-Cl	4-tBu	OH	1	$C_{19}H_{21}ClO_3$	D	127−30	60: <100 *60*: *84* *30*: *87* *10*: *92*	25: 53	25
19	4-Cl	4-iPr	OH	0	$C_{17}H_{17}ClO_3$	*e*	74−5	100: 248*	50: ≤0	>50
20	4-Cl	4-iPr	O-DCA[d]	2	$C_{19}H_{21}ClO_3 \cdot C_{12}H_{23}N$[f]	*e*	143−5	100: 89 *60*: *89*	25: 64	<25
21	4-Cl	4-iPr	ONa	5	$C_{22}H_{26}ClNaO_3$	*e*	275 dec	10: 180*** *60*: *44*	50: 200** 10: 32 5: 35	10−50
BM 13.0795								100: 250*** 30: 100 10: 93 3: 114 *100*: *134**** *60*: *124*** *30*: *88*	50(3): 71** 25(4): 60*** 10(3): 22	~25

[a] 2-Deoxyglucose (DG) uptake values are presented as means of triplicate measurements and represent the percent basal uptake obtained in vehicle-treated 3T3-L1 adipocytes unless printed in italics, in which case the data were obtained in L6 myocytes. Significant increases from vehicle-treated cells: *$p < 0.05$, **$p < 0.01$; ***$p < 0.001$. [b] Values presented are the percent glucose normalization compared to the effect of racemic englitazone (CP-68,722) at 50 mg/kg (i.e., 100% normalization). Significant differences of drug-treated vs vehicle-treated mice: *$p < 0.05$, **$p < 0.01$; ***p <0 .001, (two-tailed unpaired *t*-test). [c] ED_{50} = approximate dose of compound that induces 50% normalization of glucose relative to positive control (racemic englitazone). [d] DCA = dicyclohexylammonium salt. [e] See the Experimental Section. [f] This compound was characterized by NMR and MS only.

shown by X-ray analysis to have the *RS*/*SR* configuration, **100** must be *RR*/*SS*.

These SAR results can be rationalized by molecular modeling studies. The goal of these computations was to discover the common conformations of **7**, **26**, **84**, and **99**−**101** and to rationalize the decreased activity of compounds **7**, **99**, and **101** relative to the more potent analogs. This was approached by overlapping all of the conformational minima for the most potent analogs (**26**, **84**, **100**) to give maximum coincidence of the aromatic

Table 2



no.	X	R	R′	formula	method	mp (°C)	2DG uptake stim[a] [drug] (μM): % basal uptake	glucose-lowering *ob/ob* mouse[b] dose (mg/kg) (no. of experiments): % glucose lowering relative to positive control	ED_{50}[c]
22	H	4-iPr	ONa	$C_{19}H_{21}NaO_3$	E	>200	10: 126* 3: 162* 1: 100	10(2): 3	>10
23	3-CF_3	4-iPr	ONa	$C_{20}H_{20}F_3NaO_3$	E	>200	*30*: *121* *10*: *104* *3*: *129*	10: 64* 5: 46 1: 44	5−10
24	4-CF_3	4-iPr	OH	$C_{20}H_{21}F_3O_3$	E	122−4	*60*: *103*	5: 65*	<5
25	3-Cl	4-iPr	ONa	$C_{19}H_{20}ClNaO_3$	E	>200		10: 101*** 5: 32 1: 47*	5−10
26	4-Cl	4-iPr	OH	$C_{19}H_{21}ClO_3$	E	132−3	100: 220** 60: 110 30: 100 10: 94 3: 98 1: 86 0.3: 106 *100*: *88* *60*: *108* *30*: *87* *10*: *96* *3*: *97* *1*: *101*	50: 83* 25: 90*** 20: 104*** 10(2): 111*** 5(4): 77* 1: 50	1−5
27	4-Cl (*d* isomer)	4-iPr	OH	$C_{19}H_{21}ClO_3$	*d*	114−5 ($[\alpha]_D$ +15.1°)	100: 214**	5: 65** 2.5: 79** 1: 36	1−2.5
28	4-Cl (*l* isomer)	4-iPr	OH	$C_{19}H_{21}ClO_3$	*d*	114−6 $[\alpha]_D$ −16.7°	100: 229**	5 (2): 100*** 2.5: 88* 1: 47	1−2.5
29	3-Me	4-iPr	ONa	$C_{20}H_{23}NaO_3$	E	>230	30: 84 10: 98 3: 93	10: 83** 5: 83** 1: 63*	<1
30	4-Me	4-iPr	ONa	$C_{20}H_{23}NaO_3$	E	>250	60: 92	10: 106*** 5: 100*** 1: 58	<1
31	2-Et	4-iPr	ONa	$C_{21}H_{25}NaO_3$	E	90−3		10: 95*** 5: 53* 1: 32	5
32	3-Et	4-iPr	ONa	$C_{21}H_{25}NaO_3$	E	>200	30: 117* 10: 127** 3: 102	10: 147*** 5: 101*** 1: 76** 0.5: ≤0	0.5−1
33	4-Et	4-iPr	ONa	$C_{21}H_{25}NaO_3$	E	>250	60: 109	10: 119*** 5(2): 109*** 1(2): 86*** 0.5: 76** 0.1: 55	0.1−0.5
34	3-nPr	4-iPr	ONa	$C_{22}H_{27}NaO_3$	E	212−6	30: 229*** 10: 128 3: 136 1: 123	10: 123*** 5: 82*** 1: 47*	1
35	4-nPr	4-iPr	ONa	$C_{22}H_{27}NaO_3$	E	>200	60: 282*** 30: 97	10: 113*** 5: 134*** 1: 70*** 0.5: 69	∼0.5
36	4-iPr	4-iPr	ONa	$C_{22}H_{27}NaO_3$	E	>200	30: 93 10: 97 3: 97	10: 93** 5: ≤0	5−10
37	3-nBu	4-iPr	ONa	$C_{23}H_{29}NaO_3$	E	>200	30: 113 10: 129 3: 113	10: 91** 5: 85* 1: ≤0	1−5
38	4-nBu	4-iPr	ONa	$C_{23}H_{29}NaO_3$	E	>200	30: 200*** 10: 94 3: 82	10: 130*** 5: 92** 1: 17	1−5

Table 2 (Continued)

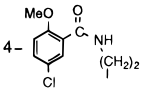
no.	X	R	R′	formula	method	mp (°C)	2DG uptake stim[a] [drug] (μM): % basal uptake	glucose-lowering *ob/ob* mouse[b] dose (mg/kg) (no. of experiments): % glucose lowering relative to positive control	ED_{50}[c]
39	4-tBu	4-iPr	OH	$C_{23}H_{30}O_3$	E	65−8	30: 213*** 10: 104 3: 103	10: 102* 5: 47 1: 41	5−10
40	2-OMe	4-iPr	OH	$C_{20}H_{24}O_4$	E	118−20	60: 120 30: 122* 10: 100	10: ≤0	>10
41	4-OMe	4-iPr	OH	$C_{20}H_{24}O_4$	E	80−2		10: 41*	>10
42	2-Ph	4-iPr	ONa	$C_{25}H_{25}NaO_3$	E	70−4	30: 167* 10: 228* 3: 148* 1: 97	10: 54*	10
43	3-Ph	4-iPr	ONa	$C_{25}H_{25}NaO_3$	E	49−52	30: 118* 10: 76 3: 87	10: 83** 5: 110** 1: 78* 0.5: 46**	0.5
44	4-Ph	4-iPr	ONa	$C_{25}H_{25}NaO_3$	E	>230	30: 126 10: 129 3: 122	10: 116*** 5: 93*** 1: 58* 0.5: 21	∼1
45	3,4-Cl_2	4-iPr	OH	$C_{19}H_{20}Cl_2O_3$	E	98−9		10: 111*** 5: 24 1: ≤0	5−10
46	2,4,6-Me_3	4-iPr	ONa	$C_{22}H_{27}NaO_3$	E	>200	60: 173** 30: 106 10: 148	10: 77**	<10
47		4-iPr	OH	$C_{29}H_{32}ClNO_5$	E[d]	127−9		10: 24	>10
48	3,4-$(CH)_4$ (β-naphthyl)	4-iPr	OH	$C_{23}H_{24}O_3$	E	88−90		10: 46	>10
49	3,4-$(CH_2)_3$	4-iPr	ONa	$C_{22}H_{25}NaO_3$	E	>230 dec		10: 126*** 5: 121*** 1: 83*** 0.5: 34	0.5−1
50	3,4-$(CH_2)_4$	4-iPr	ONa	$C_{23}H_{27}NaO_3$	E	>200		10: 99*** 5: 75*	<5
51	4-Cl	4-CH_2-Ph	ONa	$C_{23}H_{20}ClNaO_3$	E	228−30	60: 214*** 30: 109	10: 96** 5: 100*** 1: 44	1−5
52	4-Cl		ONa	$C_{24}H_{22}ClNaO_4$	E	195−206 dec		10: 74**	<10
53	4-Cl		ONa	$C_{23}H_{19}C_{l2}NaO_3$	E	200−20 dec	30: 112 10: 94 3: 90	10: ≤0	>10
54	4-Cl		ONa	$C_{23}H_{19}C_{l2}NaO_3$	E	190 dec	30: 97 10: 88 3: 100	10: 52*	10
55	4-Cl		ONa	$C_{21}H_{22}ClNaO_3S$[e]	E[d]	>250 dec	60: 108	10: 64**	<10
56	4-Cl		ONa	$C_{25}H_{22}ClNaO_3S$	E[d]	110−4	30: 157** 10: 118 3: 130 1: 98	10: 38	>10
57	4-Cl		OH	$C_{22}H_{19}ClO_4$	E	120−2		10: 108*** 5: 100** 1: 60*	<1
58	4-Cl	4-Br	OH	$C_{16}H_{14}BrClO_3$	E	104−5	30: 134* 10: 109 3: 120	10: 22	>10
59	3-Et	4-CH_2-Ph	ONa	$C_{25}H_{25}NaO_3$	E	>210 dec		10: 101*** 5(2): 102*** 1: 87** 0.5(2): 52*** 0.1: 73**	0.1−0.5

Table 2 (Continued)

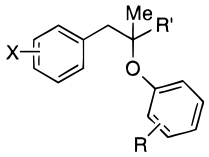
no.	X	R	R′	formula	method	mp (°C)	2DG uptake stim[a] [drug] (μM): % basal uptake	glucose-lowering *ob/ob* mouse[b] dose (mg/kg) (no. of experiments): % glucose lowering relative to positive control	ED_{50}[c]
60	3-Et		ONa	$C_{27}H_{27}NaO_3S$[f]	E[d]	>200	30: 116 10: 113 3: 104	10: 35	>10
61	4-Et	4-CH_2-Ph	ONa	$C_{25}H_{25}NaO_3$	E	>220		10: 107*** 5: 104*** 1: 44	~1
62	4-Et	4-CO-Ph	OH	$C_{25}H_{24}O_4$	E	168.5−9.5		10: 107*** 5: 108*** 1: 65** 0.5: 60*	~0.5
63	4-Et	4-O-Ph	OH	$C_{24}H_{24}O_4$	E	91−5		10: 130*** 5: 113*** 1: 48*	1
64	4-nPr	4-CH_2-Ph	ONa	$C_{26}H_{27}NaO_3$	E	>185 dec		10: 96*** 5: 91** 1: 24	1−5
65	3,4-$(CH_2)_3$	4-CH_2-Ph	ONa	$C_{26}H_{25}NaO_3$	E	200 dec		10: 120*** 5: 102*** 1: 78** 0.5: 50	0.5−1

[a] 2-Deoxyglucose (DG) uptake values are presented as means of triplicate measurements and represent the percent basal uptake obtained in vehicle-treated 3T3-L1 adipocytes unless printed in italics, in which case the data were obtained in L6 myocytes. Significant differences of drug-treated vs vehicle-treated cells: $*p < 0.05$, $**p < 0.01$; $***p < 0.001$. [b] Values presented are the percent glucose normalization compared to the effect of racemic englitazone (CP-68,722) at 50 mg/kg (i.e., 100% normalization). Significant differences of drug-treated vs vehicle-treated mice: $*p < 0.05$; $**p < 0.01$; $***p < 0.001$, (two-tailed unpaired t-test). [c] ED_{50} = approximate dose of compound that induces 50% glucose normalization relative to positive control (racemic englitazone). [d] See the Experimental Section [e] Formula $C_{21}H_{22}ClNaO_3S$ anal. C; H: calcd, 5.37; found, 4.91. MS (free acid, CI) *m/e* 408 (M + NH_4). [f] This compound was characterized by NMR and MS only.

and carboxylate groups. Emphasis was also placed on aligning the C4−H bond vector of the phenoxy substituent (corresponding to the point of attachment of the isopropyl group) and the C5−H bond vector of the indan (C4−H of **26**) (position of the chloro substituent). Interestingly, the best overall fit of **26**, **84**, and **100** was obtained from the lowest energy conformation of each molecule, illustrated in Figure 1. Given the overlap of the most potent analogs, the next step was to fit **7**, **99**, and **101** to the alignment in an attempt to understand their decreased activity. As illustrated in Figure 1, both **99** and **101** fit the alignment reasonably well. Again, the best overlap was obtained from the lowest energy conformations of **99** and **101**. However, none of the minima of **7** were found to fit the alignment. Introduction of the α-methyl group in **7**, to give **26**, causes a dramatic change in the lowest energy conformation toward more potent activity. Given the similarity of **7** and **26**, the lower activity of **7** can be explained by computing the energetic cost of adopting the preferred conformation of **26**. The cost of achieving this conformation was determined by constraining the C(phenyl)−O−C(COOH)−C(H2) and O−C(COOH)−C(H2)−C(phenyl) dihedral angles of **7** to −163.3° and 67.4° (the corresponding values found in **26**). Additionally, the plane of each aromatic ring in **7** was constrained to the same relative orientation as found in **26**. At the 6-31G(d)//6-31G(d) level of theory, this conformation of **7** is ca. 1.9 kcal/mol higher in energy than the lowest energy conformation. This energetic difference is sufficient to explain the lower activity of **7**. The decreased potency of **101** can be rationalized by assuming that relatively precise positioning of the indan aromatic ring is required for activity. As shown in Figure 1, the plane of the indan aromatic ring in **101** occupies a unique position, tilted ca. 44° relative to the other molecules in the alignment. Evidently, the positioning of the plane of the aromatic phenoxy substituent is not as critical as demonstrated by the overlap of **99**. Since all other features of **99** are aligned reasonably well with the more potent compounds (through the C6−H bond vector of the benzopyran ring and C4−H bond vector of the benzyl group), it can be assumed that the lower potency of this constrained analog is due to the near perpendicular positioning of the benzopyran ring.

In order to gain insight into the possible mechanism of action of these compounds, we carried out further biological experiments. It is clear that many compounds in this series enhanced glucose transport in adipocytes acutely, an effect that is consistent with GLUT4 translocation from an intracellular storage site to the plasma membrane and which is the reported mechanism of action of the lead compound BM 13.0795.[6] In accord with this, two compounds tested (**26** and **84**) displayed acute (3 h) hypoglycemic activity in single-dose studies in diabetic *ob/ob* mice. Under this protocol, both compounds displayed significant ($p < 0.05$) blood glucose-lowering activity at 50 mg/kg, and the efficacy of these compounds ranged from 54% to 82% of that observed for chronic treatment with racemic englitazone. However, if the hypoglycemic activity of these compounds is indeed mediated through GLUT4, it is unlikely they do so by enhancing GLUT4 translocation since we have been unable to show increased GLUT4 levels at the plasma membrane in 3T3-L1 adipocytes treated with **26** in vitro (data not shown). For some compounds, the assessment of acute effects on glucose transport after acute exposure was carried out in L6 myocytes. When

Table 3



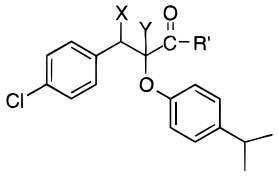
no	X	R	R′	formula	method	mp (°C)	2DG uptake stim[a] [drug] (μM): % basal uptake	glucose-lowering *ob/ob* mouse[b] dose (mg/kg) (no. of experiments): % glucose lowering relative to positive control	ED_{50}[c]
66	4-Cl	4-iPr	$CONHSO_2Me$	$C_{20}H_{24}ClNO_4S$	F	141−1.5	60: 200** 30: 255*** 10: 100	10: 96*** 5: 0 10: 100	5−10
67	4-Cl	4-iPr	$CONHSO_2CF_3$	$C_{20}H_{21}ClF_3NO_4S$	F	160 dec	60: 79 30: 273*** 10: 232*** 3: 130 1: 108	10(2): 91** 5: ≤0	5−10
68	4-Cl	4-iPr		$C_{26}H_{28}ClNO_4S$	F	150−1	30: 232*** 10: 251*** 3: 126	10: ≤0	>10
69	4-Cl	4-iPr		$C_{26}H_{28}ClNO_5S$	F	98−100	*60*: *67* *30*: *154**** *10*: *101*	10: 22	>10
70	4-Cl	4-iPr	CH_2OH	$C_{19}H_{23}ClO_2$[d]	*e*	oil	30: 118* 10: 121** 3: 118*	10: ≤0	>10
71	4-Cl	4-iPr	$CH_2NNaS(CF_3)$	$C_{20}H_{22}ClF_3NNaO_3S$[f]	G[g]	68−70	30: 159** 10: 132* 3: 127	10: ≤0	>10
72	4-Cl	4-iPr		$C_{26}H_{29}ClNNaO_3S$[h]	G	77−82		10: 7	>10
73	4-Cl	4-iPr		$C_{19}H_{21}ClN_4O$	*e*	140−2	30: 159 10: 105 3: 105	10: ≤0	>10
74	4-Cl	4-iPr	$CONHC(NH_2)=NOH$	$C_{20}H_{24}ClN_3O_2 \cdot HCl$	*e*	172−5		10: 49*** 5: 44 1: ≤0	10
75	4-Cl	4-iPr	CH_2OPO_3Ca	$C_{19}H_{22}CaClO_5P$	*e*	168−70		10: 50	≥10
76	4-Cl ($E + Z$ isomer)	4-iPr	$C(NH_2)=NOH$	$C_{19}H_{23}ClN_2O_2$[d]	*e*	foam		10: 27	>10
77	4-Cl	4-iPr	$COCH_2OH$	$C_{20}H_{23}ClO_3$[d]	*e*	oil		10: 32	>10
78	3-Et	4-iPr	$CONNaS(CF_3)O_2$	$C_{22}H_{25}F_3NNaO_4S$	F	>200		10: 43*	≥10
79	4-Et	4-iPr	$CONHS(CF_3)O_2$	$C_{22}H_{26}F_3NO_4S$	F	98−103		10: 27	>10
80	4-nPr	4-iPr	$CONHS(CF_3)O_2$	$C_{23}H_{28}F_3NO_4S$	F	134−8		10: 35	>10

[a] 2-Deoxyglucose (DG) uptake values are presented as means of triplicate measurements and represent the percent basal uptake obtained in vehicle-treated 3T3-L1 adipocytes unless printed in italics, in which case the data were obtained in L6 myocytes. Significant differences from vehicle-treated cells are indicated: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. [b] Values presented are the percent glucose normalization compared to the effect of racemic englitazone (CP-68,722) at 50 mg/kg (i.e., 100% normalization). Significant differences from vehicle-treated mice are indicated: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ (two-tailed unpaired *t*-test). [c] ED_{50} = approximate dose of compound that induces 50% normalization of glucose relative to the positive control (racemic englitazone). [d] This compound was characterized by NMR and MS only. [e] See the Experimental Section. [f] Formula $C_{20}H_{22}ClF_3NNaO_3S \cdot 1.5H_2O$ anal. C, N; H: calcd, 5.05; found, 5.50. MS (free acid, CI) *m/e* 467 (M + NH_4). [g] 2-Methylbenzenesulfonyl chloride was used instead of trifluoromethanesulfonic anhydride. [h] Formula $C_{26}H_{29}ClNNaO_3S \cdot 1.75H_2O$ anal. C, H; N: calcd 2.65; found, 2.18. MS (FAB) *m/e* 494 (M + H); HR-MS calcd 494.1533, found 494.1516.

compounds were tested in both assays, activity was generally lower in the myocyte than in the adipocyte cell lines.

Interestingly, examination of **26** also showed that it had an even more potent effect on glucose transport activity in adipocytes after chronic exposure compared to acute exposure. Therefore, analogs of **26** were tested at three doses (30, 10, and 3 μM) for effects on 2-deoxyglucose uptake after 48 h exposure; results of note are shown in Table 7. Compared to **26**, which at 30 μM stimulated glucose transport activity in the 3T3-L1 adipocytes to 291% over basal levels, none of the related analogs displayed significantly greater efficacy (range = 193−265%) at the maximal concentration tested (30 μM). Furthermore, none of the compounds presented (**32, 33, 35, 43, 59**) displayed improved intrinsic potency of glucose transport activity over **26** at 3 μM. In fact, four compounds which were 2−10-fold more potent hypoglycemics than **26** in the chronic *ob/ob* mouse model (**32**, **33**, **43**, **59**) were not found to be superior to **26** in the chronic (48 h) glucose transport screen in 3T3-L1 adipocytes. This indicated a poor direct mechanistic relationship between the chronic increase of glucose transport in vitro and blood glucose lowering in vivo in this series.

Table 4



no.	X	Y	R′	formula	method	mp (°C)	2DG uptake stim[a] [drug] (μM): % basal uptake	glucose-lowering *ob*/*ob* mouse[b] dose (mg/kg): % glucose lowering relative to positive control	ED_{50}[c]
81	H	Et	ONa	$C_{20}H_{22}ClNaO_3$	E[d]	250 dec	100: 156*	5: 36	>5
82	Me (diast A)	H	OH	$C_{19}H_{21}ClO_3$	E[d]	110−2	60: 111	10: 17	>10
83	Me (diast B)	H	ONa	$C_{19}H_{20}ClNaO_3$	E[d]	>200	60: 98	10: 41	>10
84	Me (diast A; *RS*/*SR* by X-ray)	Me	OH	$C_{20}H_{23}ClO_3$	E[d]	160 dec	60: 214** 30: 128 10: 131 3: 102 1: 99 0.3: 98	10: 142*** 5: 77* 2.5: 62** 1: <0	~2.5
85	Me (diast B; *RR*/*SS*)	Me	OH	$C_{20}H_{23}ClO_3$	E[d]	121−3	60: 209** 30: 131 10: 128	10: 46	>10
86	Et (diast A; *RS*/*SR*?)	Me	OH	$C_{21}H_{25}ClO_3$	E[d]	169−71	30: 95 10: 91 3: 97	10: 71*	<10
87	Et (diast B; *RR*/*SS*?)	Me	OH	$C_{21}H_{25}ClO_3$	E[d]	98−101	30: 109 10: 96 3: 98	10: 32	>10
88	Me (*RS*/*SR*)	Me	$NHSO_2CF_3$	$C_{21}H_{23}ClF_3NO_4S$	F	sublimes	30: 113 10: 248*** 3: 94	10: 7	>10
89	Me (*RS*/*SR*)	Me		$C_{27}H_{30}ClNO_5S$	F	120−2	30: 162* 10: 113 3: 130	10: 16	>10

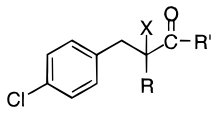
[a] 2-Deoxyglucose (DG) uptake values are presented as means of triplicate measurements and represent the percent basal uptake obtained in vehicle-treated 3T3-L1 adipocytes. Significant differences from vehicle-treated cells: *p < 0.05, **p < 0.01, ***p < 0.001. [b] Values presented are the percent glucose normalization compared to the effect of racemic englitazone (CP-68,722) at 50 mg/kg (i.e., 100% normalization). Significant differences of drug-treated vs vehicle-treated mice: *p < 0.05, **p < 0.01, ***p < 0.001 (two-tailed unpaired t-test). [c] ED_{50} approximate dose of compound that induces 50% normalization of glucose relative to the positive control (racemic englitazone). [d] See the Experimental Section.

In order to better understand the intrinsic activity to enhance glucose transport, we examined compound **26** for the ability to increase glucose transporter expression in 3T3-L1 adipocytes after 48 h incubation. Quantitative immunoblot analysis indicated that GLUT1 expression was increased to 4.3- and 5.9-fold basal levels at 10 and 30 μM **26** (p < 0.01), respectively. On the other hand, GLUT4 expression was essentially unchanged by these concentrations (data not shown). The increased GLUT1 expression correlated with increased glucose transport activity (Table 7) and is likely to be the mechanism by which compound **26** stimulates glucose transport in vitro after chronic treatment.

On the other hand, in vivo experiments with compound **26** did not support an enhancement of glucose transporter protein expression in skeletal muscle or adipose tissue as being involved in its hypoglycemic activity. The amount of immunoreactive GLUT1 and GLUT4 in *ob*/*ob* skeletal muscle did not differ between the vehicle-treated and 5 day **26**-treated groups at 50 mg/kg. Similarly, GLUT1 and GLUT4 levels were not elevated in adipocytes of *ob*/*ob* mice treated with **26** (Treadway et al., manuscript in preparation). Thus, a mechanistic relationship between chronic upregulation of skeletal muscle or adipocyte GLUT1 and GLUT4 protein content and blood glucose-lowering activity by **26** was not observed. Further evidence for the dissociation of antidiabetic effects from tissue GLUT protein levels has been obtained from chronic 14 day administration of **26** to normal rats, where a markedly increased glucose transport rate was observed despite unchanged GLUT1 or GLUT4 protein levels in adipose tissues and skeletal muscle (Treadway et al., manuscript in preparation). It is possible that **26** increases glucose transport activity in vivo through mechanisms similar to those described for stimuli such as hypoxia, inhibition of mitochondrial oxidative phosphorylation, and alkaline pH, which regulate glucose transport activity in muscle, liver, and adipose tissue and cells independent of changes in transport protein expression or translocation.[12]

Because increased glucose uptake into adipose tissue may not fully explain the glucose-lowering activity, we examined additional mechanisms that might also contribute to the compounds' hypoglycemic action. One potential mechanism that could explain the in vivo hypoglycemic activity would be reduced glucose output by the liver. Consequently, we tested four compounds

Table 5



no.	X	R	R'	formula	method	mp (°C)	2DG uptake stim[a] [drug] (μM): % basal uptake	glucose-lowering *ob/ob* mouse[b] dose (mg/kg): % glucose lowering relative to positive control	ED_{50}[c]
90	H		OH	$C_{16}H_{15}ClO_4S$	D	161-2	*60: 89*	50: ≤0	>50
91	H		OH	$C_{18}H_{19}ClO_2S$	E	100-2	*60: 102*	50: 90* 10: ≤0	10-50
92	Me		ONa	$C_{19}H_{20}ClNaO_2S$	E	250 dec	60: 187*** 30: 119* 10: 83	10: 31	>10
93	Me		OH	$C_{20}H_{23}ClO_2$	E[d]	118-20		10: 20	>10
94	Me (diast B)		OH	$C_{20}H_{22}ClFO_2$	E[d]	143-5		10: 63**	~10
95	Me (diast A)		OH	$C_{20}H_{22}ClFO_2$	E[d]	133-4		10: 50*	10
96	Me		ONa	$C_{19}H_{26}ClNaO_3$[e]	E	260 dec		10: ≤0	>10

[a] 2-Deoxyglucose (DG) uptake values are presented as means of triplicate measurements and represent the percent basal uptake obtained in vehicle-treated 3T3-L1 adipocytes unless printed in italics, in which case the data were obtained in L6 myocytes. Significant differences from vehicle-treated cells are indicated: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. [b] Values presented are the percent glucose normalization compared to the effect of racemic englitazone (CP-68,722) at 50 mg/kg (i.e., 100% normalization). Significant differences from vehicle-treated mice: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ (two-tailed unpaired *t*-test). [c] ED_{50} = approximate dose of compound that induces 50% normalization of glucose relative to the positive control (racemic englitazone). [d] See the Experimental Section. [e] This compound was characterized by NMR and MS only.

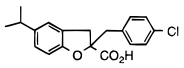
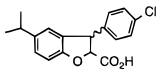
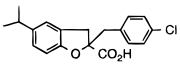
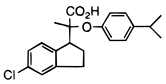
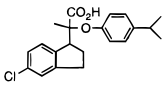
from this series, **1**, **5**, **7**, and **26**, for antigluconeogenic activity in isolated rat hepatocytes in vitro. A summary of the results is presented in Table 8. The results indicated that **1**, **5**, and **26** significantly inhibited the basal rate of gluconeogenesis in isolated rat hepatocytes. Compounds **1, 7,** and **26** also marginally inhibited glucagon-stimulated hepatocyte gluconeogenesis. These results suggest that the in vivo blood glucose-lowering activity of these compounds could, in part, be explained by their ability to suppress hepatic glucose production via an inhibition of gluconeogenesis in vivo. Whether this suppression of gluconeogenesis observed in vitro contributes significantly to blood glucose lowering observed in *ob/ob* mice is unclear. However, preliminary experiments in fasted normoglycemic rats indicate that basal hepatic glucose production (determined by [3-^{3}H]glucose infusion[17]) is not decreased by acute or chronic treatment with compound **26** (data not shown).

In the chronic *ob/ob* mouse experiments, most of the compounds that produced hypoglycemia also decreased food intake by 15−50%. To examine whether the hypoglycemic activity of these compounds was attributable to decreased food intake, a pair-feeding study was performed in *ob/ob* mice with compound **26** dosed at 5 mg/kg for 5 days. Relative to mice dosed with vehicle, compound **26** decreased food intake by 26%. Three groups of five mice, dosed with vehicle, were pair-fed to the same level as mice dosed with compound **26.** As shown in Table 9, food restriction alone had no effect on the plasma glucose concentration relative to the vehicle group fed ad libitum. However, compound **26** lowered plasma glucose by 43% relative to the pair-fed group. These results suggest that the glucose-lowering activity of compound **26** is independent of its effects on food intake.

Conclusion

This series contains many potent hypoglycemic agents, with some compounds (**32**, **33**, **59**) able to normalize plasma glucose in *ob/ob* mice at doses of approximately 1 mg/kg. The mechanism of action of these drugs is not entirely clear, but many compounds enhance glucose transport in vitro, especially in fat cells, and this action likely contributes to in vivo glucose lowering. The glucose transport effect does not seem to involve GLUT4 translocation, nor does it involve increased levels of GLUT1 or GLUT4 in vivo, but may be related to enhanced efficiency and/or intrinsic activity of glucose transporters. Further experiments are needed to confirm this mechanism. Some compounds also modestly decrease hepatocyte gluconeogenesis in vitro, but this is unlikely to contribute significantly to the hypoglycemic effect observed since gluconeogenesis inhibition was not observed in fasted rats treated with **26**. The

Table 6

no.	structure	formula	method	mp(°C)	2DG uptake stim[a] [drug] (μM): % basal uptake	glucose-lowering *ob/ob* mouse[b] dose (mg/kg) (no. of experiments): % glucose lowering relative to positive control	ED_{50}[c]
97		$C_{19}H_{19}ClO_3$	E[d]	136.5-7	*60: 66*	50: ≤0	>50
98		$C_{18}H_{17}ClO_3$	E[d]	138 subl.	*60: 89*	50: 25	>50
99		$C_{20}H_{21}ClO_3$	E[d]	167-8	*60: 114** *30: 80* *10: 82*	50: 119*** 5: ≤0	5-50
100	 (diast B; *RR/SS*)	$C_{21}H_{22}ClNaO_3$	E[d]	>200	30: 89 10: 83 3: 85	10(3): 105*** 5: 78** 1: 14	1-5
101	 (diast A; *RS/SR* by X-ray)	$C_{21}H_{23}ClO_3$	E[d]	117-8	30: 85 10: 86 3: 71	10: 35	>10

[a] 2-Deoxyglucose (DG) uptake values are presented as means of triplicate measurements and represent the percent basal uptake obtained in vehicle-treated 3T3-L1 adipocytes unless printed in italics, in which case the data were obtained in L6 myocytes. Significant differences from vehicle-treated cells: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. [b] Values presented are the percent glucose normalization compared to the effect of racemic englitazone (CP-68,722) at 50 mg/kg (i.e., 100% normalization). Significant differences of drug-treated vs vehicle-treated mice are indicated: *$p < 0.05$. **$p < 0.01$; ***$p < 0.001$, (two-tailed unpaired *t*-test). [c] ED_{50} = approximate dose of compound that induces 50% normalization of glucose relative to the positive control (racemic englitazone). [d] See the Experimental Section.

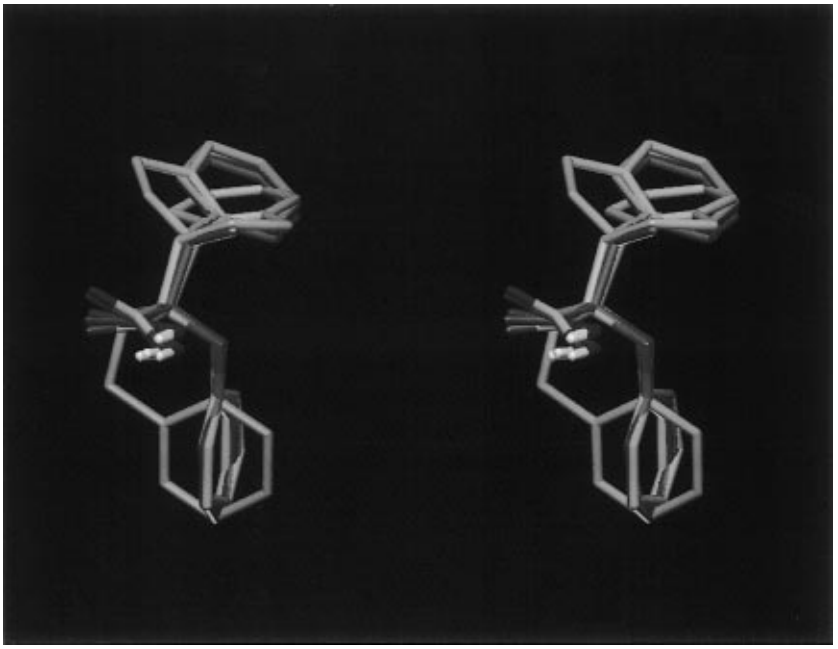


Figure 1. Overlap of **26** (blue), **84** (magenta), **99** (green), **100** (gray), and **101** (orange). The isopropyl and chloro substituents have been omitted. The stereodiagram was generated via the Sybyl[33] program.

modest decrease in food consumption observed with some of these compounds is not the cause of the hypoglycemia as shown by the pair-feeding experiment with **26**. Compounds **26, 33**, and **59** have been selected for further evaluation and profiling after chronic administration in the *ob/ob* mouse.

Experimental Section

Chemistry. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Mass spectra were obtained with a Hewlett Packard 5890 series II gas chromatograph with a 5971 mass selective detector or a Hewlett Packard 59980B particle beam LC/MS interface with a Hewlett Packard 5989A mass spectrometer. ^{1}H-NMR spectra were obtained on a Varian XL300 or a Bruker AC300 spectrometer with tetramethylsilane as internal standard. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory Inc. and agreed within 0.4% of calculated values unless otherwise noted in the tables.

General Method A. Preparation of 2-(4-Isopropylphenoxy)-3-phenylpropanoic Acid (1). To a suspension of 7.35

Table 7[a]

no. (n = no. of experiments)	conctn (μM)	[^{14}C]-2-deoxy-D-glucose uptake dpm/10 min	% basal	p value
basal ($n = 3$)		6 607 ± 285	100	
insulin ($n = 3$)	1	62 505 ± 2 790	946	***
insulin + CP-68,722 ($n = 3$)	1 and 30	69 762 ± 4 530	1056	***
26	30	19 227 ± 2 422	291	***
($n = 3$)	10	13 261 ± 1 701	200	***
	3	9 169 ± 1 717	139	NS
32	30	16 239 ± 551	246	***
($n = 1$)	10	12 797 ± 416	194	***
	3	8 642 ± 934	131	*
33	30	14 285 ± 1 183	216	***
($n = 1$)	10	7 166 ± 734	108	NS
	3	6 238 ± 618	94	NS
35	30	15 392 ± 902	233	***
($n = 2$)	10	6 598 ± 37	100	NS
	3	6 800 ± 760	103	NS
43	30	12 810 ± 2 643	193	*
($n = 2$)	10	7 765 ± 787	118	NS
	3	7 202 ± 440	109	NS
59	30	17 538 ± 1 954	265	***
($n = 2$)	10	11 824 ± 749	179	***
	3	8 455 ± 471	128	**

[a] Values are the mean ± SEM and percent of basal (unstimulated) rate of glucose transport observed. Data are from $n = 1-3$ independent experiments, each performed in triplicate; statistical analysis was performed by t-test for experimentals versus the basal control; significant differences: *$p \leq 0.05$, **$p \leq 0.01$, and ***$p \leq 0.001$.

Table 8. Effects of 100 μM **1**, **5**, **7**, **26**, and Racemic Englitazone (CP-68,722) on the Rates of Basal and Glucagon-Stimulated Gluconeogenesis in Isolated Rat Hepatocytes in Vitro[a]

no.	% basal inhibition	% GGN inhibition
1	41**	25
5	38*	3
7	32	20
26	36*	22
CP-68,722[b]	45**	59**

[a] Values are the mean percent inhibition of triplicate determinations compared to the basal (unstimulated) rate of gluconeogenesis in the absence (basal) or presence (GGN) of glucagon. Statistical analysis was performed by t-test for drug-treated vs basal (untreated) control in the absence and presence of glucagon. Significant differences: *$p < 0.05$, **$p < 0.01$. [b] CP-68,722 served as a positive control for antigluconeogenic effects as reported in ref 15.

Table 9. Summary of Data from Pair-Feeding Study with Compound **26** in *ob*/*ob* Mice[a]

group	basal glucose (mg/dL)	day 5 glucose (mg/dL)	net body wt Δ (g)	5 day food intake (g/5 mice/ 5 days)
vehicle	330 ± 16	368 ± 23	1.8 ± 0.14	178 ± 8
vehicle−food restricted	342 ± 7	390 ± 34	0.12 ± 0.37*	137 ± 0.2*
26 (5 mg/kg/ day)	341 ± 8	223 ± 8*,**	0.40 ± 0.15*	132 ± 2*

[a] Values are mean ± SEM ($n = 15$, except for food intake where $n = 3$ groups of 5 mice). *Significantly different from vehicle. **Significantly different from vehicle−food intake restricted ($p < 0.05$ by ANOVA with PLSD follow up).

g (0.184 mol) of 60% NaH in 150 mL of THF was added dropwise at 0 °C a solution of 25 g (0.184 mol) of 4-isopropylphenol in 200 mL of THF. The mixture was stirred at room temperature for 30 min, cooled to 0 °C, and treated dropwise with 18.03 mL (28.12 g, 0.184 mol) of methyl 2-bromoacetate. The reaction mixture was stirred at room temperature overnight and then evaporated. The residue was treated with H_2O and extracted with Et_2O. The organic layer was dried with Na_2SO_4 and evaporated and the residue distilled to give 27.97 g (73%) of methyl 2-(4-isopropylphenoxy)acetate: bp 160−8 °C/ 0.2 mmHg; MS (EI) *m/e* 208 (M); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 2.85 (m, 1H, CH), 3.8 (s, 3H, OMe), 4.6 (s, 2H, CH_2), 6.85 (d, 2H, H-2), 7.15 (d, 2H, H-3).

A flame-dried 3-neck round-bottom flask was charged with 5 mL of THF and 4.81 mL of 1 M lithium bis(trimethylsilyl)-amide in THF (Aldrich) and cooled to −78 °C. To this mixture was added dropwise a solution of 1.0 g (4.81 mmol) of methyl 2-(4-isopropylphenoxy)acetate in 10 mL of THF. After being stirred at −78 °C for 1 h, the mixture was treated dropwise with 0.57 mL (0.82 g, 4.8 mmol) of benzyl bromide at −78 °C and then allowed to come to room temperature overnight. The reaction mixture was treated with 1 equiv of AcOH and evaporated. The residue was dissolved in EtOAc, washed with 1 N HCl and H_2O, dried over Na_2SO_4, and chromatographed on silica gel with hexane/EtOAc (10:1) to give 0.45 g (31%) of methyl 2-(4-isopropylphenoxy)-3-phenylpropionate: MS (EI) *m/e* 298 (M).

This material was dissolved in 6 mL of dioxane, treated with 70 mg (1.1 equiv) of $LiOH \cdot H_2O$ in 3 mL of H_2O, and stirred at room temperature for 2 h. After evaporation, the residue was treated with H_2O, acidified, extracted with EtOAc, and dried over Na_2SO_4 to give 360 mg (84%) of 2-(4-isopropylphenoxy)-3-phenylpropanoic acid which crystallized from hexane: MS (FAB) *m/e* 285 (M + 1); NMR (DMSO-d_6) δ 1.15 (d, 6H, Me), 2.75 (m, 1H, CH) 3.15 (dd, 2H, CH_2), 4.45 (dd, 1H, H-α), 6.7 (d, 2H, H-2), 7.0 (d, 2H, H-3), 7.15 (m, 1H), 7.25 (t, 2H), 7.3 (m, 2H, aromatic H′).

General Method B. Preparation of 2-(4-Isopropylphenoxy)-3-[2-(trifluoromethyl)phenyl]propanoic Acid (2). To a suspension of 7.35 g (0.184 mol) of 60% NaH in 100 mL of THF was added dropwise at 0 °C 25 g (0.184 mol) of 4-isopropylphenol in 50 mL of THF. After 1 h at 0 °C, 15.85 mL of ethyl chloroacetate was added dropwise, and the mixture was allowed to come to room temperature and worked up as described above in general method A to give after distillation 20.65 g (51%) of ethyl 2-(4-isopropylphenoxy)acetate: bp 123−52 °C/0.2 mmHg; MS (EI) *m/e* 222 (M); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.3 (t, 3H, Me), 2.85 (m, 1H, CH), 4.25 (q, 2H, CH_2), 4.6 (s, 2H, CH_2), 6.8 (d, 2H, H-2), 7.15 (d, 2H, H-3).

A 10 g (45 mmol) sample of this material was dissolved in 20 mL of THF and treated with 1.8 g (45 mmol) of NaOH in 20 mL of H_2O. After stirring at room temperature overnight, the mixture was evaporated, the residue was taken into H_2O, acidified with 1 N HCl, and extracted with EtOAc to give after recrystallization from EtOAc/hexane 5.89 g (67%) of 2-(4-isopropylphenoxy)acetic acid: mp 84.5−6 °C; MS (FAB) *m/e* 194 (M).

A 3 g (15.5 mmol) sample of this material was treated with 288 mg (5 mmol) of boric acid and 1.65 g (18.5 mmol) of 2-amino-2-methylpropanol according to the procedure of Barton et al.[18] by refluxing in xylene overnight to give 3.15 g (82%) of 4,5-dihydro-4,4-dimethyl-2-(4-isopropylphenoxymethyl)-oxazole as an oil: MS (FAB) *m/e* 248 (M + H); NMR (DMSO-d_6) δ 1.2 (d, 6H, Me), 1.3 (s, 6H, Me), 2.85 (m, 1H, CH), 4.05 (s, 2H, CH_2), 4.65 (s, 2H, CH_2), 6.9 (d, 2H, H-2), 7.15 (d, 2H, H-3).

A 1 g (4.05 mmol) sample of this material in 20 mL of THF was treated at −78 °C with 1.78 mL (1.1 equiv) of 2.5 M BuLi and then after 1 h at −78 °C dropwise with 0.68 mL (1.06 g, 1.1 equiv) of 2-(trifluoromethyl)benzyl bromide. After 2 h at −78 °C the reaction mixture was worked up and chromatographed on silica gel with EtOAc/hexane (1:2) to give 863 mg (53%) of 4,5-dihydro-4,4-dimethyl-2-[2-(4-isopropylphenoxy)-3-[2-(trifluoromethyl)phenyl]ethyl]oxazole as an oil: MS (FAB) *m/e* 406 (M + H); NMR ($CDCl_3$) δ 1.15 (d, 6H, Me), 1.25 (s, 6H, Me), 2.8 (m, 1H, CH), 3.4−3.5 (m, 2H, CH_2), 4.05 (q, 2H, CH_2), 5.0 (q, 1H, CH-α), 6.75 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.45−7.6 (m, 4H, aromatic H′).

A 605 mg (1.6 mmol) sample of this material, dissolved in 15 mL of THF, was treated with 15 mL of 4.5 N aqueous HCl and kept at reflux overnight. After workup and chromatography on silica gel with EtOAc/hexane (1:1) containing 1%

AcOH, 259 mg (46%) of 2-(4-isopropylphenoxy)-3-[2-(trifluoromethyl)phenyl]propanoic acid was obtained as a colorless oil which did not crystallize: MS (FAB) *m/e* 353 (M + H); NMR ($CDCl_3$) δ 1.15 (d, 6H, Me), 2.8 (m, 1H, CH), 3.2−3.6 (m, 2H, CH_2), 4.7 (q, 1H, CH), 6.85 (d, 2H, H-2), 7.05 (d, 2H, H-3), 7.35−7.65 (m, 4H, aromatic H′). This material was converted by treatment with dicyclohexylamine in Et_2O to the dicyclohexylammonium salt: MS (FAB) *m/e* 534 (M + H).

General Method C. Preparation of 2-(4-Isopropylphenoxy)-3-[3-(trifluoromethyl)phenyl]propanoic Acid (3). A suspension of 1.47 g (37 mmol) of 60% NaH in 10 mL of THF was cooled to 0 °C and treated dropwise with 5 g (37 mmol) of 4-isopropylphenol in 20 mL of THF. After warming to room temperature and stirring for 30 min, 5.94 mL (7.15 g, 37 mmol) of diethyl chloromalonate was added dropwise over 30 min. The mixture was stirred for 2 h, poured into water, and extracted with Et_2O to give 9.51 g (88%) of diethyl 2-(4-isopropylphenoxy)malonate as a colorless oil: MS (FAB) *m/e* 294 (M + H); NMR ($CDCl_3$) δ 1.15 (d, 6H, Me), 1.25 (m, 6H, Me), 2.8 (m, 1H, CH), 4.3 (m, 4H, CH_2), 5.15 (s, 1H, H-α), 6.8 (d, 2H, H-2), 7.15 (d, 2H, H-3).

A 2 g (6.8 mmol) sample of this material in 10 mL of THF was added dropwise at 0 °C to a suspension of 0.27 g (6.8 mmol) of 60% NaH in 10 mL of THF. After the gas evolution ceased, 1.32 g (6.8 mmol) of 3-(trifluoromethyl)benzyl chloride was added dropwise at 0 °C. After standing overnight at room temperature, the reaction mixture was worked up and chromatographed on silica gel with hexane/EtOAc (10:1) to give 1.04 g (34%) of diethyl 2-(4-isopropylphenoxy)-2-[3-(trifluoromethyl)benzyl]malonate as an oil: MS (EI) *m/e* 452 (M); NMR ($CDCl_3$) δ 1.1−1.3 (m, 12H, Me), 2.85 (m, 1H, CH), 3.7 (s, 2H, CH_2), 4.15 (m, 4H, CH_2), 6.9 (d, 2H, H-2), 7.15 (d, 2H, H-3), 7.3−7.6 (m, 4H, aromatic H′).

A 390 mg (0.86 mmol) sample of this material was dissolved in 3 mL of dioxane, treated with 70 mg (1.75 mmol) of NaOH in 1 mL of H_2O, and stirred at room temperature overnight. After evaporation, addition of water, acidification with 1 N HCl, and extraction with EtOAc, 220 mg of a mixture of mono- and diacids was obtained, which was fully decarboxylated by heating for 10 min at 110 °C to give 2-(4-isopropylphenoxy)-3-[3-(trifluoromethyl)phenyl]propanoic acid as an oil: NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 2.85 (m, 1H, CH), 3.3 (q, 2H, CH_2), 4.85 (t, 1H, H-α), 6.8 (d, 2H, H-2), 7.15 (d, 2H, H-3), 7.4−7.55 (m, 4H, aromatic H′), 11.2 (bs, 1H, COOH); ^{19}F-NMR ($CDCl_3$) s at 63 ppm. Treatment with dicyclohexylamine in Et_2O gave 95 mg (20%) of the dicyclohexylammonium salt: MS (FAB) *m/e* 534 (M + H).

General Method D. Preparation of 3-(3-Chlorophenyl)-2-(4-isopropylphenoxy)propanoic Acid (6). A solution of 1 g (5.15 mmol) of (4-isopropylphenoxy)acetic acid (see general method B) in 10 mL of THF was cooled to −78 °C and treated dropwise with 6.87 mL (2 equiv) of 1.5 M LDA in THF. After stirring at −78 °C for 1h, 0.68 mL (1.06 g, 5.15 mmol) of 3-chlorobenzyl chloride was added dropwise. The reaction mixture was allowed to warm to room temperature overnight, poured into water, acidified with 1 N HCl, and evaporated to dryness. The residue was extracted with EtOAc and chromatographed on silica gel with hexane/EtOAc (1:1) containing 1% AcOH to give 3-(3-chlorophenyl)-2-(4-isopropylphenoxy)-propanoic acid: NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 2.85 (m, 1H, CH), 3.2 (d, 2H, CH_2), 4.8 (t, 1H, H-α), 6.8 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.2−7.4 (m, 4H, aromatic H′). Conversion to the dicyclohexylammonium salt gave 450 mg (17%): MS (FAB) *m/e* 500 (M + H).

General Method E. Preparation of 3-(4-Chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanoic Acid (26). A mixture of 65.26 g (0.479 mol) of 4-isopropylphenol and 72.79 g (0.527 mol) of K_2CO_3 in 100 mL of anhydrous DMF was treated dropwise under mechanical stirring with 62.23 mL of ethyl 2-bromopropionate at room temperature. The reaction mixture was then heated to 70 °C and kept at that temperature under stirring overnight. After cooling, the mixture was poured into 600 mL of water, the pH was adjusted to 6 with 2 N HCl, and the product was extracted with 2 × 250 mL of EtOAc. The organic extracts were washed with 5 N NaOH to remove excess phenol and with water, dried over $MgSO_4$, and filtered and the filtrate evaporated. The oily residue was distilled in a Kugelrohr apparatus at 0.5 mmHg to give 91.25 g (80%) of ethyl 2-(4-isopropylphenoxy)propionate: bp 90−115 °C; MS (EI) *m/e* 236 (M); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.24 (t, 3H, Me), 1.38 (d, 3H, α-Me), 2.85 (m, 1H, CH), 4.2 (q, 2H, CH_2), 4.7 (q, 1H, H-α), 6.8 (d, 2H, H-2), 7.1 (d, 2H, H-3).

A 4-neck 2 L round-bottom flask equipped with addition funnels, a mechanical stirrer, an internal thermometer, and a nitrogen inlet was flame-dried under nitrogen, allowed to cool to room temperature, and charged with 1 L of dry THF and 55.31 mL (47.51 g, 0.336 mol) of *N*-isopropylcyclohexylamine. The mixture was cooled to −78 °C and treated dropwise with 134.5 mL (0.336 mol) of 2.5 M *n*-butyllithium in hexane at such a rate that the internal temperature did not rise above −65 °C (this required about 40 min). After removal of the cooling bath the mixture was stirred for 1 h, allowed to come to room temperature, and then cooled again to −78 °C and treated dropwise over 30 min with a solution of 72.25 g (0.3057 mol) of ethyl 2-(4-isopropylphenoxy)propionate in 25 mL of THF, keeping the internal temperature below −70 °C. The reaction mixture was stirred at −78 °C for 20 min and then treated dropwise with a solution of 125.66 g (0.611 mol) of 4-chlorobenzyl bromide in 80 mL of THF, keeping the internal temperature below −70 °C. The reaction mixture was stirred overnight and allowed to come to room temperature, and the solvent was removed by evaporation in vacuo. The residue was treated with water, the pH was adjusted to 5−6 with 2 N HCl, and the mixture was extracted with EtOAc. The aqueous layer was saturated with NaCl and again extracted with EtOAc. The combined organic extracts were washed with water, dried over $MgSO_4$, and evaporated in vacuo to give 159.8 g of an oil which contained 54% of the desired ethyl 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropionate by GC/MS: MS (EI) *m/e* 360 (M); NMR of pure product ($CDCl_3$) δ 1.2 (m, 9H, Me), 1.4 (s, 3H, α-Me), 2.85 (m, 1H, CH), 3.1 and 3.3 (ABq, 2H, CH_2), 4.2 (q, 2H, CH_2), 6.75 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.25 (ABq, 4H, aromatic H′).

To a solution of 149.25 g (0.2233 mol) of this crude ester in 950 mL of EtOH was added 179 mL of 5 N NaOH, and the mixture was warmed to 60 °C for 4h. After cooling to room temperature, the EtOH was removed in vacuo, and the residue was partitioned between water and Et_2O. The aqueous phase was acidified with 6 N HCl to pH 1 and extracted twice with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated to give 18.7 g of a crystalline solid which was mostly the desired product by NMR. The Et_2O phase was shaken with 6 N HCl, dried over $MgSO_4$, and evaporated to 112 g of a solid which contained about 50% of desired product by NMR. Both solids were triturated with hexane to give a total of 68.96 g (92%) of clean (NMR) product. A recrystallization from cyclohexane gave 55.7 g (75%) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropionic acid: MS (CI) *m/e* 350 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.4 (s, 3H, α-Me), 2.85 (m, 1H, CH), 3.1 and 3.3 (ABq, 2H, CH_2), 6.8 (d, 2H, H-2), 7.2 (d, 2H, H-3), 7.25 (ABq, 4H, aromatic H′).

General Method F. Preparation of Sulfonimides: *N*-[3-(4-Chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanoyl]-2-methylbenzenesulfonamide (68). To a solution of 530 mg (1.59 mmol) of **26** in 30 mL of CH_2Cl_2 were added at 0 °C 291 mg (1.5 equiv) of 4-(dimethylamino)pyridine, 458 mg (1.5 equiv) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, and 273 mg (1 equiv) of 2-methylbenzenesulfonamide. After stirring for 15 min at 0 °C, the reaction mixture was allowed to stir at room temperature overnight, diluted with CH_2Cl_2, washed with aqueous citric acid and brine, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc/hexane (35:65) to give 551 mg (71%) of *N*-[3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanoyl]-2-methylbenzenesulfonamide. After crystallization form hexane was obtained 346 mg (45%): MS (CI) *m/e* 504 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.36 (s, 3H, α-Me), 2.26 (s, 3H, 2″-Me), 2.88 (m, 1H, CH), 3.03 (ABq, 2H, CH_2), 6.8 (d, 2H, H-2), 7.1 (d, 2H, H-3), 6.94 and 7.06 (ABq, 4H, aromatic H′), 7.28 (d, 1H, H-3″), 7.39 (t, 1H, H-5″), 7.56 (t, 1H, H-4″), 8.14 (d, 1H, H-6″), 9.0 (bs, 1H, NH).

General Method G. Preparation of *N*-[3-(4-Chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropyl]trifluoromethanesulfonamide (71). A 10.17 g (75 mmol) sample of 4-isopropylphenol was converted with 10 g (75 mmol) of 2-bromopropionitrile and 11.35 g of K_2CO_3 in 25 mL of DMF, in analogy to the procedure described in General Method E, to 10.25 g (73%) of 2-(4-isopropylphenoxy)propionitrile: MS (EI) *m/e* 189 (M); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.7 (d, 3H, α-Me), 2.84 (m, 1H, CH), 4.84 (q, 1H, CH), 6.9 (d, 2H, H-2), 7.16 (d, 2H, H-3).

A 4.31 g (22.8 mmol) sample of this material was treated with 1.1 equiv of LICA and 1.1 equiv of 4-chlorobenzyl bromide according to the procedure described in General Method E to give 4.78 g (67%) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropionitrile: MS (EI) *m/e* 313 (M); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.5 (s, 3H, α-Me), 2.88 (m, 1H, CH), 3.2 (ABq, 2H, CH_2), 7.0 (d, 2H, H-2), 7.14 (d, 2H, H-3), 7.2 (ABq, 4H, aromatic H′).

A solution of 4.78 g (15 mmol) of this material in 25 mL of THF was cooled to 0 °C, treated dropwise with 61 mL (4 equiv) of 1 M BH_3 in THF, and then allowed to come to room temperature and stirred overnight. Another 25 mL of BH_3 in THF was then added, and the mixture was refluxed for 4h and then cooled to 0 °C, and treated with 6 N HCl. The solvent was stripped, the residue treated with water and made alkaline with 2 N NaOH. The product was extracted with EtOAc and chromatographed on silica gel to give 2.58 g (53%) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanamine: MS (CI) *m/e* 318 (M + H); NMR ($CDCl_3$) δ 1.25 (d, 6H, Me), 1.1 (s, 3H, α-Me), 1.55 (bs, 2H, NH_2), 2.65 (ABq, 2H, CH_2), 2.8 (m, 1H, CH), 2.95 (ABq, 2H, CH_2), 6.8 (d, 2H, H-2), 7.0 (d, 2H, H-3), 7.24 (ABq, 4H, aromatic H′).

A 301 mg (0.95 mmol) sample of this material was dissolved in 10 mL of CH_2Cl_2, cooled to −78 °C, and treated with 0.16 mL (116 mg, 1.2 equiv) of triethylamine and 0.175 mL (294 mg, 1.1 equiv) of trifluoromethanesulfonic anhydride. The mixture was allowed to stir at −78 °C for 45 min, poured over ice, and worked up to give 350 mg (82%) of *N*-[3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropyl]trifluoromethanesulfonamide: MS (CI) *m/e* 467 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.1 (s, 3H, α-Me), 2.9 (m, 1H, CH), 2.92−3.04 (ABq, 2H, CH_2), 3.3−3.44 (ABq, 2H, benzylic CH_2), 5.4 (bs, 1H, NH), 6.8 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.2 (ABq, 4H, aromatic H′). This material was converted with NaOH in EtOH to the crystalline sodium salt.

2-(4-Chlorophenyl)-2-(4-isopropylphenoxy)acetic Acid (19). A 5 g sample of *dl*-4-chloromandelic acid was converted to 2-bromo-2-(4-chlorophenyl)acetic acid according to the method of Gotthardt et al.[19] to give 4.03 g (60%): MS (EI) *m/e* 249 (M); NMR ($CDCl_3$) δ 5.3 (s, 1H), 7.4 (d, 2H), 7.5 (d, 2H).

A 3 g (12 mmol) sample of this material was esterified with MeOH/HBr to give 3.04 g (86%) of crude methyl 2-bromo-2-(4-chlorophenyl)acetate. A 1 g (3.8 mmol) sample of this material was treated with 0.52 g (3.8 mmol) of 4-isopropylphenol and 0.17 g (3.8 mmol) of 60% NaH as described in General Method A to give 1.04 g (86%) of methyl 2-(4-chlorophenyl)-2-(4-isopropylphenoxy)acetate: MS (EI) *m/e* 318 (M).

This material was saponified with 165 mg (1.2 equiv) of $LiOH \cdot H_2O$ in 8 mL of THF and 8 mL of H_2O at room temperature overnight to give after recrystallization from EtOAc/hexane 230 mg (23%) of 2-(4-chlorophenyl)-2-(4-isopropylphenoxy)acetic acid: MS (FAB) *m/e* 304 (M + H); NMR ($CDCl_3$) δ 1.2−1.3 (m, 6H, Me), 2.85 (m, 1H, CH), 5.6 (s, 1H, CH), 6.85 (d, 2H, H-2), 7.15 (d, 2H, H-3), 7.35 (d, 2H) and 7.5 (d, 2H) (aromatic H′).

4-(4-Chlorophenyl)-2-(4-isopropylphenoxy)butanoic Acid (20). A 410 mg (1.34 mmol) sample of 2-bromo-4-(4-chlorophenyl)butyrate, obtained by the method of Dice and Bowden[20] by alkylation of diethyl malonate with 2-(4-chlorophenyl)ethyl chloride in the presence of NaOEt in EtOH followed by monosaponification with KOH to the potassium salt followed by treatment with Br_2 in CCl_4, was converted with 53 mg of 60% NaH and 182 mg of 4-isopropylphenol as described in General Method A to 200 mg (41%) of ethyl 4-(4-chlorophenyl)-2-(4-isopropylphenoxy)butyrate: MS (EI) *m/e* 360 (M); NMR ($CDCl_3$) δ 1.2−1.3 (m, 9H, Me), 2.1−2.4 (m, 2H, CH_2), 2.6−2.9 (m, 3H, CH, benzylic CH_2), 4.15 (q, 2H, O-CH_2), 4.5 (dd, 1H, (α-H), 6.8 (d, 2H, H-2), 7.15 (m, 4H, aromatic H′), 7.2 (d, 2H, H-3).

This material was saponified with 28 mg of $LiOH \cdot H_2O$ in 5 mL of dioxane and 5 mL of water at room temperature overnight to give 12 mg (4.2%) of 4-(4-chlorophenyl)-2-(4-isopropylphenoxy)butanoic acid as the dicyclohexylammonium salt: MS (FAB) *m/e* 332 (M); NMR ($CDCl_3$) δ 1.25 (d, 6H, Me), 2.2−2.3 (m, 2H, CH_2), 2.7−2.9 (m, 3H, CH, benzylic CH_2), 4.55 (dd, 1H, α-H), 6.8 (d, 2H, H-2), 7.2 (d, 2H, H-3), 7.15 (ABq, 4H, aromatic H′).

7-(4-Chlorophenyl)-2-(4-isopropylphenoxy)heptanoic Acid (21). This compound was prepared in analogy to the synthesis of **20** by alkylation of diethyl malonate with 5-(4-chlorophenyl)pentyl bromide in K_2CO_3/DMF, saponification to the monopotassium salt with KOH/EtOH, treatment with Br_2/AcOH and K_2CO_3/THF according to the procedure of Goel and Krolls,[21] reaction with 4-isopropylphenol and NaH, and saponification with 1 N NaOH in MeOH: MS (CI) *m/e* 392 (M + NH_4); NMR (DMSO-d_6) δ 1.1 (d, 6H, Me), 1.25 (m, 2H, CH_2), 1.4 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.55 (t, 2H, benzylic CH_2), 2.75 (m, 1H, CH), 4.0 (dd 1H, α-H), 6.65 (d, 2H, H-2), 7.0 (d, 2H, H-3), 7.15 (d, 2H) and 7.25 (d, 2H) aromatic H′).

Resolution of 26 into Its Enantiomers 27 and 28. A 1 g (3 mmol) sample of **26** was dissolved in 5 mL of Et_2O and treated with a solution of 0.365 g (3 mmol) of (*S*)-α-methylbenzylamine in 5 mL of Et_2O. The solution was stripped and the residue recrystallized seven times from hexane when no further resolution could be observed by NMR. Conversion of this salt to the free acid and recrystallization from hexane gave 180 mg (36%) of the *d* isomer of **26**: mp 114−5 °C; $[\alpha]_D$ + 15.1° (*c* = 1, MeOH). Similarly, resolution of a 1 g sample of **26** with (*R*)-α-methylbenzylamine gave 93 mg (18%) of the *l* isomer of **26** (mp 114−6 °C) after recrystallization from hexane: $[\alpha]_D$ −16.7° (*c* = 1, MeOH).

3-[4-[2-[(5-Chloro-2-methoxybenzoyl)amino]ethyl]-phenyl]-2-(4-isopropylphenoxy)-2-methylpropanoic Acid (47). A 1.46 g (4 mmol) sample of ethyl 3-[4-(cyanomethyl)-phenyl]-2-(4-isopropylphenoxy)-2-methylpropanoate, prepared as in General Method E from 4-(cyanomethyl)benzyl bromide, was reduced with $NaBH_4/CF_3COOH$ to give 668 mg (44%) of ethyl 3-[4-(2-aminoethyl)phenyl]-2-(4-isopropylphenoxy)-2-methylpropanoate: MS (CI) *m/e* 370 (M + H); NMR ($CDCl_3$) δ 1.2−1.3 (m, 9H, Me), 1.4 (s, 3H, α-Me), 1.6 (bs, 2H, NH_2), 2.7 (t, 2H, CH_2), 2.8 (m, 1H, CH), 2.95 (t, 2H, benzylic CH_2), 3.2 (ABq, 2H, CH_2), 4.2 (q, 2H, CH_2), 6.75 (d, 2H, H-2), 7.05 (d, 2H, H-3), 7.15 (ABq, 4H, (aromatic H′).

This material was condensed with 0.33 g (1 equiv) of 5-chloro-2-methoxybenzoic acid, 0.52 g (1.5 equiv) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, and 0.33 g (1.5 equiv) of 4-(dimethylamino)pyridine in CH_2Cl_2 at 0 °C to give after workup 0.51 g (52%) of ethyl 3-[4-[2-[(5-chloro-2-methoxybenzoyl)amino]ethyl]phenyl]-2-(4-isopropylphenoxy)-2-methylpropanoate: MS (CI) *m/e* 538 (M + H); NMR ($CDCl_3$) δ 1.2 (m, 9H, Me), 1.4 (s, 3H, α-Me), 2.82 (m, 1H, CH), 2.9 (t, 2H, benzylic CH_2), 3.2 (ABq, 2H, CH_2), 3.7 (m, 5H, Me, CH_2), 4.2 (q, 2H, CH_2), 6.7 (d, 2H, H-2), 6.8 (d, 1H, H-3″), 7.0 (d, 2H, H-3), 7.2 (ABq, 4H, aromatic H′), 7.3 (dd 1H, H-4″), 7.8 (bs, 1H, NH), 8.1 (d, 1H, H-6″).

This material was saponified as described in General Method E to give after crystallization from benzene the desired acid in 58% yield: MS (CI) *m/e* 510 (M + H); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.4 (s, 3H, α-Me), 2.8 (m, 3H, CH, benzylic CH_2), 3.2 (ABq, 2H, CH_2), 3.7 (m, 5H, Me, CH_2), 6.8 (m, 3H, H-2, H-3″), 7.04 (d, 2H, H-3), 7.2 (ABq, 4H, aromatic H′), 7.3 (dd, 1H, H-4″), 7.85 (bs, 1H, NH), 8.1 (d, 1H, H-6″).

Preparation of 4-(4-Hydroxyphenyl)-4*H*-tetrahydrothiopyran and 4-(4-Hydroxyphenyl)-4*H*-2,3-dihydrothiopyran (Starting Material for 55). A 60 g (0.347 mol) sample of 4-bromophenol was converted to its *tert*-butyldimethylsilyl ether by the method of Kendall et al.[22] A 74.18 g (0.258 mol) sample of this ether was then treated with 6.277 g (1 equiv) of Mg in THF to form the Grignard reagent, which was allowed to react with 20 g (0.1721 mol) of tetrahydropyran-4-one. The crude adduct was isolated and heated at reflux

with 200 mL of MeOH and 57 mL of 12 N HCl for 1.5 h to give, after recrystallization from diisopropyl ether, 25.86 g (78%) of 4-(4-hydroxyphenyl)-4*H*-2,3-dihydrothiopyran: mp 100−2 °C dec; MS (EI) *m/e* 192 (M); NMR ($CDCl_3$) δ 2.66 (m, 2H, CH_2-S), 2.88 (m, 2H, CH_2), 3.34 (m, 2H, allylic CH_2-S), 6.88 (m, 1H, vinyl-CH), 6.80 (d, 2H, H-3), 7.2 (d, 2H, H-2).

A 5.25 g (27.3 mmol) sample of this material was hydrogenated in EtOH over 5% $Pd/BaSO_4$ in a Parr shaker at 46 psi. This hydrogenation required 1 week with five changes of fresh catalyst. We ultimately obtained 3.0 g (57%) of 4-(4-hydroxyphenyl)-4*H*-tetrahydrothiopyran as a tan solid, 95% pure by GC/MS: MS (EI) *m/e* 194 (M); NMR ($CDCl_3$) δ 1.7 (m, 2H), 2.0 (m, 2H), 2.4 (m, 1H), 2.6 (m, 2H), 2.8 (m, 2H), 6.88 (m, 1H, vinyl-CH), 6.67 (d, 2H, H-3), 7.0 (d, 2H, H-2).

Preparation of 4-(4-Hydroxyphenyl)-4*H*-2,3-dihydrobenzothiopyran (Starting Material for 56 and 60). A 20.99 g (73 mmol) sample of 4-bromo[(*tert*-butyldimethylsilyl)-oxy]benzene (prepared as described above) was allowed to react with 1.77 g (73 mmol) of Mg in THF and then with 10 g (60 mmol) of thiochroman-4-one. The crude reaction product was isolated and stirred at room temperature with 150 mL of MeOH and 12 mL of 12 N HCl to give after chromatography on silica gel with CH_2Cl_2 containing 2% MeOH 10.25 g (70%) of 4-(4-hydroxyphenyl)-2*H*-benzothiopyran: MS (EI) *m/e* 240 (M); NMR ($CDCl_3$) δ 3.4 (d, 2H, CH_2-S), 4.94 (d, 1H, OH), 6.0 (t, 1H, vinyl-CH), 6.7 (d, 2H), 6.8 (d, 2H), 7.0 (m, 1H), 7.12 (m, 1H), 7.3 (d, 2H).

A 7.3 g (30 mmol) sample of this material was hydrogenated in a Parr shaker at 46 psi over 5% $Pd/BaSO_4$ in THF for 3 days with three changes of fresh catalyst to give, after chromatography on silica gel with hexane containing 20% THF and 2% AcOH, 3.93 g (53%) of 4-(4-hydroxyphenyl)-4*H*-2,3-dihydrobenzothiopyran: MS (EI) *m/e* 242 (M); NMR ($CDCl_3$) δ 2.22 (m, 2H, CH_2), 2.82 (m, 2H, CH_2-S), 4.10 (t, 1H, CH), 6.68 (d, 2H), 6.8−6.9 (m, 3H, 7.0 t, 1H), 7.08 (m, 1H), 7.14 (d, 1H).

Preparation of 3-(4-Chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanol (70). To a solution of 3.07 g (9.24 mmol) of **26** in 30 mL of THF was added dropwise 18.48 mL (2 equiv) of 1 M BH_3 in THF. After stirring overnight, the THF was stripped, the residue was treated with 6 N HCl at 0 °C, and the product was extracted with EtOAc. The organic layer was washed with water, concentrated, and chromatographed on silica gel with EtOAc/hexane (1:4) to give 1.87 g (63%) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanol as an oil: MS (CI) *m/e* 336 (M + NH_4); NMR ($CDCl_3$) δ 1.0 (s, 3H, α-Me), 1.2 (d, 6H, Me), 2.9 (m, 1H, CH), 3.2 (ABq, 2H, benzylic CH_2), 6.8 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.2 (ABq, 4H, aromatic H′).

Preparation of 5-[2-(4-Chlorophenyl)-1-(4-isopropylphenoxy)-1-methylethyl]tetrazole (73). A mixture of 745 mg (2.38 mmol) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropionitrile (see general method G), 170 mg (2.62 mmol) of NaN_3, 140 mg (2.62 mmol) of NH_4Cl, and 7.5 mL of DMF was heated to 110 °C for 16 h. Another 80 mg of NH_4Cl was added in 20 mg portions every few hours. The reaction mixture was cooled to room temperature, treated with water, and extracted several times with EtOAc. The organic extracts were washed with water and brine, dried, and stripped to give 230 mg (27%) of crude product. After preparative TLC chromatography on silica gel with CH_2Cl_2 containing 5% AcOH and 2% MeOH and crystallization from cyclohexane was obtained 50 mg (6%) of pure 5-[2-(4-chlorophenyl)-1-(4-isopropylphenoxy)-1-methylethyl]tetrazole: MS (CI) *m/e* 374 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.8 (s, 3H, α-Me), 2.8 (m, 1H, CH), 3.35 (ABq, 2H, benzylic CH_2), 6.55 (d, 2H, H-2), 7.05 (ABq, 4H, aromatic H′), 7.15 (d, 2H, H-3).

Preparation of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanoyl]guanidine (74). A 1 g (43 mmol) sample of Na was dissolved in 50 mL of absolute EtOH, 4.19 g (43 mmol) of guanidine hydrochloride was added, and the mixture was stirred at room temperature for 30 min. After addition of 3.17 g (8.8 mmol) of ethyl 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropionate (see general method E), the mixture was heated to 60 °C overnight. The solvent was stripped and the residue treated with water and extracted with $CHCl_3$. Chromatography on silica gel with EtOAc containing 20% hexane and 2.5% MeOH gave 1.09 g (33%) of [3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanoyl]-guanidine: MS (CI) *m/e* 374 (M + H); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.3 (s, 3H, α-Me), 2.8 (m, 1H, CH), 3.1 (ABq, 2H, benzylic CH_2), 4.1 (bs, 1H, NH), 6.7 (m, 3H, H-2, NH), 6.9−7.1 (m, 4H, H-3, NH), 7.2 (ABq, 4H, aromatic H′). This material was converted to its hydrochloride by treatment with HCl gas in Et_2O and recrystallized from EtOAc/hexane.

Preparation of Calcium Mono-3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropyl Phosphate (75). A solution of 500 mg (1.57 mmol) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanol (**70**) and 0.219 mL (158 mg, 1.57 mmol) of triethylamine in 6 mL of CH_2Cl_2 was cooled to 0 °C, treated dropwise with 0.144 mL (241 mg, 1.57 mmol) of $POCl_3$, and stirred at room temperature for 2h. The solvent was stripped; the residue was dissolved in THF, treated with 1 mL of 6 N HCl, and stirred for 3 days at room temperature. The solvent was then stripped, and the crude product [559 mg, 89%; MS (CI) *m/e* 301 (M − PO_4H_2); NMR ($CDCl_3$) δ 1.1 (bs, 3H, α-Me), 1.2 (d, 6H, Me), 2.8 (m, 1H, CH), 3.0 (bs, 2H, benzylic CH_2), 3.6 (t, 2H, O-CH_2), 3.9 (bs, 1H, OH), 4.04 (bs, 1H, OH), 6.8 (bd, 2H, H-2), 7.1 (bd, 2H, H-3), 7.2 (bs, 4H, aromatic H′)] was dissolved in 20 mL of THF and added dropwise to a suspension of 59 mg (1 equiv) of CaH_2 in THF. After stirring at room temperature for 4h, the solvent was stripped and the residue recrystallized from MeOH to give a first crop of 50 mg of calcium mono-3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropyl phosphate: NMR MeOH-d_4) δ 1.1 (bs, 3H, α-Me), 1.28 (d, 6H, Me), 2.9 (m, 1H, CH), 3.1 (bs, 2H, benzylic CH_2), 3.9 (bd, 2H, O-CH_2), 7.0 (bs, 2H, H-2), 7.2 (bs, 2H, H-3), 7.4 (d, 4H, aromatic H′).

Preparation of 3-(4-Chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanoic Acid Amidoxime (76). This compound was prepared by the method of Ellingboe et al.[23] To a solution of 104 mg (1.5 mmol) of hydroxylamine hydrochloride in 2.5 mL of MeOH was added 1.28 mL of a 1.17 M solution of NaOMe in MeOH at 0 °C followed by dropwise addition of 470 mg (1.5 mmol) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropionitrile (see general method G). The mixture was stirred at room temperature for 48 h and filtered and the filtrate evaporated to give after flash chromatography on silica gel with CH_2Cl_2 containing 2% MeOH 250 mg (48%) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpropanoic acid amidoxime as a foam: MS (EI) *m/e* 287 (M − C(NOH)NH_2); NMR ($CDCl_3$) δ 1.25 (dd, 6H, Me), 1.4 (s, 3H, α-Me), 2.85 (m, 1H, CH), 3.0−3.3 (m, 2H, benzylic CH_2), 4.82 (bs, 1H), 5.65 (bs, 0.35H), 6.45 (bs, 0.5H), 6.75 (d, 2H, H-2), 7.05 (d, 2H, H-3), 7.24 (ABq, 4H, aromatic H′), 7.35 (bs, 0.5H); 3:1 mixture of *Z* and *E* isomers.

Preparation of Hydroxymethyl 2-(4-Chlorophenyl)-1-(4-isopropylphenoxy)-1-methylethyl Ketone (77). A 1.2 g sample of **26** was converted to its acid chloride by refluxing with 1.3 mL (2.12 g, 18 mmol) of $SOCl_2$ and 20 mL of $CHCl_3$ for 4 h. The solvent was stripped and the residue azeotroped three times with benzene. The residue was dissolved in 25 mL of Et_2O and added in portions to a solution of diazomethane in Et_2O (obtained from 1.6 g (10.8 mmol) of 1-methyl-3-nitro-1-nitrosoguanidine, 100 mL of 1 N NaOH, and 100 mL of Et_2O; dried with K_2CO_3). After 10 min the solvent was evaporated and the residue flash-chromatographed on silica gel with CH_2Cl_2/hexane (1:1) to give 0.75 g (64%) of the diazo ketone: MS (EI) *m/e* 356 (M); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.3 (s, 3H, α-Me), 2.85 (m, 1H, CH), 3.0 and 3.1 (ABq, 2H, benzylic CH_2), 5.3 (s, 0.5H), 5.7, (s, 0.5H), 6.78 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.25 (ABq, 4H aromatic H′).

A 495 mg (1.39 mmol) sample of this material was dissolved in 40 mL of Et_2O and treated with 16 mL of HBr-saturated Et_2O. After nitrogen evolution ceased, the solvent was stripped and the residue azeotroped with benzene to give the bromomethyl ketone as a pale yellow syrup: MS (EI) *m/e* 408, 410 (M); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.4 (s, 3H, α-Me), 2.85 (m, 1H, CH), 3.0 and 3.25 (ABq, 2H, benzylic CH_2), 4.05 and 4.35 (ABq, 2H, CH_2-Br), 6.75 (d, 2H, H-2), 7.15 (ABq, 4H, aromatic H′), 7.25 (d, 2H, H-3).

This material was combined with 136 mg (1.38 mmol) of KOAc in 5 mL of EtOH and heated to 80 °C overnight. The solvent was stripped and the residue flash-chromatographed on silica gel with CH_2Cl_2/hexane to give 250 mg (46%) of the acetoxymethyl ketone: MS (EI) *m/e* 388 (M); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.35 (s, 3H, α-Me), 2.15 (s, 3H, Me-CO), 2.85 (m, 1H, CH), 3.05 and 3.25 (ABq, 2H, benzylic CH_2), 5.35 and 5.65 (ABq, 2H, CH_2-O), 6.75 (d, 2H, H-2), 7.15 (ABq, 4H, aromatic H′), 7.35 (d, 2H, H-3).

A 137 mg (0.35 mmol) sample of this material was dissolved in 7 mL of MeOH, cooled to 0 °C, and treated with 23 mg (0.35 mmol) of KCN. After stirring for 30 min at 0 °C, 12 drops of AcOH was added followed by 100 mL of CH_2Cl_2 and 50 mL of water. The organic phase was collected, dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC on silica gel with Et_2O/hexane (1:1) to give 70 mg (57%) of hydroxymethyl 2-(4-chlorophenyl)-1-(4-isopropylphenoxy)-1-methylethyl) ketone as a syrup: MS (CI) *m/e* 364 (M + NH_4); NMR ($CDCl_3$) δ 1.25 (d, 6H, Me), 1.35 (s, 3H, α-Me), 2.7−2.9 (m, 2H, CH, OH), 3.05 and 3.25 (ABq, 2H, benzylic CH_2), 4.3−4.75 (m, 2H, CH_2-O), 6.75 (d, 2H, H-2), 7.15 (d, 4H, aromatic H′), 7.25 (d, 2H, H-3).

Preparation of 3-(4-Chlorophenyl)-2-ethyl-2-(4-isopropylphenoxy)propanoic Acid (81). This compound was prepared in analogy to General Method E, using ethyl α-bromobutyrate as starting material. In the final saponification step, NaOH or LiOH failed to hydrolyze the ester. However, when a 1.5 g (4 mmol) sample of ethyl 3-(4-chlorophenyl)-2-ethyl-2-(4-isopropylphenoxy)propanoate was dissolved in 40 mL of EtOH and treated with 8 of mL 2 N KOH and kept at reflux for 48 h, 865 mg (56%) of 3-(4-chlorophenyl)-2-ethyl-2-(4-isopropylphenoxy)propanoic acid was obtained after the usual workup and flash chromatography with Et_2O/hexane (1:1): MS (CI) *m/e* 364 (M + NH_4); NMR (DMSO-d_6): δ 0.75 (t, 3H, Me), 1.15 (d, 6H, Me), 1.5 (q, 2H, α-CH_2), 2.8 (m, 2H, CH), 3.2 (ABq, 2H, benzylic CH_2), 6.8 (d, 2H, H-2), 7.0 (d, 2H, H-3), 7.1 and 7.2 (ABq, 4H, aromatic H′). This material was converted to the Na salt with NaOH in MeOH.

Preparation of 3-(4-Chlorophenyl)-2-(4-isopropylphenoxy)butanoic Acid (82, 83). A 26.7 g (0.17 mol) batch of α-methyl-4-chlorobenzyl alcohol was dissolved in benzene, cooled to 0 °C, and treated with HBr gas for 40 min. The upper phase was collected, dried over $MgSO_4$, and evaporated to give 28.31 g (76%) of α-methyl-4-chlorobenzyl bromide. A 18.83 g (81 mmol) batch of this material was used to alkylate 6 g (27 mmol) of ethyl 2-(4-isopropylphenoxy)acetate according to general method E to give after chromatography on silica gel with hexane and rechromatography with hexane/THF (10:1) 593 mg (6%) of ethyl 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)butanoate: MS (EI) *m/e* 360 (M); NMR ($CDCl_3$) δ 1.1−1.25 (m, 9H, Me), 1.38 (d) and 1.42 (d, 3H) (β-Me), 2.8 (m, 1H, CH), 3.36 (m, 1H, β-CH), 4.0−4.2 (m, 2H, O-CH_2), 4.51 (d) and 4.56 (d, 1H) (α-CH), 6.7 (d, 2H, H-2), 7.05 (d, 2H, H-3), 7.24 (s, 4H, aromatic H′).

After saponification with NaOH in EtOH according to general method E was obtained 455 mg (83%) of crude product. Purification by preparative TLC with EtOAc/hexane (1:1) gave 196 mg of pure 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-butanoic acid as a mixture of diastereomers. Crystallization from pentane gave 81 mg of diastereomer A (**82**): MS (CI) *m/e* 350 (M + NH_4); NMR ($CDCl_3$) δ 1.18 (d, 6H, Me), 1.42 (d, 3H, β-Me), 2.83 (m, 1H, CH), 3.4 (m, 1H, β-CH), 4.65 (d, 1H, α-CH), 6.76 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.26 (s, 4H, aromatic H′). The mother liquor of this crop [96 mg; MS (CI) *m/e* 350 (M + NH_4); NMR ($CDCl_3$) δ 1.18 (d, 6H, Me), 1.46 (d, 3H, β-Me), 2.83 (m, 1H, CH), 3.4 (m, 1H, β-CH), 4.62 (d, 1H, (α-CH), 6.71 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.26, (s, 4H, aromatic H′)] was converted to the Na salt of **83** with NaOMe in MeOH.

Preparation of 3-(4-Chlorophenyl)-2-(4-isopropylphenoxy)-2-methylbutanoic Acid (84, 85). A 14.2 g (64.7 mmol) sample of α-methyl-4-chlorobenzyl bromide (see preparation of **82**, **83** above) was used to alkylate 5.12 g (21.7 mmol) of ethyl 2-(4-isopropylphenoxy)propanoate with 1.05 equiv of LICA according to general method E to give after chromatography on silica gel with hexane followed by hexane/CH_2Cl_2 (1:1) 4.89 g (60%) of ethyl 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylbutanoate: GC/MS 41:56 mixture of diastereomers; MS (EI) *m/e* 374 (M); NMR ($CDCl_3$) δ 1.18 (d, 6H, Me), 1.2 (t) and 1.25 (t, 3H) Me), 1.21 (s) and 1.31 (s, 3H) α-Me), 1.37 (d) and 1.43 (d, 3H) (β-Me), 2.83 (m, 1H, CH), 3.26 (d) and 3.36 (d, 1H) (β-CH), 4.11 (q) and 4.2 (q, 2H) (O-CH_2), 6.68 (d) and 6.75 (d, 2H) H-2), 7.01 (d, 2H, H-3), 7.25 (ABq, 4H, aromatic H′).

Attempts to saponify this material with NaOH or LiOH or under acidic conditions with H_2SO_4 or AcOH/HCl failed, giving little or no product and side reactions. However, a 1.8 g (4.8 mmol) sample of this material was saponified successfully by the method of Gassman and Schenk[24] by adding a solution in 10 mL of Et_2O to a slurry of 8.68 g of KO*t*-Bu in 70 mL of Et_2O and 0.2 mL of water and stirring at room temperature overnight. The mixture was cooled to 0 °C, 150 mL of water was added, and the phases were separated. The aqueous phase was acidified with 12 N HCl and extracted twice with CH_2Cl_2 to give 930 mg (56%) of 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylbutanoic acid as a 60:40 mixture of diastereomers: GC/MS (CI) *m/e* 364 (M + NH_4). Fractional crystallization from benzene/hexane gave 200 mg (12%) of diastereomer A (**84**): MS (CI) *m/e* 364 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.23 (s, 3H, α-Me), 1.49 (d, 3H, β-Me), 2.83 (m, 1H, CH), 3.27 (d, 1H, β-CH), 6.78 (d, 2H, H-2), 7.06 (d, 2H, H-3), 7.3 (ABq, 4H, aromatic H′); X-ray analysis showed this compound to have the *RS*/*SR* configuration. Crystallization of the mother liquor from Et_2O/hexane gave 281 mg (17%) of the other diastereomer (B, **85**): MS (CI) *m/e* 364 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.32 (s, 3H, α-Me), 1.42 (d, 3H, β-Me), 2.8 (m, 1H, CH), 3.26 (d, 1H, β-CH), 6.74 (d, 2H, H-2), 7.03 (d, 2H, H-3), 7.2 (ABq, 4H, aromatic H′).

Preparation of 3-(4-Chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpentanoic Acid (86, 87). A sample of 4-chloropropiophenone was reduced with $NaBH_4$ in MeOH and converted with HBr gas into the bromide in analogy to the method described above in the preparation of **82**, **83**. This material was used to prepare ethyl 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)-2-methylpentanoate by general method E. Saponification was carried out with KO*t*-Bu as described above for **84**, **85** to give 824 mg of a mixture of diastereomers: GC/MS (CI) *m/e* 378 (M + NH_4). Fractional crystallization from hexane gave 93 mg of diastereomer A (**86**): MS (CI) *m/e* 378 (M + NH_4); NMR ($CDCl_3$) δ 0.75 (t, 3H, Me), 1.2 (m, 9H, *i*-Pr-Me, α-Me), 1.9−2.2 (m, 2H, CH_2), 2.85 (m, 1H, CH), 3.0 (dd, 1H, β-CH), 6.85 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.33 (s, 4H, aromatic H′); tentatively assigned the *RS*/*SR* configuration in analogy with **84**. Also obtained was 568 mg of diastereomer B (**87**): MS (CI) *m/e* 378 (M + NH_4); NMR ($CDCl_3$) δ 0.8 (t, 3H, Me), 1.2 (d, 6H, *i*-Pr-Me), 1.4 (s, 3H, α-Me) 1.9−2.0 (m, 2H, CH_2), 2.85 (m, 1H, CH), 3.0 (dd, 1H, β-CH), 6.8 (d, 2H, H-2), 7.1 (d, 2H, H-3), 7.28 (s, 4H, aromatic H′).

Preparation of 3-(4-Chlorophenyl)-2-(4-isopropylbenzyl)-2-methylpropanoic Acid (93). A 2.5 g (24.5 mmol) sample of ethyl propanoate was alkylated with LICA and 4-chlorobenzyl bromide according to general method E to give 2.54 g (46%) of ethyl 3-(4-chlorophenyl)-2-methylpropanoate: MS (EI) *m/e* 226 (M); NMR ($CDCl_3$) δ 1.1−1.3 (m, 6H, Me), 2.6−2.75 (m, 2H, benzylic CH_2), 2.9−3.1 (m, 1H, α-CH), 4.15 (q, 2H, O-CH_2), 7.1 (d, 2H, H-2), 7.22 (d, 2H, H-3).

This material was alkylated according to general method E with LICA and 4-isopropylbenzyl bromide to give in 63% yield ethyl 3-(4-chlorophenyl)-2-(4-isopropylbenzyl)-2-methylpropanoate: MS (EI) *m/e* 358 (M); NMR ($CDCl_3$) δ 1.05 (s, 3H, α-Me), 1.1−1.3 (m, 9H, Me), 2.65 (dd, 2H, benzylic CH_2), 2.85 (m, 1H, CH), 3.15 (t, 2H, benzylic CH_2), 4.05 (q, 2H, O-CH_2), 6.95−7.15 m, 6H), 7.2−7.3 (m, 2H).

This material proved very resistant to saponification. The only conditions which gave a 12% yield of the desired product involved refluxing an EtOH solution with 4 equiv of 1 N NaOH overnight to give 3-(4-chlorophenyl)-2-(4-isopropylbenzyl)-2-methylpropanoic acid: MS (CI) *m/e* 348 (M + NH_4); NMR ($CDCl_3$) δ 1.05 (s, 3H, α-Me), 1.25 (d, 6H, Me), 2.65−2.75 (dd, 2H, benzylic CH_2), 2.85 (m, 1H, CH), 3.2−3.35 (dd, 2H, benzylic CH_2), 7.15 (m, 6H), 7.25 (m, 2H).

Preparation of 2-(4-Chlorobenzyl)-3-fluoro-3-(4-isopropylphenyl)-2-methylpropanoic Acid (94, 95). A 1.2 g (5.3 mmol) sample of ethyl 3-(4-chlorophenyl)-2-methylpropanoate (see preparation of **93**) was treated according to general method E with 1 equiv of LICA and 1 equiv of 4-isopropylbenzaldehyde to give after chromatography on silica gel with hexane/Et_2O (3:1) 1.01 g (51%) of ethyl 2-(4-chlorobenzyl)-3-hydroxy-3-(4-isopropylphenyl)-2-methylpropanoate: MS (CI) *m/e* 375 (M + H); NMR ($CDCl_3$) δ 1.0 (s, 3H, α-Me), 1.15 (t, 3H, Me), 1.25 (d, 6H, Me), 2.55 and 3.2 (ABq, 2H, benzylic CH_2), 2.9 (m, 1H, CH), 3.2 (d, 2H, OH), 4.1 (q, 2H, O-CH_2), 4.8 (d, 1H, CH), 7.05 (d, 2H), 7.2−7.3 (m, 6H).

A 1 g (2.67 mmol) sample of this material was dissolved in 5 mL of CH_2Cl_2 and added at −78 °C to a solution of 430 mg (2.67 mmol) of diethylaminosulfur trifluoride[25] in 5 mL of CH_2Cl_2. After 1 h at −78 °C the mixture was allowed to warm to room temperature overnight, cold water was added, and the organic layer was separated and washed with bicarbonate and water. The solvent was stripped and the residue chromatographed on silica gel with hexane/Et_2O (4:1) to give 240 mg (24%) of diastereomer A [LP fraction; MS (CI) *m/e* 394 (M + NH_4); NMR ($CDCl_3$) δ 1.05 (s, 3H, α-Me), 1.15 (t, 3H, Me), 1.25 (d, 6H, Me), 2.9 (m, 1H, CH), 2.95 and 3.35 (ABq, 2H, benzylic CH_2), 4.0 (q, 2H, O-CH_2), 5.7 (s) and 5.85 (s, 1H) (CHF), 7.1 (m, 2H), 7.2−7.3 (m, 6H)] and 466 mg (47%) of diastereomer B [MP fraction; MS (CI) *m/e* 394 (M + NH_4); NMR ($CDCl_3$) δ 1.05 (s, 3H, α-Me), 1.20 (t, 3H, Me), 1.25 (d, 6H, Me), 2.3 and 3.15 (ABq, 2H, benzylic CH_2), 2.95 (m, 1H, CH), 4.15 (q, 2H, O-CH_2), 5.65 (s) and 5.75 (s, 1H) (CHF), 6.95 (d, 2H), 7.2 (d, 2H), 7.25 (s, 4H)] of ethyl 2-(4-chlorobenzyl)-3-fluoro-3-(4-isopropylphenyl)-2-methylpropanoate.

Diastereomer B was saponified with 1 equiv of KO*t*-Bu in DMSO at 40 °C for 4 h to give 2-(4-chlorobenzyl)-3-fluoro-3-(4-isopropylphenyl)-2-methylpropanoic acid (diastereomer B, **94**): mp 143−5 °C; MS (CI) *m/e* 366 (M + NH_4); NMR ($CDCl_3$) δ 1.05 (s, 3H, α-Me), 1.25 (d, 6H, Me), 2.35 and 3.15 (ABq, 2H, benzylic CH_2), 2.95 (m, 1H, CH), 5.7 (s) and 5.9 (s, 1H) (CHF), 7.0 (d, 2H), 7.2 (d, 2H), 7.25 (s, 4H). Diastereomer A of the ester was saponified with 1 equiv of KO*t*-Bu in DMSO at room temperature overnight to give 2-(4-chlorobenzyl)-3-fluoro-3-(4-isopropylphenyl)-2-methylpropanoic acid (diastereomer A, **95**): MS (CI) *m/e* 366 (M + NH_4); NMR ($CDCl_3$) δ 1.1 (s, 3H, α-Me), 1.15 (t, 3H, Me), 1.25 (d, 6H, Me), 2.9 (m, 1H, CH), 2.95 and 3.35 (ABq, 2H, benzylic CH_2), 5.7 (s) and 5.85 (s, 1H) (CHF), 7.1 (d, 2H), 7.2−7.3 (m, 6H).

Preparation of 2-(4-Chlorobenzyl)-2,3-dihydro-5-isopropylbenzofuran-2-carboxylic Acid (97). A 10 g (29 mmol) sample of ethyl 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)propanoate (prepared according to general method E), dissolved in 80 mL of toluene, was added to 10.64 g of paraformaldehyde followed by 80 mL of AcOH. The mixture was cooled to 0 °C, perfused with HCl gas for 2 h, and then allowed to stir at room temperature overnight. Since GC/MS analysis indicated only 50% conversion, the mixture was cooled again to 0 °C, treated with 5 g of paraformaldehyde, perfused again with HCl gas for 2 h, and then allowed to stir at room temperature overnight. After stripping the solvent and azeotroping with hexane, the residue was dissolved in EtOAc and washed with brine to give 10.52 g of crude product. This was chromatographed on silica gel with CH_2Cl_2/hexane (1:1) to give 4.06 g (35%) of ethyl 2-[2-(chloromethyl)-4-isopropylphenoxy]-3-(4-chlorophenyl)propanoate: MS (EI) *m/e* 394 (M); NMR ($CDCl_3$) δ 1.2 (m, 9H, Me), 2.8 (m, 1H, CH), 3.2 (d, 2H, benzylic CH_2), 4.16 (q, 2H, CH_2-O), 4.5 and 4.66 (ABq, 2H, CH_2-Cl), 4.8 (t, 1H, α-CH), 6.6 (d, 1H, H-6), 7.0 (m, 1H, H-3), 7.2 (m, 1H, H-5), 7.26 (s, 4H, aromatic H′).

A 3.47 g (8.77 mmol) sample of this material was dissolved in 20 mL of THF, cooled to −78 °C, and treated dropwise with 1 equiv of LICA (prepared according to general method E from 1.44 mL (8.77 mmol) of *N*-isopropylcyclohexylamine). The mixture was stirred overnight at −78 °C in a dry ice−acetone bath and allowed to warm very slowly to room temperature. After the usual workup and chromatography on silica gel with hexane containing 10% CH_2Cl_2 and 5% THF, we obtained 1.37 g (44%) of ethyl 2-(4-chlorobenzyl)-2,3-dihydro-5-isopropylbenzofuran-2-carboxylate: MS (EI) *m/e* 358 (M); NMR ($CDCl_3$) δ 1.2 (m, 9H, Me), 2.82 (m, 1H, CH), 3.24 (ABq, 2H, benzylic CH_2), 3.2 and 3.46 (ABq, 2H, 3-CH_2), 4.16 (q, 2H, CH_2-O), 6.8 (d, 1H, H-7), 6.98 (s, 1H, H-4), 7.0 (d, 1H, H-6), 7.24 (ABq, 4H, aromatic H′).

A 1.2 g (3.4 mmol) sample of this material was saponified with 4 equiv of 1 N NaOH in EtOH at room temperature overnight to give after gradient chromatography on silica gel with hexane containing 10−40% EtOAc and 2% AcOH 520 mg (46%) of 2-(4-chlorobenzyl)-2,3-dihydro-5-isopropylbenzofuran-2-carboxylic acid: MS (CI) *m/e* 348 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 2.82 (m, 1H, CH), 3.16 and 3.33 (ABq, 2H, benzylic CH_2), 3.26 and 3.58 (ABq, 2H, 3-CH_2), 6.8 (d, 1H, H-7), 7.0 (m, 2H, H-4, H-6), 7.2 (ABq, 4H, aromatic H′).

Preparation of 3-(4-Chlorophenyl)-2,3-dihydro-5-isopropylbenzofuran-2-carboxylic Acid (98). In analogy to the method of Fuson et al.[26] a 6.9 g (50.8 mmol) sample of 4-isopropylphenol was treated with 1 equiv of NaH and 1 equiv of ethyl 2-bromo-2-(4-chlorobenzoyl)acetate as described in general method A to give 15.37 g (84%) of ethyl 2-(4-chlorobenzoyl)-2-(4-isopropylphenoxy)acetate: MS (CI) *m/e* 378 (M + NH_4); NMR ($CDCl_3$) δ 1.1−1.3 (m, 9H, Me), 2.8 (m, 1H, CH), 4.1 (q) and 4.3 (q, 2H) (CH_2-O), 6.8 (d, 2H, H-2), 7.0−7.1 (m, 4H), 7.4 (d, 2H), 8.0 (d, 1H, α-CH).

A 7.37 g (20.4 mmol) sample of this material was cooled to −40 °C and treated dropwise with 10 mL (9 equiv) of concentrated H_2SO_4. The mixture was allowed to come slowly to room temperature, stirred for 3 h, and poured over ice. Extraction with EtOAc and chromatography on silica gel with hexane/Et_2O (10:1) gave 2.0 g (30%) of ethyl 3-(4-chlorophenyl)-5-isopropylbenzofuran-2-carboxylate: MS (EI) *m/e* 342 (M); NMR ($CDCl_3$) δ 1.2−1.4 (m, 9H, Me), 3.0 (m, 1H, CH), 4.16 (q, 2H, CH_2-O), 7.32−7.4 (m, 2H), 7.4−7.6 (m, 5H).

A 1.13 g (3.29 mmol) sample of this material was dissolved in 15 mL of EtOH, treated with 0.489 g (2.25 equiv) of 85% KOH in 3 mL of water, and stirred at room temperature overnight. After workup we obtained 0.65 g (62%) of 3-(4-chlorophenyl)-5-isopropylbenzofuran-2-carboxylic acid: MS (CI) *m/e* 332 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 3.0 (m, 1H, CH), 7.2−7.5 (m, 7H).

A 200 mg (0.6 mmol) sample of this material was reduced with 10 g (10 equiv) of 3% sodium amalgam in 25 mL of saturated aqueous $NaHCO_3$ under mechanical stirring at room temperature overnight. After workup we obtained 83 mg (41%) of 3-(4-chlorophenyl)-2,3-dihydro-5-isopropylbenzofuran-2-carboxylic acid as a 2:1 mixture of *Z* and *E* isomers which could not be separated by chromatography or crystallization: MS (CI) *m/e* 334 (M + NH_4); NMR ($CDCl_3$) δ 1.16 (d, 6H, Me), 3.0 (m, 1H, CH), 4.75 (d) and 4.95 (d, 1H) H-3), 4.84 (d) and 5.02 (d, 1H) H-2), 6.8−6.9 (m, 1H, H-7), 7.0−7.2 (m, 2H, H-4, H-6), 7.26 (ABq, 4H, aromatic H′).

Preparation of 2-(4-Chlorobenzyl)-2,3-dihydro-6-isopropyl-4*H*-benzopyran-2-carboxylic Acid (99). A 14.49 g (41.77 mmol) sample of ethyl 3-(4-chlorophenyl)-2-(4-isopropylphenoxy)propanoate (prepared according to general method E) was alkylated with 1 equiv of LICA and 1 equiv of benzyl 2-bromoacetate according to general method E to give 6.1 g (29%) of benzyl 4-(4-chlorophenyl)-3-(ethoxycarbonyl)-3-(4-isopropylphenoxy)butanoate as an oil: MS (CI) *m/e* 512 (M + NH_4); NMR ($CDCl_3$) δ 1.15 (m, 9H, Me), 2.7 and 2.9 (ABq, 2H, benzylic CH_2), 2.85 (m, 1H, CH), 3.4 and 3.55 (ABq, CO-CH_2), 4.15 (q, O-CH_2), 5.05 (ABq, 2H, O-CH_2-benzyl), 6.75 (d, 2H H-2), 7.05 (d, 2H, H-3), 7.2−7.4 (m, 9H).

This material (6.1 g, 12.32 mmol) was dissolved in 123 mL of AcOH and hydrogenated at atmospheric pressure over 1.2 g of 5% Pd/C until H_2 uptake ceased (1 h) to give 4.25 g (85%) of 4-(4-chlorophenyl)-3-(ethoxycarbonyl)-3-(4-isopropylphenoxy)butanoic acid as an oil: MS (CI) *m/e* 422 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (m, 9H, Me), 2.7 and 2.9 (ABq, 2H, benzylic CH_2), 2.85 (m, 1H, CH), 3.4 and 3.55 (ABq, CO-CH_2), 4.2 (q, O-CH_2), 6.8 (d, 2H, H-2), 7.05 (d, 2H, H-3), 7.25 (ABq, 4H, aromatic H′).

A 4.23 g (10.45 mmol) sample of this material was dissolved in 50 mL of CH_2Cl_2, cooled to 5 °C, and treated dropwise with a solution of 2.22 mL (15.7 mmol) of trifluoroacetic anhydride in 25 mL of CH_2Cl_2 (15 min) and then with a solution of 0.09 mL (1.05 mmol) of trifluoromethanesulfonic acid in 25 mL of

CH_2Cl_2 (15 min). The mixture was stirred at 5 °C for 30 min and then at room temperature for 1 h. After washing with bicarbonate and brine, drying, evaporation, and flash chromatography on silica gel with hexane/CH_2Cl_2 (1:1) was obtained 2.87 g (71%) of ethyl 2-(4-chlorobenzyl)-2,3-dihydro-6-isopropyl-4-oxo-4*H*-benzopyran-2-carboxylate as an oil: MS (CI) *m/e* 404 (M + NH_4); NMR ($CDCl_3$) δ 1.1 (t, 3H, Me), 1.2 (d, 6H, Me), 2.8 and 3.1 (ABq, 2H, benzylic CH_2), 2.85 (m, 1H, CH), 3.25 (ABq, 3-CH_2), 4.05 (q, O-CH_2), 7.0 (d, 1H, H-8), 7.2 (ABq, 4H, aromatic H′), 7.35 dd 1H, H-7), 7.65 (d, 1H, H-5).

A 2.59 g (6.7 mmol) batch of this material was dissolved in 33 mL of MeOH, cooled to 5 °C, and treated in portions with 506 mg (13.4 mmol) of $NaBH_4$. After workup and chromatography on silica gel with CH_2Cl_2 was obtained 2.25 g (82%) of ethyl 2-(4-chlorobenzyl)-2,3-dihydro-4-hydroxy-6-isopropyl-4*H*-benzopyran-2-carboxylate as a mixture of diastereomers: MS (CI) *m/e* 406 (M + NH_4); NMR ($CDCl_3$) δ 1.1−1.2 (m, 9H, Me), 1.7 (bs, 1H, OH), 1.75−1.85 (m, and 1.92 (dd) and 2.0 (dd, 1H) H-3 axial), 2.60 and 2.75 (dd) and 2.60 and 2.65 (dd, 1H) H-3 equatorial), 2.85 (m, 1H, CH), 3.1 and 3.25 (ABq) and 3.1 and 3.3 (ABq, 2H) (benzylic CH_2), 4.1 (q, O-CH_2), 4.75 (m, 1H, H-4), 6.85 (d) and 6.9 (d, 1H) H-8), 7.05 (dd) and 7.1 (dd, 1H) H-7), 7.05 (d) and 7.25 (d, 1H) H-5), 7.25 (s, 4H, aromatic H′).

A 2.24 g (5.76 mmol) batch of this material was dissolved in 25 mL of trifluoroacetic acid, cooled to 0 °C, and treated dropwise with 1.84 mL (11.52 mmol) of triethylsilane (10 min). The mixture was stirred at 0 °C for 2 h and then poured into ice−water and EtOAc to give, after isolation and chromatography on silica gel with hexane/CH_2Cl_2 (4:1), 920 mg (43%) of ethyl 2-(4-chlorobenzyl)-2,3-dihydro-6-isopropyl-4*H*-benzopyran-2-carboxylate as a syrup: MS (CI) *m/e* 390 (M + NH_4); NMR ($CDCl_3$) δ 1.1−1.2 (m, 9H, Me), 1.7−1.9 (m, 1H, H-4 axial), 2.25 −2.4 (m, 1H, H-3 axial), 2.6−2.8 (m, 2H, H-3, H-4 equatorial), 2.7−2.85 (m, 1H, CH), 3.15 (ABq, 2H, benzylic CH_2), 4.1 (q, O-CH_2), 6.75−7.0 (m, 3H, H-5,7,8), 7.25 (s, 4H, aromatic H′).

A 910 mg (2.44 mmol) sample of this material was dissolved in 50 mL of EtOH and saponified with 9.76 mL (4 equiv) of 1 N NaOH at room temperature overnight to give, after recrystallization from cyclohexane, 330 mg (39%) of 2-(4-chlorobenzyl)-2,3-dihydro-6-isopropyl-4*H*-benzopyran-2-carboxylic acid: MS (CI) *m/e* 362 (M + NH_4); NMR ($CDCl_3$) δ 1.2 (d, 6H, Me), 1.9−2.05 (m, 1H, H-4 axial), 2.3 −2.4 (m, 1H, H-3 axial), 2.7−2.85 (m, 3H, H-3, H-4 equatorial, CH), 3.15 (ABq, 2H, benzylic CH_2), 6.85 (d, 1H, H-8), 6.9 (d, 1H, H-5), 7.02 (dd, 1H, H-7), 7.20 (ABq, 4H, aromatic H′).

Preparation of 2-(5-Chloroindan-1-yl)-2-(4-isopropylphenoxy)-2-methylacetic Acid (100, 101). A 4.726 g (20 mmol) sample of ethyl 2-(4-isopropylphenoxy)propanoate (prepared according to general method E) was treated with 1 equiv of LICA and 3.332 g (20 mmol) of 5-chloro-1-indanone according to general method E to give, after flash chromatography on silica gel with Et_2O/hexane (1:1), 3.06 g (38%) of ethyl 2-(5-chloro-1-hydroxyindan-1-yl)-2-(4-isopropylphenoxy)-2-methylacetate: NMR ($CDCl_3$) δ 1.05 (t) and 1.25 (t, 3H) Me), 1.2 (d, 6H, Me), 2.05−2.25 (m, 1H), 2.6−3.0 (m, 4H), 4.2 (q) and 4.35 (q, 2H) (O-CH_2), 6.65−6.80 (m, 3H), 7.0−7.1 (m, 2H), 7.15 (m, 1H), 7.55 (d) and 7.65 (d, 1H).

A 1.76 g (4.37 mmol) sample of this material was dissolved in 40 mL EtOH and treated with 4.4 of mL 12 N HCl. The mixture was heated at reflux for 30 min, the solvent was stripped, and the residue was dissolved in Et_2O and washed with water. After drying ($MgSO_4$) and stripping, the residue was chromatographed on silica gel with CH_2Cl_2/hexane (1:1) to give 1.1 g (66%) of ethyl (5-chloroinden-1-yl)-2-(4-isopropylphenoxy)-2-methylacetate: MS (EI) 384 (M); NMR ($CDCl_3$) δ 1.25 (t) and 1.35 (t, 3H) Me), 1.25 (d, 6H, Me), 1.85 (s, 3H, α-Me), 2.8 (m, 1H, CH), 3.4 (d, 2H, 3-CH_2), 4.2 (q, 2H, O-CH_2), 6.65 (m, 1H, H-2), 6.8 (d, 2H, H-2′), 7.0 (d, 2H, H-3′), 7.25 (d, 1H, H-6), 7.4 (d, 1H, H-4), 7.7 (d, 1H, H-7).

A 0.817 g (2.12 mmol) sample of this material was dissolved in 10 mL of AcOH and hydrogenated over 0.3 g of 5% Pd/C at atmospheric pressure for 3 h to give, after flash chromatography on silica gel with CH_2Cl_2/hexane (3:1), 533 mg (65%) of ethyl 2-(5-chloroindan-1-yl)-2-(4-isopropylphenoxy)-2-methylacetate as a mixture of diastereomers: MS (CI) *m/e* 404 (M + NH_4); NMR ($CDCl_3$) δ 1.1−1.3 (m, 9H, Me), 1.35 (s, 3H, α-Me), 2.3−2.4 (m, 2H, H-2, H-3 axial), 2.7−3.1 (m, 3H, H-2, H-3 equatorial, CH), 3.7 (t, H-1), 4.2 (q, 2H, O-CH_2), 6.7 (d, 2H, H-2′), 7.0−7.15 (m, 3H, H-3′, H-6), 7.2 (s, 1H, H-4), 7.25 (d, 1H, H-7).

A 230 mg (0.6 mmol) sample of this material was saponified with KO*t*-Bu in Et_2O/water as described in the preparation of **84**, **85**. The diastereomers were separated by preparative TLC on silica gel with Et_2O/hexane (1:1) containing 2% AcOH to give 139 mg (65%) of diastereomer A [LP, **101**; MS (CI) *m/e* 376 (M + NH_4); NMR (DMSO-d_6) δ 1.15 (d, 6H, Me), 1.22 (s, 3H, α-Me), 2.2−2.4 (m, 2H, H-2, H-3 axial), 2.7−3.1 (m, 3H, H-2, H-3 equatorial, CH), 3.75 (t, H-1), 6.72 (d, 2H, H-2′), 7.09 (d, 2H, H-3′), 7.15 (m, 1H), 7.3 (m, 2H)], after recrystallization from hexane 70 mg (mp 117−8 °C), and 53 mg (25%) of diastereomer B (MP, **100**) as an oil: MS (CI) *m/e* 376 (M + NH_4); NMR (DMSO-d_6) δ 1.1 (s, 3H, α-Me), 1.15 (d, 6H, Me), 2.7−3.0 (m, 3H, H-2, H-3 axial, CH), 3.25−3.4 (bm, 2H, H-2, H-3 equatorial), 3.75 (t, H-1), 6.8 (d, 2H, H-2′), 7.15 (d, 2H, H-3′), 7.20 (d, 1H, H-6), 7.3 (s, 1H H-4), 7.55 (d, 1H, H-7). This was converted to the Na salt with NaOEt in EtOH to give 18 mg.

Biology. 1. In Vitro Characterization. Glucose Transport Activity. Acute glucose transport modulation in vitro was assessed by measuring 2-deoxyglucose transport in 3T3-L1 adipocytes or L6 myocytes. 3T3-L1 or L6 fibroblasts were grown to confluency in 6-well cluster dishes. Adipocyte differentiation was induced by supplementing the media with a combination of 1 μM insulin, 250 nM dexamethasone, and 500 μM 3-isobutyl-1-methylxanthine for 48 h followed by insulin alone for an additional 48 h. L6 cells were grown in 2% fetal bovine serum in α-MEM and differentiated into myocytes without further medium supplementation. Transport experiments were performed 7−11 days postinduction of differentiation. The test compounds were prepared in 100% DMSO (final concentration 0.1%, v/v) and then added to fresh media 1 h prior to measuring glucose transport activity. Glucose uptake was measured in Krebs-Ringer phosphate buffer, pH 7.4, using 0.5 μCi/mL [^{14}C]-2-deoxy-D-glucose (50 μM; DuPont-NEN) for 10 min at 37 °C. The assay was terminated by aspiration and washing the cells with ice-cold PBS. Samples were extracted with 1% Triton X-100 and counted in a scintillation counter. Data are expressed as the mean percent increase of triplicate determinations of glucose transport rate over the basal (unstimulated) rate.

Chronic 48 h glucose transport modulation in vitro was assessed in the 3T3-L1 cell line prepared as described above. Seven days postinduction of differentiation, the test compounds prepared in 100% DMSO (final concentration 0.1%, v/v) were added to fresh media at 48 and 24 h prior to measuring glucose transport activity as described above. Data are expressed as described above for the acute treatments.

Gluconeogenesis Inhibition Activity. Hepatocytes were isolated by collagenase digestion of livers from fed male Sprague−Dawley rats (~200 g of body weight) as previously described.[27] Cells were suspended (~40 mg of weight/mL) in Krebs-Henseleit bicarbonate buffer, pH 7.4, containing 1.5% (w/v) gelatin (Difco, Detroit, MI) and continuously gassed with O_2/CO_2 (19:1). Hepatocyte suspensions of 1.5 mL were incubated in 25 mL of polypropylene Erlenmeyer flasks and placed in a shaking water bath maintained at 37 °C. Stock solutions of compounds were prepared in 100% DMSO; final concentration of DMSO did not exceed 0.5%. The isolated rat hepatocytes were incubated in the absence or presence of compounds at a final concentration of 100 μM for 20 min; then [U^{14}C]lactic acid (NEC-599, DuPont-NEN; 2 mM, 0.625 μCi) ± 0.3 nM glucagon were added, and the incubation was continued for an additional 20 min. The conversion of [^{14}C]lactic acid to [^{14}C]-glucose was then determined as described.[15,28]

2. In Vivo Characterization. Oral Hypoglycemic Activity. The blood glucose-lowering activities of the test compounds were measured with 6−8 week old C57BL/6J-*ob*/*ob* mice (obtained from Jackson Laboratories, Bar Harbor, ME). Animals were housed 5/cage under standard animal care practices. After a 5 day acclimation period, the animals were weighed, and 25 μL of blood was collected via the retro-orbital

sinus prior to any treatment. The blood sample was immediately diluted 1:5 with heparinized saline and held on ice for subsequent centrifugation and glucose analysis of the supernatant. Animals were grouped 5/cage with equal mean blood glucose concentrations in each group and then dosed (oral gavage) daily for 4 days with drug in vehicle or vehicle alone (0.25% (w/v) methyl cellulose in water with no pH adjustment). Animals were bled 20−24 h after the fourth administration of drug or vehicle for blood glucose levels. The weight of each animal was recorded on days 1 and 5; net food intake (grams per cage of five animals) was also measured over the 5 day period. The diluted plasma sample was analyzed for glucose with the VP Super System Auto analyzer (Abbott Laboratories, Irving, TX). Racemic englitazone was dosed at 50 mg/kg as a positive control.

The results are reported in the tables as glucose normalization as percent of glucose lowering achieved by the standard (racemic englitazone) at 50 mg/kg. As a rule, this dose of racemic englitazone was sufficient to lower plasma glucose levels of the *ob/ob* mice to that of their lean litter mates (~170 mg/dL). In data from 23 separate representative experiments, the mean of the average day 5 glucose value in the vehicle-treated control mice was 315 mg/dL (range 213−379 mg/dL) and the mean coefficient of variation (CV%) was 26% (range 13−41%). In these same experiments the mean of the average day 5 glucose value in the mice treated with racemic englitazone (the positive control) was 171 mg/dL (range 144−219 mg/dL) and the mean CV% was 22% (range 8−64%). For statistical analysis of the data the glucose values of drug-treated and vehicle-treated animals were compared by an unpaired two-tailed Student's *t*-test.

Pair-Feeding Study. This study followed the oral hypoglycemic activity protocol except that after the first day of dosing, three pair-fed vehicle groups received the same amount of food as the mice dosed with compound **26** had consumed the previous day.

Acute in Vivo Treatment. To determine acute hypoglycemic activity of compounds **26** and **84** following a single oral dose, *ob/ob* mice were treated with vehicle alone on days 1−4 using the protocol above. On day 5, mice were dosed with drug in vehicle or vehicle alone, and acute blood glucose lowering was determined 3 h later. The results are calculated as percent decrease in mean blood glucose concentration of experimental groups relative to the vehicle control group. Potency of the acutely administered compounds is expressed as percent effect of chronic racemic englitazone treatment.

Glucose Transporter Expression. Chronic effects of some compounds on glucose transporter expression were assessed by quantitative immunoblot analysis of GLUT1 and GLUT4 protein levels in extracts from 3T3-L1 adipocytes following 48 h treatment in vitro. In brief, cells were lysed directly in SDS−sample buffer, subjected to 10% SDS−polyacrylamide gel electrophoresis, transferred to nitrocellulose, and then immunoblotted with antibodies R1/2A and R1184 to detect GLUT1 and GLUT4 bands, respectively.[14,29] Immunoreactive bands were visualized with [^{125}I]goat anti-rabbit IgG (DuPont-NEN, Boston, MA) using autoradiography and quantitated by excising them and measuring radioactivity in a gamma counter.

Computational Methods. Restricted Hartree−Fock calculations were carried out for **7, 26, 84**, and **99**−**101**. The geometries for this series of molecules were fully optimized by means of analytical energy gradients[30] with the 6-31G(d) basis set.[31] The ab initio molecular orbital calculations were carried out with the Gaussian 94 series of programs on a Silicon Graphics computer.[32] For each molecule in the series a variety of conformations were generated corresponding to ca. 60° torsions about each rotatable bond. Additionally, for **100** and **101** the pseudorotation of the five-membered ring was explored. For each molecule, the isopropyl and chloro groups were removed as a computational convenience; this is not expected to have an impact on the interpretation of the results (vide supra).

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