Studies on Non-Thiazolidinedione Antidiabetic Agents. 2.[1] Novel Oxyiminoalkanoic Acid Derivatives as Potent Glucose and Lipid Lowering Agents

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We previously reported that (*Z*)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-(4-phenoxyphenyl)acetic acid (3) showed potent glucose and lipid lowering effects in genetically obese and diabetic mice, KKA^y. This compound also showed transcriptional activity for peroxisome proliferator-activated receptor (PPAR)-γ. We expanded on the structure–activity relationships of oxyiminoalkanoic acid derivatives based on this transcriptional activity (*in vitro*). Insertion of a carbon chain between the imino carbon and the carboxyl moiety of (*Z*)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-phenylacetic acid (2) resulted in a marked increase in transcriptional activity at PPARγ. *In vivo* potencies of synthesized compounds, which showed strong functional activity at PPARγ, were tested using KKA^y mice. Among these compounds, (*E*)-4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-phenylbutyric acid (27) exhibited marked glucose and lipid lowering activity while showing no significant body weight gain. Compound (27) (TAK-559) showed favorable pharmacokinetic properties with good absorption and duration, and was considered as an attractive candidate for further evaluation.

Key words antidiabetic agent; oxyiminoalkanoic acid; peroxisome proliferator-activated receptor; type 2 diabetes; KKA^y mice

Insulin resistance is a fundamental abnormality of type 2 diabetes and impaired glucose tolerance (IGT).[2] Type 2 diabetes is defined by a high plasma glucose level, which leads to a gradual progression of complications, including neuropathy, nephropathy, retinopathy, arteriosclerosis, and coronary artery disease.[3—6] Treatment usually consists of a regimen of diet and exercise, and oral antihyperglycemic agents such as sulfonylureas, biguanides, and α-glucosidase inhibitors. Insulin is also used in severe cases.[7] Recent clinical studies suggested that intensive control of HbA_{1c} levels reduced complications for both type 1 and type 2 diabetes, and revealed the importance of drugs for reducing plasma glucose levels.[8—11] However, drugs can cause problems including compliance, hypoglycemia, and obesity.[12,13] Thus, new antidiabetic drugs that have improved compliance and reduced side effects are still required.

Recently, 2,4-thiazolidinedione analogs, including pioglitazone (**1**)[14] (Chart 1), have been launched as antidiabetic agents.[15—17] There are a number of groups that endeavor to produce new antidiabetic agents in this area.[18—29] Although the mechanisms of insulin resistance and action of 2,4-thiazolidinedione analogs and related compounds are not yet fully understood, a number of reports suggest that pioglitazone reduces insulin resistance. For example, treatment with pioglitazone increased the insulin action for the decrease of hepatic glucose production and for the increase of peripheral glucose utilization in Wistar fatty rats.[30,31] In addition, pioglitazone improved the defects of the insulin-stimulated tyrosine phosphorylation of insulin receptors and insulin receptor substrate 1 (IRS-1) and phosphatidylinositol (PI) 3-kinase activation in skeletal muscle of the fatty rats.[32] These effects were not observed in Wistar lean rats. It was also suggested that tumor necrosis factor-α (TNF-α) plays a key role in the systemic insulin resistance of type 2 diabetes.[33] Pioglitazone reduced the TNF-α level in muscle which was accompanied by an improvement of metabolic abnormalities in Wistar fatty rats.[34] A recent study suggests that antidiabetic thiazolidinediones interact with a family of nuclear receptors known as the peroxisome proliferator-activated receptor (PPAR)-γ.[35] It was also observed that the extent of the activation of PPARγ *in vitro* mirrored antihyperglycemic activity in diabetic ob/ob mice.[36] There might be a correlation between TNF-α and PPARγ.

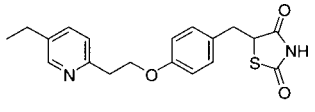

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Chart 1

Thiazolidinediones such as pioglitazone, rosiglitazone, and troglitazone have made a great contribution to therapy for type 2 diabetes. However, weight gain has been reported as a side effect of these drugs.[13] Thus, improvement of the thiazolidinedione class of antidiabetic agents is still worth pursuing.

In the previous paper, we reported the discovery of two novel oxyiminoacetic acid derivatives as potent glucose and lipid lowering agents, (*Z*)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-phenylacetic acid (**2**) and (*Z*)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-benzyloxyimino}-2-(4-phenoxyphenyl)acetic acid (**3**) (Fig. 1).[1] These oxyiminoacetic acids showed transcriptional activity for PPARγ, indicating that the mechanisms of action of oxyiminoacetic acid derivatives involve PPARγ, at least in part.[36] So, we were interested in finding more potent PPARγ agonists. We synthesized a new series of oxyiminoalkanoic acids (structure A, Fig. 1) to investigate the effect of linkage between the imino carbon and carboxy group based on PPARγ transcriptional activity. Compounds, which showed potent PPARγ activity, were tested using KKA^y mice[37] to evaluate not only antidiabetic activity but also the effect on

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body weight. In this paper, we describe the synthesis, structure–activity relationships (SAR), and biological analysis of oxyiminoalkanoic acids.

Chemistry

The methods used to prepare the oxyiminoalkanoic acids are outlined in Chart 2. The starting benzaldehydes (**4**) were reduced by sodium borohydride to benzyl alcohol derivatives (**5**), which were treated with thionyl chloride to give benzyl chlorides (**6**). Alkylation of oximes (**7**) with **6** gave imino ethers (**8**) (method A). Alternatively, compounds (**8**) were synthesized by a three-step process (method B). Alkylation of *N*-hydroxyphthalimide with **6** followed by treatment with hydrazine provided alkoxyamines (**10**). Condensation of **10** with ketones (**11**) afforded **8** as a mixture of isomers, which were easily separated by column chromatography. Saponification of **8** with aqueous LiOH afforded the desired alkanoic acid derivatives (**12**).

Oxyiminoalkanoic acid derivatives were also prepared by method C (Chart 3). Protection of 4-hydroxybenzaldehyde by chloromethyl methyl ether or by *tert*-butyldimethylsilyl chloride to give **13** followed by reduction with sodium borohydride furnished benzyl alcohols (**14**). Mitsunobu reaction of **14** with *N*-hydroxyphthalimide in the presence of diethyl azodicarboxylate and triphenylphosphine gave phthalimides (**15**), which were converted into alkoxyamines (**16**) by treatment with hydrazine. Condensation of **16** with **11**, followed by deprotection of methoxymethyl- or silyl-ether afforded **17**

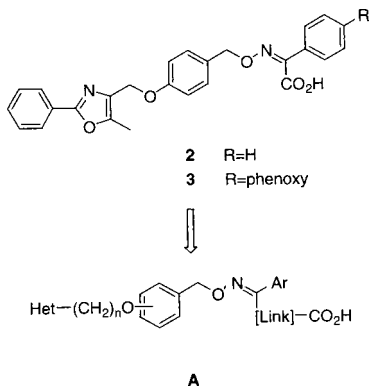
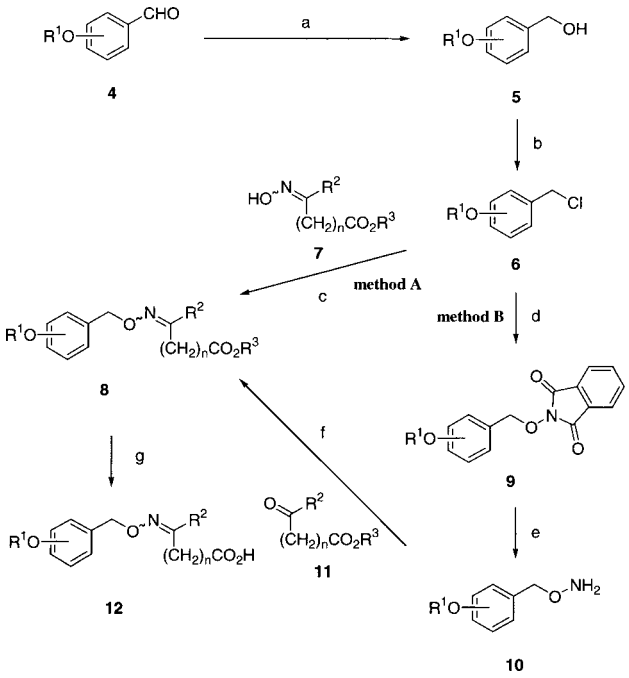
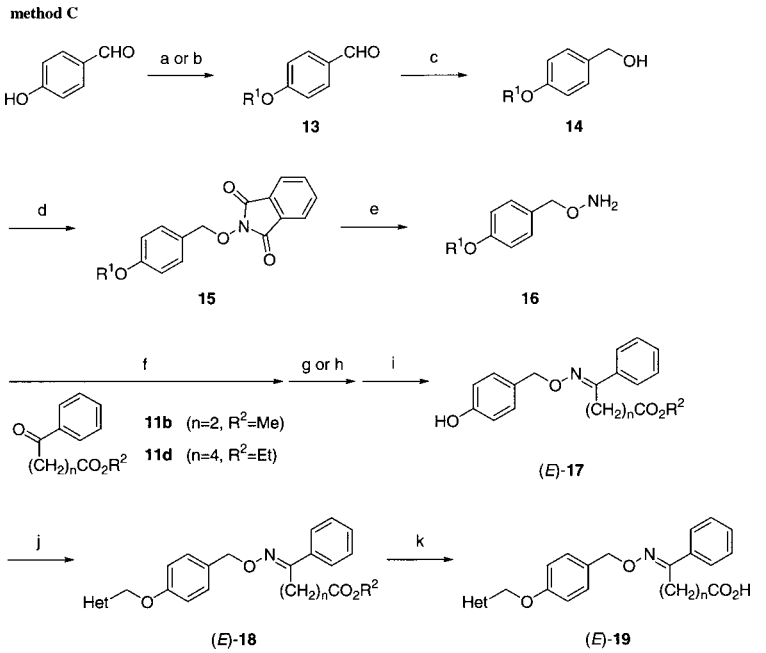


Fig. 1



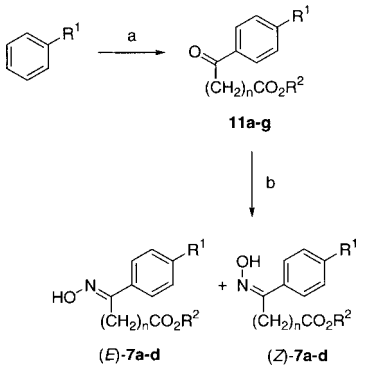
Reagents: (a) $NaBH_4$; (b) $SOCl_2$; (c) NaH; (d) *N*-hydroxyphthalimide, K_2CO_3; (e) H_2NNH_2; (f) AcOH, NaOAc; (g) aqueous LiOH.

Chart 2



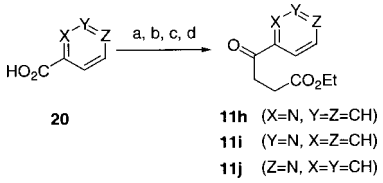
Reagents: (a) MOMCl, K_2CO_3; (b) *t*-$BuMe_2SiCl$, imidazole; (c) $NaBH_4$; (d) *N*-hydroxyphthalimide, DEAD, PPh_3; (e) H_2NNH_2; (f) AcOH, NaOAc; (g) aqueous HCl; (h) Bu_4NF; (i) column chromatography; (j) Het-CH_2Cl, K_2CO_3; (k) aqueous LiOH.

Chart 3



Reagents: (a) $ClCO(CH_2)_nCO_2R^2$, $AlCl_3$; (b) H_2NOH, NaOAc.

Chart 4



Reagents: (a) CDI; (b) *t*-BuOAc, LDA; (c) NaH, $BrCH_2CO_2Et$; (d) TsOH or CF_3CO_2H.

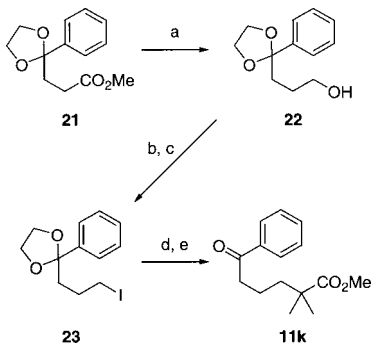
Chart 5

as a mixture of isomers (*ca.* 5 : 1). The major isomer of **17** (or **8** synthesized by method B in Chart 2) is presumed to have *E* configuration, considering a report described that reactions of alkyl phenyl ketones with methoxyamine yielded oximes having the hydroxy *trans* to phenyl.[38] (*Z*)-Isomers of **17** were removed by column chromatography. Only (*E*)-isomers were used for the next reaction. Alkylation of (*E*)-**17** with appropriate chloromethylheterocycles followed by saponification with aqueous LiOH yielded oxyiminoalkanoic acids (**19**).

The methods employed to prepare the intermediates (**7** and **11**) in Charts 2 and 3 are shown in Chart 4. Friedel–Crafts acylation of substituted benzenes with acid chlorides gave acylated benzenes (**11**) which were treated with hydroxylamine to provide oximes (**7**) as a mixture of isomers. These isomers were easily separated by column chromatography. The major isomer of oximes is also presumed to have *E* configuration considering a report.[39] This assumption is supported by X-ray analysis of **27** (data not shown). Compound (**27**), prepared from major isomer of methyl 4-(hydroxyimino)-4-phenylbutyrate (**7a**), was identified to have *E* configuration (the alkoxy of imino group *trans* to phenyl).

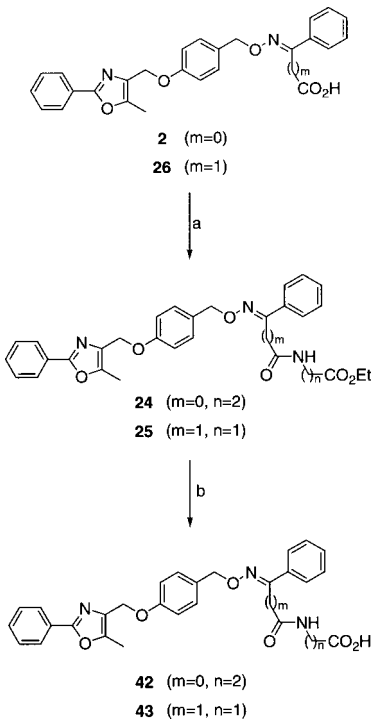
Pyridine analogues (**11h**—**j**) were prepared *via* a four-step procedure[40] (Chart 5). Carbonyldiimidazole (CDI) was used to condense pyridinecarboxylic acids (**20**) and lithium enolate of *tert*-butyl acetate to give pyridyl β-keto esters. Alkylation of the β-keto esters with ethyl bromoacetate followed by removal of the *tert*-butyl group and decarboxylation under acidic conditions gave the desired pyridyl γ-ketoesters (**11h**—**j**).

α,α-Dimethylester (**11k**) was synthesized from **21**[41] (Chart 6). Reduction of **21** with lithium aluminum hydride gave alcohol (**22**). Methanesulfonylation of **22** and subsequent reaction with sodium iodide gave iodoalkane (**23**).



Reagents: (a) $LiAlH_4$; (b) MsCl, Et_3N; (c) NaI; (d) methyl isobutyrate, LDA; (e) dil. H_2SO_4.

Chart 6



Reagents: (a) $H_2N(CH_2)_nCO_2Et \cdot HCl$, WSC, HOBt, Et_3N; (b) aqueous LiOH.

Chart 7

Treatment of **23** with lithium enolate of methyl isobutyrate and subsequent deprotection under acidic conditions provided α,α-dimethylester (**11k**).

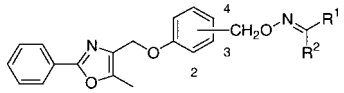
Compounds (**2**, **26**) were condensed with amino acid ethyl ether to give **24** and **25**, which were saponificated with aqueous LiOH to give **42** and **43**, respectively (Chart 7).

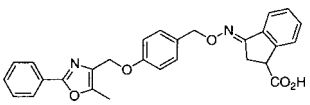
The analytical data of all oxyiminoalkanoic acids (**26**—**57**) synthesized are shown in Tables 1 and 2.

Results and Discussion

All compounds synthesized were evaluated for the ability to activate PPARγ in a transactivation assay in CHO-K1 cells. The results are shown in Tables 1 and 2. First of all, the effect of inserting an alkyl chain between the imino carbon and the carboxyl moiety of **2** was scrutinized. Surprisingly, a marked increase in activity was observed on insertion of alkyl chains of various lengths. The insertion of one, two, or

Table 1. Physical Data and PPARγ Transcriptoinal Activities of Oxyiminoalkanoic Acids



Entry	R^1	R^2	2—4	mp (°C)	Formula	*Anal.*[a]	Transactivation PPARγ EC_{50} (μM)[c]
26	phenyl	CH_2CO_2H	4	107—108[b]	$C_{27}H_{24}N_2O_5$	C, H, N	0.053
27	phenyl	$(CH_2)_2CO_2H$	4	137—138	$C_{28}H_{26}N_2O_5$	C, H, N	0.024
28	phenyl	$(CH_2)_2CO_2H$	3	108—109	$C_{28}H_{26}N_2O_5$	C, H, N	0.020
29	phenyl	$(CH_2)_2CO_2H$	2	116—117	$C_{28}H_{26}N_2O_5$	C, H, N	0.69
30	phenyl	$(CH_2)_3CO_2H$	4	129—130	$C_{29}H_{28}N_2O_5$	C, H, N	0.062
31	phenyl	$(CH_2)_4CO_2H$	4	112—113	$C_{30}H_{30}N_2O_5$	C, H, N	0.0025
32	$(CH_2)_4CO_2H$	phenyl	4	101—102	$C_{30}H_{30}N_2O_5$	C, H, N	0.056
33	phenyl	$(CH_2)_4CO_2H$	3	114—115	$C_{30}H_{30}N_2O_5$	C, H, N	0.0035
34	phenyl	$(CH_2)_5CO_2H$	4	84—85	$C_{31}H_{32}N_2O_5$	C, H, N	0.0039
35	phenyl	$(CH_2)_6CO_2H$	4	116—117	$C_{32}H_{34}N_2O_5$	C, H, N	0.26
36	phenyl	$(CH_2)_7CO_2H$	4	67—68	$C_{33}H_{36}N_2O_5$	C, H, N	12
37	4-fluorophenyl	$(CH_2)_2CO_2H$	4	139—140	$C_{28}H_{25}FN_2O_5$	C, H, N	0.047
38	4-phenoxyphenyl	$(CH_2)_2CO_2H$	4	131—132	$C_{34}H_{30}N_2O_6$	C, H, N	0.048
39	2-pyridyl	$(CH_2)_2CO_2H$	4	116—117	$C_{27}H_{25}N_3O_5$	C, H, N	0.045
40	3-pyridyl	$(CH_2)_2CO_2H$	4	158—159	$C_{27}H_{25}N_3O_5$	C, H, N	0.25
41	4-pyridyl	$(CH_2)_2CO_2H$	4	161—162	$C_{27}H_{25}N_3O_5$	C, H, N	0.17
42	phenyl	$CONH(CH_2)_2CO_2H$	4	121—122	$C_{29}H_{27}N_3O_6$	C, H, N	0.11
43	phenyl	$CH_2CONHCH_2CO_2H$	4	176—177	$C_{29}H_{27}N_3O_6$	C, H, N	0.38
44	phenyl	$(CH_2)_3C(CH_3)_2CO_2H$	4	111—112	$C_{32}H_{34}N_2O_5$	C, H, N	0.032
45			4	148—149	$C_{28}H_{24}N_2O_5$	C, H, N	0.83

a) Analytical results were within 0.4% of the theoretical value. *b*) Decomposed at the temperature. *c*) EC_{50}, the concentration of test compound required to induce 50% of the maximum activity.

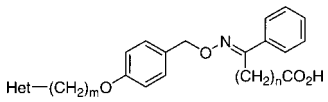
three carbons at that position in compound (**2**) resulted in a 30 to 80-fold increase in functional activity (**26**, **27**, **30**). Compounds with a four-(**31**, EC_{50}=2.5 nM) or five-(**34**, EC_{50}=3.9 nM) carbon insertion were 750- and 490-fold more active than **2**, respectively. Further extension of the carbon chain decreased potency (**35**, **36**). Thus, an important relationship was found between the length of the inserted carbon chain and the functional activation of PPARγ. Straight chains were preferable to branched (**44** *vs.* **31**), fixed (**45** *vs.* **27**), and amide-containing (**42**, **43** *vs.* **31**) chains as linkages at that position. Next, the effect of the substitution pattern on the central benzene ring was examined. *Para*- and *meta*-isomeric compounds were almost equi-potent (**27** *vs.* **28**; **31** *vs.* **33**), and were more potent than the *ortho*-analogue (**27**, **28** *vs.* **29**). Exchange of the phenyl group adjacent to the imino carbon with the 3-pyridyl or 4-pyridyl group resulted in a decrease in functional activity (**40**, **41** *vs.* **27**), although the 2-pyridyl derivative kept potency (**39** *vs.* **27**). This result suggested that a hydrophobic substituent was preferred at that position. The methyl group at the 5-position of the oxazole ring played an important role in the activity (**46** *vs.* **27**). This result is similar to the case of *in vivo* antihyperglycemic activity of thiazolidinedione analogs.[42] The 5-methyl-1,3-oxazole structure was preferable to other azoles (**47**—**50** *vs.* **27**). Substitution of the phenyl moiety on the oxazole ring at the 2-position of the 2-furyl or 2-thienyl moiety maintained or improved potency (**51**, **52** *vs.* **27**; **56**, **57** *vs.* **31**). Extension of the methoxy spacer between the oxazole ring and the central benzene ring did not increase potency (**55** *vs.* **27**). *E*-Isomer seems to be more potent at least *in vitro* assay, though there is only one example (**32** *vs.* **31**).

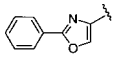
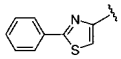
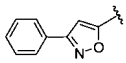
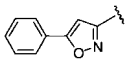
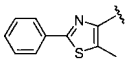
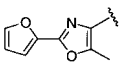
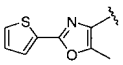
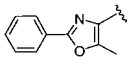
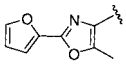
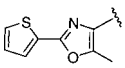
Next, the antidiabetic activities of oxyiminoalkanoic acids were evaluated using KKA^y mice.[37] Test compounds were selected based on transcriptional activity for PPARγ (EC_{50}<0.1 μM). The results are shown in Table 3. A number of these compounds significantly reduced plasma glucose levels even at a dosage of 0.001% in the diet (but not **28**, **30**, **33**, **38**, **44**). It is noteworthy that compound (**27**) showed potent glucose and lipid lowering activities while showing no significant body weight gain compared with the control. These profiles were preferable for antidiabetic agents. Considering the report that describes the structure–activity relationship for PPARγ agonist activity *in vitro* accurately predicts the *in vivo* glucose lowering activity in diabetic mice,[36] it is not clear why compounds (**28**, **30**, **33**, **38**, **44**), which possessed potent PPARγ transcriptional activity, were not as effective for glucose lowering as **27**. A possible interpretation of this fact is that these compounds might not be absorbed sufficiently or might be metabolized rapidly when administered orally to KKA^y mice. Anyway, further investigation of ineffective compounds seemed not to be worth carrying out.

Compound (**27**) was investigated further. Table 4 shows glucose and lipid lowering activities of **27** and pioglitazone hydrochloride in KKA^y mice. Compound (**27**) exhibited a 9-fold increase in glucose lowering activity and a 50-fold increase in lipid lowering activity compared to pioglitazone hydrochloride.

Pharmacokinetic analysis (Table 5) suggested that com-

Table 2. Physical Data and PPARγ Transcriptoinal Activities of Oxyiminoalkanoic Acids



Entry	Het	*m*	*n*	mp (°C)	Formula	*Anal.*[a]	Transactivation PPARγ EC_{50} (μM)[b]
46		1	2	144—145	$C_{27}H_{24}N_2O_5$	C, H, N	0.25
47		1	2	104—105	$C_{29}H_{28}N_2O_4S$	C, H, N	0.16
48		1	2	96—97	$C_{27}H_{24}N_2O_5$	C, H, N	0.98
49		1	2	100—101	$C_{27}H_{24}N_2O_5$	C, H, N	0.31
50		1	2	99—100	$C_{28}H_{26}N_2O_4S$	C, H, N	0.36
51		1	2	124—125	$C_{26}H_{24}N_2O_6$	C, H, N	0.042
52		1	2	142—143	$C_{26}H_{24}N_2O_5S$	C, H, N	0.017
53		2	2	oil	$C_{25}H_{27}N_3O_4 \cdot 3/4AcOEt$	C, H, N	0.91
54		2	2	72—73	$C_{24}H_{26}N_4O_4$	C, H, N	2.1
55		2	2	106—107	$C_{29}H_{28}N_2O_5$	C, H, N	0.34
56		1	4	112—113	$C_{28}H_{28}N_2O_6$	C, H, N	0.0049
57		1	4	101—102	$C_{28}H_{28}N_2O_5S$	C, H, N	0.00084

a) Analytical results were within 0.4% of the theoretical value. *b*) EC_{50}, the concentration of test compound required to induce 50% of the maximum activity.

pound (**27**) has favorable pharmacokinetic characteristics. The $AUC_{0—24\,h}$ (261.36±18.52 μg·h/ml/*p.o.* and 30.57±2.11 μg·h/ml/i.v.) and bioavailability (85.5±8.4%) were high enough, which suggests that the system is well exposed to compound (**27**).

In summary, we showed that a new series of oxyiminoalkanoic acid derivatives had strong transcriptional activity for PPARγ and potent antidiabetic effects in genetically obese and diabetic KKA^y mice. Compound (**27**), which had strong glucose and lipid lowering activity while showing no significant body weight gain, exhibited a 9-fold increase in glucose lowering activity and a 50-fold increase in lipid lowering activity compared to pioglitazone hydrochloride. Compound (**27**, TAK-559) possessed very good pharmacokinetic characteristics and selected as a candidate for further evaluation.

Experimental

Biological Procedures. (a) PPARγ-Retinoid X Receptor α (RXRα) Heterodimer Transactivation Assay The full-length human PPARγ1, full-length human RXRα and PPAR responsive luciferase reporter were stably expressed in CHO-K1 cells. These cells were cultured in HAM F12 medium (NISSUI SEIYAKU) containing 10% fetal bovine serum (Life Technologies, Inc., U.S.A.), inoculated into a 96-well white plate (Corning Coaster Corporation, U.S.A.) at a density of 2×10^4 cells/well, and cultured in a carbonate gas incubator at 37 °C overnight. The white plate was washed with PBS (Phosphate-buffered saline), and 90 μl of HAM F12 medium containing 0.1% fatty acid-free bovine serum albumin (BSA) and 10 μl of test substance were added. The plate was then cultured in the carbonate gas incubator at 37 °C for 48 h. The medium was removed, 40 μl of PICAGENE 7.5 (Wako Pure Chemical Ind. Ltd.) was added, and after stirring, luciferase activity was determined using Lumistar (BMG Labtechnologies GmbH, Germany). Induction magnitude was calculated based on the luciferase activity of each test substance with the luciferase activity in the non-treatment group assigned a value of 1. The values of concentration and induction magnitude were analyzed using a PRISM 2.01 (GraphPad Software Inc., U.S.A.) to cal-

Table 3. Glucose and Lipid Lowering Activities, and Body Weight Gain in KKA^y Mice Treated with Oxyiminoalkanoic Acids

Entry	PG reduction[a—c] (%)	TG reduction[a—c] (%)	BW gain ratio[d]
26	35**	47**	2.1
27	47**	63**	1.2
28	33	19	—
30	27	L	—
31	50**	31**	3.5
32	57**	49**	4.1
33	L	L	—
34	23*	L	2.4
37	39**	L	1.5
38	19[e]	19[e]	—
39	43**	43**	2.2
44	L[e]	L[e]	—
51	40**	L	2.0
52	49**	36*	3.4
56	48**	24	1.5
57	48**	30**	3.4

a) Maximum reductions in plasma glucose (PG) and plasma triglyceride (TG) levels at a dosage of 0.001% in the diet were calculated as percent reduction with respect to the control value. *b*) L indicates less than a 15% reduction at that dose. *c*) Statistically significant at $*p<0.05$, $**p<0.01$ by Dunnett's test. *d*) The ratio of body weight (BW) gain calculated by the following formula: [BW gain ratio]=[BW gain (administered)]/[BW gain (control)]. *e*) At a dosage of 0.01% in the diet.

Table 4. Glucose and Lipid Lowering Activities of **27** and Pioglitazone Hydrochloride in KKA^y Mice

	Plasma glucose lowering activity ED_{25} (mg/kg/d)[a]	Plasma triglyceride lowering activity ED_{25} (mg/kg/d)[a]
27	0.65	0.12
Pioglitazone hydrochloride	6	6

a) Effective dose for 25% reduction, estimated from a dose–response curve for three doses.

Table 5. Pharmacokinetic Parameters of Compound **27** in SD(IGS) Rats[a]

Pharmacokinetic parameter	*p.o.*	i.v.
Dose (mg/kg)	10	1
$AUC_{0—24\,h}$ (μg·h/ml)	261.36±18.52	30.57±2.11
$C_{5\,min}$ (μg/ml)	—	6.74±1.35
C_{max} (μg/ml)	20.04±1.01	—
T_{max} (h)	4.00±0.00	—
$T_{1/2}$ (h)	2.83±0.25	4.49±1.04
Bioavailability (%)	85.5±8.4	—

a) The results are the mean±S.D. of three male animals in each group.

culate the EC_{50}, the effective concentration of test compound required to induce 50% of the maximum activity.

(b) Glucose and Lipid Lowering Experiments The glucose and lipid lowering activities of the compounds were tested using KKA^y mice.[37] After being fed a powdered laboratory chow (CE-2, Clea Japan, Inc., Tokyo, Japan) over 3 d, female mice (9—13 weeks old) were divided into experimental groups of five animals each based on their blood glucose levels. The test compounds were given as a dietary admixture at 0.01 or 0.001% in the diet. The mice were fed the experimental diet and water *ad libitum* for 4 d. Blood samples were taken from the orbital vein. The plasma glucose levels were determined enzymatically using Iatrochem-GLU(A) (Iatron Laboratories, Inc., Tokyo, Japan) or L type Wako Glu 2 (Wako Pure Chemical Ind., Ltd., Tokyo, Japan). The plasma triglyceride levels were also determined enzymatically using Iatro-MA701 TG kits (Iatron Laboratories, Inc.) or L type Wako TG·H (Wako Pure Chemical Ind., Ltd.). The respective values are shown as percent reduction with respect to the control value. A 0.001% dosage was approximately 1.3—1.6 mg/kg/d. In case of diabetic KKA^y mice, the control values of PG and TG were approximately 450—550 mg/dl and 550—700 mg/dl, respectively. In case of normal C57BL mice, the values of PG and TG were approximately 200 mg/dl and 80 mg/dl, respectively.

Pharmacokinetic Analysis. (a) Single-Dose Pharmacokinetics Experiments were carried out in SD (IGS) rats (8 weeks old, male). The animals were fed the CE-2 diet and water *ad libitum*. They were dosed with the drug at 1 mg/kg/i.v. as an *N*,*N*-dimethylacetamide–PEG 400 (1 : 1) solution, or at 10 mg/kg/*p.o.* as a 0.5% MC suspension. Blood samples were collected at different time points (pre, 5, 10, 15, 30 min, 1, 2, 4, 8, and 24 h for the intravenous study; pre, 15, 30 min, 1, 2, 4, 8, and 24 h for the oral study, respectively) from a tail vein. The samples were analyzed by HPLC to calculate pharmacokinetic parameters such as $AUC_{0—24\,h}$, $C_{5\,min}$, C_{max}, T_{max}, $T_{1/2}$, and bioavailability. $AUC_{0—24\,h}$ is the area under the drug plasma concentration *versus* time curve. $C_{5\,min}$ is the observed plasma concentration 5 min after administration. C_{max} is the observed maximum plasma concentration. T_{max} is the time at which C_{max} is achieved. $T_{1/2}$ is the half-life of the drug. Bioavailability is calculated by the following formula:

$$[\text{bioavailability}]\,(\%)=[AUC_{0—24\,h}\,(p.o.)\times\text{dose (i.v.)}]/[AUC_{0—24\,h}\,(\text{i.v.})\times\text{dose }(p.o.)]\times 100$$

(b) Analysis of Plasma Samples (i) Sample Preparation: Acetonitrile was added to each plasma sample (100 μl). The mixture was stirred by irradiation with supersonic waves before centrifugal separation was carried out. The supernatant liquid was subjected to centrifugal condensation under reduced pressure at 30 °C. The residue was dissolved in acetonitrile–0.01 mol/l ammonium acetate (60 : 40, v/v, 200 μl). The mixture was stirred by irradiation with supersonic waves. Then centrifugal separation was carried out to remove insoluble substances. The supernatant liquid was used for HPLC analysis.

(ii) HPLC Assay: Inertsil ODS-3 (ϕ4.6×250 mm) was used for HPLC analysis. Analyses of compounds were carried out using acetonitrile–0.01 mol/l ammonium acetate (60 : 40, v/v) as a mobile phase at a flow rate of 1.0 ml/min at 40 °C, and the detection wavelength was 270 nm. Under these conditions, the retention time for **27** was 14.4 min.

Chemical Methods Melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out at Takeda Analytical Research Laboratories, Ltd., and all values are within ±0.4% of calculated values unless otherwise noted. IR spectra were recorded on a JASCO IR-810. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 spectrometer in solutions of $CDCl_3$ or DMSO-d_6 using tetramethylsilane as an internal standard. Chemical shifts are expressed as δ (ppm) values for protons relative to the internal standard. All compounds exhibited ^{1}H-NMR spectra and analytical data consistent with their proposed structures. Column chromatography was performed with a Merck Silica Gel 60 (0.063—0.200 mm). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, sext=sextet, sept=septet, m=multiplet, br=broad, dec.=decomposed. Data of a powder X-ray crystal diffraction were determined by RINT1100 Type (Rigakudenki, Japan) using Cu-Kα_1 ray (voltage: 40 kV; electric current: 40 mA) as a ray source and were expressed by angles of diffraction 2θ (°) and spacing d values (Å).

(*E*)-3-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-3-phenylpropionic Acid (26) (a) A mixture of 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**6a**, 5.00 g, 15.9 mmol), *N*-hydroxyphthalimide (2.59 g, 15.9 mmol), potassium carbonate (4.40 g, 31.9 mmol), and *N*,*N*-dimethylformamide (DMF) (50 ml) was stirred at room temperature for 20 h, then diluted with water (500 ml). The crystals were collected by filtration, washed with water, and dried under reduced pressure to give *N*-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxy}phthalimide (**9a**, 6.49 g, 93%) as colorless crystals, which were used for next reaction without further purification. mp 155—156 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 4.99 (2H, s), 5.16 (2H, s), 7.01 (2H, d, J=8.8 Hz), 7.42—7.50 (5H, m), 7.70—7.84 (4H, m), 7.98—8.04 (2H, m). IR (KBr) cm^{-1}: 1786, 1736, 1516, 1389, 1257, 974, 698. *Anal.* Calcd for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36. Found: C, 70.73; H, 4.67; N, 6.19.

(b) Hydrazine monohydrate (1.15 ml, 23.7 mmol) was added to a solution of *N*-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxy}phthalimide (**9a**, 5.22 g, 11.9 mmol) in EtOH (40 ml)–THF (40 ml) at room temperature. The mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was diluted with aqueous potassium carbonate and ex-

tracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**, 3.32 g, 90%) as colorless crystals. mp 68—69 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 4.64 (2H, s), 5.00 (2H, s), 5.35 (2H, br s), 7.02 (2H, d, J=8.8 Hz), 7.32 (2H, d, J=8.8 Hz), 7.42—7.47 (3H, m), 7.99—8.05 (2H, m); IR (KBr) cm^{-1}: 1610, 1512, 1246, 1176, 1005, 866, 714, 692. *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.74; H, 5.66; N, 9.04.

(c) A mixture of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**, 1.00 g, 3.22 mmol), ethyl benzoylacetate (**11a**, 0.612 ml, 3.54 mmol), acetic acid (0.554 ml, 9.67 mmol), sodium acetate (528 mg, 6.44 mmol), and EtOH (20 ml) was refluxed for 12 h. The reaction mixture was diluted with 1 M HCl and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 3, v/v) to give ethyl (*E*)-3-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-3-phenylpropionate (1.29 g, 83%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.1 Hz), 2.44 (3H, s), 3.76 (2H, s), 4.09 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.20 (2H, s), 7.01 (2H, d, J=8.4 Hz), 7.30—7.50 (8H, m), 7.61—7.67 (2H, m), 7.97—8.05 (2H, m); IR (neat) cm^{-1}: 2931, 1738, 1612, 1512, 1240, 1011, 692.

(d) Ethyl (*E*)-3-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-3-phenylpropionate (1.16 g, 2.39 mmol) was dissolved in THF (60 ml)–water (40 ml), then lithium hydroxide monohydrate (402 mg, 9.58 mmol) was added to the mixture. The whole was stirred at room temperature for 18 h. The solution was made acidic by addition of dil. HCl and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give **26** (1.08 g, 99%) as crystals. Recrystallization from AcOEt–hexane gave colorless crystals. mp 107—108 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 3.81 (2H, s), 4.98 (2H, s), 5.20 (2H, s), 6.98 (2H, d, J=8.8 Hz), 7.28—7.45 (8H, m), 7.59—7.68 (2H, m), 7.97—8.03 (2H, m). IR (KBr) cm^{-1}: 2931, 1713, 1610, 1514, 1248, 1022, 764, 692. *Anal.* Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.10; H, 5.45; N, 5.97.

(*E*)-4-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-phenylbutyric Acid (27) (a) A mixture of methyl 3-benzoylpropionate (**11b**, 15.0 g, 78.0 mmol), hydroxylamine hydrochloride (6.50 g, 93.6 mmol), sodium acetate (9.60 g, 117 mmol), and MeOH (150 ml) was refluxed for 8 h. After evaporation of the solvent, the residue was diluted with water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 3, v/v) to give less polar methyl (*E*)-4-(hydroxyimino)-4-phenylbutyrate [(*E*)-**7a**, 14.7 g, 91%] as a pale-yellow oil and polar methyl (*Z*)-4-(hydroxyimino)-4-phenylbutyrate [(*Z*)-**7a**, 1.37 g, 8%] as crystals. Recrystallization of (*Z*)-**7a** from AcOEt–hexane gave colorless crystals. The data for (*E*)-**7a**: ^{1}H-NMR ($CDCl_3$) δ: 2.58—2.67 (2H, m), 3.09—3.17 (2H, m), 3.66 (3H, s), 7.35—7.44 (3H, m), 7.56—7.67 (2H, m), 8.00—8.80 (1H, br). IR (neat) cm^{-1}: 3406, 2953, 1736, 1439, 1284, 1201, 1174, 937, 762, 696. The data for (*Z*)-**7a**: mp 76—77 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.58 (2H, t, J=7.4 Hz), 2.87 (2H, t, J=7.4 Hz), 3.67 (3H, s), 7.30—7.55 (5H, m). IR (KBr) cm^{-1}: 3253, 1726, 1435, 1329, 1203, 1169, 962, 897, 764, 696, 638. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.65; H, 6.20; N, 6.80.

(b) Sodium hydride (60% in oil, 3.00 g, 75.0 mmol) was added to a solution of methyl (*E*)-4-(hydroxyimino)-4-phenylbutyrate [(*E*)-**7a**, 15.5 g, 75.0 mmol] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**6a**, 23.5 g, 75.0 mmol) in DMF (100 ml) at 0 °C under nitrogen. The mixture was stirred at that temperature for 2 h. The solution was acidified with 1 M HCl, then made basic by addition of aqueous sodium hydrogen carbonate, and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 3, v/v) to leave an oil. The oil was dissolved in THF (100 ml)–MeOH (50 ml), then 2 M NaOH (50 ml) was added to the mixture. The whole was stirred at room temperature for 2 h, then made acidic by addition of 1 M HCl (101 ml) and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give crystals, which were recrystallized from AcOEt–hexane to give 27 (24.5 g, 86%) as colorless crystals (A form): mp 126—127 °C. The data of powder X-ray crystal diffraction of **27** A form are shown in Table 6.

A part of these crystals were recrystallized again from EtOH to give colorless crystals (B form). mp 137—138 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.54—2.63 (2H, m), 3.01—3.11 (2H, m), 5.01 (2H, s), 5.17 (2H, s), 7.02 (2H, d, J=8.8 Hz), 7.31—7.48 (8H, m), 7.60—7.66 (2H, m), 7.98—8.05 (2H, m). IR (KBr) cm^{-1}: 2931, 1724, 1512, 1250, 1018, 982, 771, 692. *Anal.* Calcd for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.95. Found: C, 71.46; H, 5.59; N, 5.94. The data of powder X-ray crystal diffraction of **27** B form are shown in Table 7.

Table 6. Data of Powder X-Ray Crystal Diffraction of **27** A Form

Angle of diffraction: 2θ (°)	Spacing: d value (Å)
5.98	14.8
10.7	8.28
12.1	7.30
18.0	4.93
21.0	4.23
24.6	3.62

Table 7. Data of Powder X-Ray Crystal Diffraction of **27** B Form

Angle of diffraction: 2θ (°)	Spacing: d value (Å)
5.04	17.5
9.92	8.91
11.3	7.81
14.8	5.98
19.1	4.65
20.7	4.29
21.7	4.09
25.1	3.54

(*E*)-4-{3-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-phenylbutyric Acid (29) (a) A mixture of 4-chloromethyl-5-methyl-2-phenyl-1,3-oxazole (37.0 g, 0.178 mol), salicilaldehyde (25.0 g, 0.205 mol), K_2CO_3 (27.1 g, 0.196 mol) and DMF (150 ml) was stirred at 70—80 °C for 4 h. The reaction mixture was poured into H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give 2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-benzaldehyde (**4b**, 41.8 g, 77.5%). Recrystallization from AcOEt–Et_2O gave crystals. mp 95 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 5.14 (2H, s), 7.07 (1H, t, J=7.5 Hz), 7.22 (1H, d, J=8.5 Hz), 7.4—7.5 (3H, m), 7.57 (1H, ddd, J=8.5, 7.5, 2 Hz), 7.86 (1H, dd, J=8, 2 Hz), 7.95—8.1 (2H, m), 10.51 (1H, s). *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.45; H, 4.99; N, 4.77.

(b) Sodium borohydride (325 mg, 8.59 mmol) was added to a cold (0 °C) stirred solution of 2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-benzaldehyde (**4b**, 5.00 g, 17.0 mmol) in MeOH (30 ml)–THF (30 ml). After stirring 0.5 h at room temperature, water was added to the reaction mixture, and the whole was stirred for 1 h. The crystals of 2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol (**5b**, 4.17 g, 83%) were isolated by filtration. Recrystallization from AcOEt–acetone gave colorless crystals. mp 155—156 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 4.70 (2H, s), 5.07 (2H, s), 6.95—7.00 (2H, m), 7.02—7.07 (1H, m), 7.25—7.34 (1H, m), 7.42—7.47 (3H, m), 6.95—7.08 (2H, m), 7.24—7.35 (2H, m), 7.40—7.50 (3H, m), 7.97—8.05 (2H, m). *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.16; H, 5.94; N, 4.66.

(c) Thionyl chloride (1.69 g, 14.2 mmol) was added to a solution of 2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol (**5b**, 4.00 g, 13.5 mmol) in toluene (60 ml), and the mixture was stirred at room temperature for 0.5 h. To the mixture was added ice-cooled water and extracted with AcOEt. The extract was washed with ice-cooled brine, dried over magnesium sulfate, and concentrated *in vacuo* to give 4-{[2-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**6c**, 3.50 g, 82%) as crystals. Recrystallization from AcOEt–hexane gave colorless crystals. mp 103—104 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 4.68 (2H, s), 5.09 (2H, s), 6.94—7.10 (2H, m), 7.25—7.50 (5H, m), 7.97—8.05 (2H, m). *Anal.* Calcd for $C_{18}H_{16}NO_2Cl$: C, 68.90; H, 5.14; N, 4.46. Found: C, 69.14; H, 5.10; N, 4.67.

(d) Sodium hydride (60% in oil, 200 mg, 5.00 mmol) was added to a solution of methyl (*E*)-4-(hydroxyimino)-4-phenylbutyrate [(*E*)-**7a**, 990 mg, 5.15 mmol] and 4-[(2-chloromethylphenoxy)methyl]-5-methyl-2-phenyl-1,3-oxazole (**6c**, 1.50 g, 4.78 mmol) in DMF (40 ml) at 0 °C under nitrogen. After stirring for 2 h, the mixture was acidified with 2 M HCl and extracted with AcOEt. The extract was washed with brine, dried over magnesium sul-

fate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4, v/v) to give methyl (*E*)-4-{2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-phenylbutyrate (1.65 g, 71%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.53—2.63 (2H, m), 3.04—3.13 (2H, m), 3.61 (3H, s), 5.07 (2H, s), 5.33 (2H, s), 6.95—7.08 (2H, m), 7.25—7.50 (8H, m), 7.57—7.65 (2H, m), 7.97—8.04 (2H, m).

(e) Methyl (*E*)-4-{2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-phenylbutyrate (1.60 g, 3.30 mmol) was dissolved in THF (10 ml)–MeOH (5 ml), and 1 M NaOH (5 ml) was added to the mixture. The whole was stirred at room temperature for 2 h, then made acidic by addition of 1 M HCl (5.5 ml) and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give **29** (1.42 g, 91%) as colorless crystals. mp 116—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 2.63—2.72 (2H, m), 2.96—3.05 (2H, m), 5.00 (2H, s), 5.19 (2H, s), 6.96—7.08 (2H, m), 7.25—7.48 (8H, m), 7.53—7.63 (2H, m), 7.97—8.04 (2H, m). *Anal.* Calcd for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.95. Found: C, 71.41; H, 5.66; N, 5.59.

(*E*)-4-{3-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-phenylbutyric Acid (28) (a) Using the procedure for preparation of **29**, step c, 3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol (**5a**, 84% yield) was prepared from 3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzaldehyde (**4a**) as colorless crystals. mp 101—102 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 4.69 (2H, d, J=6.2 Hz), 5.01 (2H, s), 6.95—7.00 (2H, m), 7.02—7.07 (1H, m), 7.25—7.34 (1H, m), 7.42—7.47 (3H, m), 7.99—8.05 (2H, m). IR (KBr) cm^{-1}: 3304, 1595, 1252, 1009, 779, 720. *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.27; H, 5.85; N, 4.60.

(b) Using the procedure for preparation of **29**, step d, 4-{[3-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**6b**, 84% yield) was prepared from 3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol (**5a**) as colorless crystals. mp 79—80 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 4.57 (2H, s), 5.01 (2H, s), 6.95—7.03 (2H, m), 7.06—7.08 (1H, m), 7.24—7.33 (1H, m), 7.40—7.48 (3H, m), 7.97—8.05 (2H, m). IR (KBr) cm^{-1}: 2879, 1599, 1446, 1255, 1014, 704. *Anal.* Calcd for $C_{18}H_{16}NO_2Cl$: C, 68.90; H, 5.14; N, 4.46. Found: C, 69.15; H, 5.18; N, 4.68.

(c) Using the procedure for preparation of **26**, step a, *N*-{3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxy}phthalimide (**9b**, 90% yield) was prepared from 4-{[3-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**6b**) as colorless crystals. mp 146—147 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 5.02 (2H, s), 5.21 (2H, s), 6.99—7.06 (1H, m), 7.13 (1H, d, J=7.6 Hz), 7.20—7.27 (1H, m), 7.32 (1H, d, J=7.6 Hz), 7.39—7.47 (3H, m), 7.70—7.80 (4H, m), 7.98—8.05 (2H, m). IR (KBr) cm^{-1}: 1726, 1599, 1491, 1394, 1171, 974, 876, 787, 690. *Anal.* Calcd for $C_{26}H_{20}N_2O_5 \cdot 1/4H_2O$: C, 70.18; H, 4.64; N, 6.30. Found: C, 70.37; H, 4.49; N, 6.37.

(d) Using the procedure for preparation of **26**, step b, 3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10b**, 97% yield) was prepared from *N*-{3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxy}-phthalimide (**9b**) as pale-yellow crystals. mp 81—82 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 4.69 (2H, s), 5.01 (2H, s), 5.41 (2H, br s), 6.94—7.06 (3H, m), 7.32 (1H, d, J=8.0 Hz), 7.40—7.48 (3H, m), 7.99—8.05 (2H, m). IR (KBr) cm^{-1}: 2910, 1601, 1444, 1255, 1016, 779, 716. *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.77; H, 5.81; N, 8.39.

(e) Using the procedure for preparation of **26**, step c, methyl (*E*)-4-{3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-phenylbutyrate (61% yield) was prepared from 3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10b**) and methyl 4-oxo-4-phenylbutyrate (**11b**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.53—2.62 (2H, m), 3.04—3.13 (2H, m), 3.62 (3H, s), 5.01 (2H, s), 5.22 (2H, s), 6.94—7.08 (3H, m), 7.28—7.48 (7H, m), 7.60—7.66 (2H, m), 7.97—8.05 (2H, m). IR (neat) cm^{-1}: 2949, 1738, 1448, 1260, 1173, 1024, 775, 692.

(f) Using the procedure for preparation of **29**, step e, **28** (82% yield) was prepared from methyl (*E*)-4-{3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-4-phenylbutyrate as colorless crystals. mp 108—109 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 2.61 (2H, t, J=7.5 Hz), 3.15 (2H, t, J=7.5 Hz), 5.11 (2H, s), 5.25 (2H, s), 6.91—6.97 (2H, m), 7.20—7.50 (8H, m), 7.59—7.65 (2H, m), 7.96—8.02 (2H, m). IR (KBr) cm^{-1}: 1716, 1603, 1489, 1277, 1014, 881, 690. *Anal.* Calcd for $C_{28}H_{26}N_2O_5$: C, 71.48; H, 5.57; N, 5.95. Found: C, 71.59; H, 5.45; N, 5.81.

(*E*)-5-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-5-phenylpentanoic Acid (30) (a) A mixture of ethyl 5-oxo-5-phenylpentanoate (**11c**, 8.00 g, 36.3 mmol), hydroxylamine hydrochloride (3.03 g, 43.6 mmol), sodium acetate (4.47 g, 54.5 mmol), and EtOH (70 ml) was refluxed for 15 h. After evaporation of the solvent, the residue was dissolved in water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 3, v/v) to give ethyl (*E*)-5-(hydroxyimino)-5-phenylpentanoate [(*E*)-**7b**, 7.55 g, 88%] as crystals. Recrystallization from hexane gave colorless crystals. mp 28—30 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1 Hz), 1.83—1.99 (2H, m), 2.39 (2H, t, J=7.3 Hz), 2.82—2.91 (2H, m), 4.13 (2H, q, J=7.1 Hz), 7.33—7.42 (3H, m), 7.60—7.70 (3H, m). IR (KBr) cm^{-1}: 3388, 2980, 1732, 1201, 1155, 937, 766, 696. *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.50; H, 7.42; N, 5.97.

(b) Using the procedures for preparation of **29**, steps d and e, **30** (80% yield) was prepared from ethyl (*E*)-5-(hydroxyimino)-5-phenylpentanoate [(*E*)-**7b**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**6a**) as colorless crystals. mp 129—130 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.74 (2H, quin, J=7.6 Hz), 2.25 (2H, t, J=7.6 Hz), 2.44 (3H, s), 2.80 (2H, t, J=7.6 Hz), 5.00 (2H, s), 5.16 (2H, s), 7.00 (2H, d, J=8.6 Hz), 7.32—7.47 (8H, m), 7.60—7.68 (2H, m), 7.98—8.04 (2H, m). IR (KBr) cm^{-1}: 2926, 1701, 1514, 1236, 1009, 924, 692. *Anal.* Calcd for $C_{29}H_{28}N_2O_5$: C, 71.88; H, 5.82; N, 5.78. Found: C, 71.82; H, 5.75; N, 5.66.

(*E*)-6-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-6-phenylhexanoic Acid (31) (a) A mixture of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**, 500 mg, 1.61 mmol), ethyl 6-oxo-6-phenylhexanoate (**11d**, 415 mg, 1.77 mmol), acetic acid (0.276 ml, 4.83 mmol), sodium acetate (264 mg, 3.22 mmol), and EtOH (20 ml) was refluxed for 13 h, then diluted with AcOEt, washed with 1 M HCl, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4, v/v) to give less polar ethyl (*E*)-6-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-6-phenylhexanoate (620 mg, 73%) as a colorless oil and polar ethyl (*Z*)-6-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-6-phenylhexanoate (120 mg, 14%) as a colorless oil. The data for (*E*)-adduct: ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.1 Hz), 1.45—1.73 (4H, m), 2.28 (2H, t, J=7.3 Hz), 2.44 (3H, s), 2.78 (2H, t, J=7.5 Hz), 4.09 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.15 (2H, s), 7.01 (2H, d, J=8.4 Hz), 7.33—7.48 (8H, m), 7.58—7.64 (2H, m), 7.99—8.05 (2H, m). IR (neat) cm^{-1}: 2931, 1734, 1610, 1512, 1238, 1011, 694. The data for (*Z*)-adduct: ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.1 Hz), 1.38—1.71 (4H, m), 2.26 (2H, t, J=7.3 Hz), 2.43 (3H, s), 2.53 (2H, t, J=7.5 Hz), 4.09 (2H, q, J=7.1 Hz), 4.99 (2H, s), 5.02 (2H, s), 6.97 (2H, d, J=8.4 Hz), 7.23—7.47 (10H, m), 7.97—8.05 (2H, m). IR (neat) cm^{-1}: 2931, 1712, 1612, 1512, 1238, 1009, 696.

(b) Using the procedure for preparation of **29**, step e, **31** (90% yield) was prepared from ethyl (*E*)-6-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-6-phenylhexanoate as colorless crystals. mp 112—113 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.23—1.52 (4H, m), 2.12 (2H, t, J=7.3 Hz), 2.45 (3H, s), 2.78 (2H, t, J=6.9 Hz), 5.03 (2H, s), 5.16 (2H, s), 7.00 (2H, d, J=8.8 Hz), 7.32—7.45 (8H, m), 7.57—7.63 (2H, m), 7.96—8.01 (2H, m). IR (KBr) cm^{-1}: 2937, 1728, 1512, 1240, 1176, 1030, 920, 692. *Anal.* Calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 71.99; H, 6.12; N, 5.56.

(*Z*)-6-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-6-phenylhexanoic Acid (32) Using the procedure for preparation of **29**, step e, **32** (99% yield) was prepared from ethyl (*Z*)-6-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-6-phenylhexanoate as colorless crystals. mp 101—102 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.13—1.45 (4H, m), 1.99—2.08 (2H, m), 2.45—2.52 (5H, m), 4.98 (2H, s), 5.06 (2H, s), 7.00 (2H, d, J=8.8 Hz), 7.26—7.47 (10H, m), 7.96—8.02 (2H, m). IR (KBr) cm^{-1}: 2941, 1713, 1510, 1234, 997, 696. *Anal.* Calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 72.30; H, 6.21; N, 5.39.

(*E*)-6-{3-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-6-phenylhexanoic Acid (33) (a) Using the procedure for preparation of **26**, step c, ethyl (*E*)-6-{3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-6-phenylhexanoate (58% yield) was prepared from 3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10b**) and ethyl 6-oxo-6-phenylhexanoate (**11d**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.1 Hz), 1.47—1.80 (4H, m), 2.29 (2H, t, J=7.5 Hz), 2.43 (3H, s), 2.80 (2H, t, J=7.5 Hz), 4.08 (2H, q, J=7.1 Hz), 5.01 (2H, s), 5.20 (2H, s), 6.93—7.08 (3H, m), 7.25—7.47 (7H, m), 7.58—7.64 (2H, m), 7.97—8.05 (2H, m). IR (neat) cm^{-1}: 2933, 1732, 1448, 1263, 1024, 775, 692.

(b) Using the procedure for preparation of **29**, step e, **33** (88% yield)

was prepared from ethyl (*E*)-6-{3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-6-phenylhexanoate as colorless crystals. mp 114—115 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.70 (4H, m), 2.30 (2H, t, J=6.8 Hz), 2.49 (3H, s), 2.82 (2H, t, J=6.8 Hz), 5.07 (2H, s), 5.19 (2H, s), 6.92—7.05 (2H, m), 7.15 (1H, br s), 7.29—7.48 (7H, m), 7.57—7.63 (2H, m), 7.97—8.02 (2H, m). IR (KBr) cm^{-1}: 2935, 1701, 1599, 1446, 1261, 1028, 916, 692. *Anal.* Calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 72.08; H, 6.04; N, 5.78.

(*E*)-7-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-7-phenylheptanoic Acid (34) (a) Using the procedure for preparation of **26**, step c, ethyl (*E*)-7-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-7-phenylheptanoate (77% yield) was prepared from 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**) and ethyl 7-oxo-7-phenylheptanoate (**11e**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.08—1.70 (9H, m), 2.24 (2H, t, J=7.5 Hz), 2.44 (3H, s), 2.76 (2H, t, J=7.5 Hz), 4.11 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.15 (2H, s), 7.02 (2H, d, J=8.8 Hz), 7.33—7.48 (8H, m), 7.57—7.63 (2H, m), 7.99—8.05 (2H, m). IR (neat) cm^{-1}: 2933, 1732, 1612, 1514, 1238, 1176, 1011, 694.

(b) Using the procedure for preparation of **29**, step e, **34** (82% yield) was prepared from ethyl (*E*)-7-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-7-phenylheptanoate as colorless crystals. mp 84—85 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.58 (6H, m), 2.11 (2H, t, J=7.5 Hz), 2.46 (3H, s), 2.74 (2H, t, J=7.5 Hz), 5.03 (2H, s), 5.15 (2H, s), 7.01 (2H, d, J=8.8 Hz), 7.32—7.47 (8H, m), 7.60—7.66 (2H, m), 7.97—8.03 (2H, m). IR (KBr) cm^{-1}: 2935, 1726, 1512, 1238, 1176, 1009, 937, 690. *Anal.* Calcd for $C_{31}H_{32}N_2O_5$: C, 72.64; H, 6.29; N, 5.46. Found: C, 72.38; H, 6.28; N, 5.50.

(*E*)-8-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-8-phenyloctanoic Acid (35) (a) A mixture of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**, 1.50 g, 4.83 mmol), ethyl 8-oxo-8-phenyloctanoate (**11f**, 2.54 g, 9.67 mmol), acetic acid (0.830 ml, 14.5 mmol), sodium acetate (793 mg, 9.67 mmol), and EtOH (40 ml) was refluxed for 18 h, then diluted with AcOEt. The mixture was washed with water and brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 5, v/v) to give less polar ethyl (*E*)-8-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-8-phenyloctanoate (2.02 g, 76%) as a colorless oil and polar ethyl (*Z*)-8-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-8-phenyloctanoate (408 mg, 15%) as a colorless oil. The data for (*E*)-adduct: ^{1}H-NMR ($CDCl_3$) δ: 1.18—1.65 (11H, m), 2.25 (2H, t, J=7.5 Hz), 2.44 (3H, s), 2.75 (2H, t, J=7.5 Hz), 4.12 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.15 (2H, s), 7.01 (2H, d, J=8.8 Hz), 7.33—7.46 (8H, m), 7.58—7.64 (2H, m), 7.99—8.05 (2H, m). IR (neat) cm^{-1}: 2933, 1732, 1612, 1514, 1240, 1176, 1011, 694. The data for (*Z*)-adduct: ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.65 (11H, m), 2.25 (2H, t, J=7.5 Hz), 2.43 (3H, s), 2.50 (2H, t, J=7.2 Hz), 4.12 (2H, q, J=7.1 Hz), 4.99 (2H, s), 5.02 (2H, s), 6.97 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz), 7.27—7.48 (8H, m), 7.99—8.04 (2H, m). IR (neat) cm^{-1}: 2929, 1732, 1610, 1512, 1238, 1174, 1009, 696.

(b) Using the procedure for preparation of **29**, step e, **35** (92% yield) was prepared from ethyl (*E*)-8-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-8-phenyloctanoate as colorless crystals. mp 116—117 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.07—1.52 (8H, m), 2.10 (2H, t, J=7.4 Hz), 2.46 (3H, s), 2.74 (2H, t, J=7.4 Hz), 5.01 (2H, s), 5.17 (2H, s), 7.00 (2H, d, J=8.4 Hz), 7.30—7.47 (8H, m), 7.60—7.67 (2H, m), 7.98—8.04 (2H, m). IR (KBr) cm^{-1}: 2926, 1720, 1514, 1244, 1012, 777, 694. *Anal.* Calcd for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 72.92; H, 6.39; N, 5.23.

(*E*)-9-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-9-phenylnonanoic Acid (36) A mixture of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (500 mg, 1.61 mmol), methyl 9-oxo-9-phenylnonanoate (**11g**, 464 mg, 1.77 mmol), sodium acetate (264 mg, 3.22 mmol), 1 M HCl (3 ml), and EtOH (20 ml) was refluxed for 72 h. The mixture was diluted with AcOEt, washed with water and brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 6, v/v) to leave an oil. The oil was dissolved in THF (10 ml)–MeOH (5 ml), then 1 M NaOH (5 ml) was added to the mixture. The whole was stirred at room temperature for 1 h, then made acidic by addition of dil. HCl and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give **36** (323 mg, 37%) as colorless crystals. mp 67—68 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.60 (10H, m), 2.17 (2H, t, J=7.3 Hz), 2.47 (3H, s), 2.76 (2H, t, J=7.3 Hz), 5.02 (2H, s), 5.15 (2H, s), 7.01 (2H, d, J=8.8 Hz), 7.32—7.48 (8H, m), 7.61—7.67 (2H, m), 7.99—8.05 (2H, m). IR (KBr) cm^{-1}: 2920, 1693, 1514, 1252, 1024, 937, 690. *Anal.* Calcd for $C_{33}H_{36}N_2O_5$: C, 73.31; H, 6.71; N, 5.18. Found: C, 73.00; H, 6.49; N, 5.19.

(*E*)-4-(4-Fluorophenyl)-4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}butyric Acid (37) (a) Ethyl succinyl chloride (40.8 ml, 286 mmol) was added dropwise to a suspension of aluminum chloride (41.6 g, 312 mmol) in 1,2-dichloroethane (300 ml) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. To this was added 4-fluorobenzene (25.0 g, 260 mmol). The whole was stirred at 60 °C for 15 h, then poured onto ice (500g). After stirring at room temperature for 1 h, the organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in EtOH (300 ml), then hydroxylamine hydrochloride (21.7 g, 312 mmol) and sodium acetate (32.0 g, 390 mmol) were added. The whole was refluxed for 20 h. After evaporation of the solvent, the residue was dissolved in water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4, v/v) to give ethyl (*E*)-4-(4-fluorophenyl)-4-(hydroxyimino)butyrate [(*E*)-**7c**, 7.45 g, 12%] as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.1 Hz), 2.56—2.65 (2H, m), 3.05—3.14 (2H, m), 4.11 (2H, q, J=7.1 Hz), 7.01—7.14 (2H, m), 7.56—7.66 (2H, m), 8.05—8.40 (1H, br). IR (neat) cm^{-1}: 3402, 1734, 1512, 1234, 1161, 839.

(b) Using the procedures for preparation of **29**, steps d and e, **37** (47% yield) was prepared from ethyl (*E*)-4-(4-fluorophenyl)-4-(hydroxyimino)butyrate [(*E*)-**7c**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**6a**) as colorless crystals. mp 139—140 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.52—2.63 (2H, m), 2.97—3.07 (2H, m), 5.00 (2H, s), 5.15 (2H, s), 6.97—7.10 (4H, m), 7.23—7.46 (5H, m), 7.56—7.66 (2H, m), 7.97—8.04 (2H, m). IR (KBr) cm^{-1}: 2926, 1720, 1510, 1249, 1020, 928, 835. *Anal.* Calcd for $C_{28}H_{25}N_2O_5F$: C, 68.84; H, 5.16; N, 5.73. Found: C, 68.68; H, 5.07; N, 5.69.

(*E*)-4-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-(4-phenoxyphenyl)butyric Acid (38) (a) Ethyl succinyl chloride (14.3 ml, 100 mmol) was added dropwise to a suspension of aluminum chloride (14.7 g, 110 mmol) in CH_2Cl_2 (120 ml) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. The mixture was added dropwise to a solution of diphenylether (34.0 g, 200 mmol) in CH_2Cl_2 (50 ml) at 0 °C. The whole was stirred at 0 °C for 3 h, then poured onto ice (200 g). After stirring at room temperature for 1 h, the organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in EtOH (150 ml), then hydroxylamine hydrochloride (8.34 g, 120 mmol) and sodium acetate (12.3 g, 150 mmol) were added. The whole was refluxed for 15 h. After evaporation of the solvent, the residue was dissolved in water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4, v/v) to give ethyl (*E*)-4-(hydroxyimino)-4-(4-phenoxyphenyl)butyrate [(*E*)-**7d**, 10.5 g, 34%] as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.1 Hz), 2.57—2.66 (2H, m), 3.06—3.15 (2H, m), 4.12 (2H, q, J=7.1 Hz), 6.97—7.19 (5H, m), 7.31—7.42 (2H, m), 7.59 (2H, d, J=9.2 Hz), 7.90—8.60 (1H, br). IR (neat) cm^{-1}: 3401, 1734, 1587, 1489, 1240, 872, 694.

(b) Using the procedure for preparation of **29**, step d, ethyl (*E*)-4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-(4-phenoxyphenyl)butyrate (66% yield) was prepared from ethyl (*E*)-4-(hydroxyimino)-4-(4-phenoxyphenyl)butyrate [(*E*)-**7d**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**6a**) as colorless crystals. mp 118—119 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.1 Hz), 2.44 (3H, s), 2.49—2.59 (2H, m), 2.99—3.09 (2H, m), 4.09 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.15 (2H, s), 6.94—7.18 (7H, m), 7.31—7.47 (7H, m), 7.61 (2H, d, J=8.8 Hz), 7.99—8.05 (2H, m). IR (KBr) cm^{-1}: 1734, 1587, 1487, 1238, 1144, 1001, 945, 908, 694. *Anal.* Calcd for $C_{36}H_{34}N_2O_6$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.16; H, 6.17; N, 4.72.

(c) Using the procedure for preparation of **29**, step e, **38** (99% yield) was prepared from ethyl (*E*)-4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-4-(4-phenoxyphenyl)butyrate as colorless crystals. mp 131—132 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.55—2.64 (2H, m), 2.99—3.08 (2H, m), 5.00 (2H, s), 5.15 (2H, s), 6.93—7.17 (7H, m), 7.29—7.47 (7H, m), 7.60 (2H, d, J=9.2 Hz), 7.98—8.04 (2H, m). IR (KBr) cm^{-1}: 2929, 1722, 1587, 1510, 1489, 1240, 1018, 839, 692. *Anal.* Calcd for $C_{34}H_{30}N_2O_6$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.36; H, 5.40; N, 5.04.

(*E*)-4-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-(2-pyridyl)butyric Acid (39) (a) Carbonyldiimidazole (7.25 g, 44.7 mmol) was added to a solution of 2-pyridinecarboxylic acid (5.00 g, 40.6 mmol) in THF (200 ml) at 0 °C. The mixture was stirred at 0 °C for

0.5 h and at room temperature for additional 2 h. This solution was added dropwise to a precooled (−78 °C) solution of *tert*-butyl lithioacetate, obtained from *tert*-butyl acetate (17.5 ml, 130 mmol) and LDA (130 mmol) at −78 °C, in THF (100 ml) over 1 h under nitrogen. After the reaction temperature was kept at this temperature for 15 min, it was quenched by addition of 1 M HCl (250 ml) and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4, v/v) to leave an oil. The oil was dissolved in THF (100 ml), cooled to 0 °C, then sodium hydride (60% in oil, 1.06 g, 26.4 mmol) was added. The mixture was stirred at 0 °C for 10 min, then ethyl bromoacetate (2.00 ml, 18.0 mmol) was added in one portion, and the whole was stirred at 0 °C for 8 h. After addition of 0.1 M HCl (300 ml) and extraction with AcOEt, the extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 5, v/v) to leave an oil. The oil was dissolved in toluene (200 ml) and treated with *p*-toluenesulfonic acid monohydrate (2.00 g, 10.5 mmol) at 80 °C for 20 h. After cooling to room temperature, the solution was diluted with AcOEt, washed with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 2, v/v) to give ethyl 4-oxo-4-(2-pyridyl)butyrate (**11h**, 1.56 g, 19%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.1 Hz), 2.76 (2H, d, J=6.7 Hz), 3.57 (2H, d, J=6.7 Hz), 4.16 (2H, q, J=7.1 Hz), 7.48 (1H, dd, J=4.8, 7.6 Hz), 7.84 (1H, dt, J=1.8, 7.6 Hz), 8.05 (1H, d, J=7.6 Hz), 8.69 (1H, dd, J=1.8, 4.8 Hz). IR (neat) cm^{-1}: 2983, 1732, 1701, 1215, 995, 779.

(b) Using the procedure for preparation of **26**, step c, ethyl (*E*)-4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-(2-pyridyl)butyrate (75% yield) was prepared from 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**) and ethyl 4-oxo-4-(2-pyridyl)-butyrate (**11h**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.1 Hz), 2.44 (3H, s), 2.55—2.64 (2H, m), 3.19—3.28 (2H, m), 4.07 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.19 (2H, s), 7.01 (2H, d, J=8.8 Hz), 7.19—7.24 (1H, m), 7.36 (2H, d, J=8.8 Hz), 7.39—7.46 (3H, m), 7.64 (1H, dt, J=1.8, 7.6 Hz), 7.87 (1H, d, J=8.0 Hz), 7.99—8.05 (2H, m), 8.54—8.59 (1H, m). IR (neat) cm^{-1}: 2929, 1732, 1512, 1238, 1176, 1011, 775, 714.

(c) Using the procedure for preparation of **29**, step e, **39** (87% yield) was prepared from ethyl (*E*)-4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-4-(2-pyridyl)butyrate as colorless crystals. mp 116—117 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 2.72—2.80 (2H, m), 3.10—3.18 (2H, m), 5.01 (2H, s), 5.21 (2H, s), 7.02 (2H, d, J=8.8 Hz), 7.30—7.48 (6H, m), 7.77 (1H, dt, J=1.8, 7.4 Hz), 7.91—8.05 (3H, m), 8.53—8.58 (1H, m). IR (KBr) cm^{-1}: 2935, 1720, 1512, 1252, 1020, 982, 789. *Anal.* Calcd for $C_{27}H_{25}N_3O_5$: C, 68.78; H, 5.34; N, 8.91. Found: C, 68.70; H, 5.34; N, 8.92.

(*E*)-4-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-(3-pyridyl)butyric Acid (40) (a) Using the procedure for preparation of **39**, step a, ethyl 4-oxo-4-(3-pyridyl)butyrate (**11i**, 38% yield) was prepared from 3-pyridinecarboxylic acid as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.1 Hz), 2.79 (2H, t, J=6.6 Hz), 3.33 (2H, t, J=6.6 Hz), 4.17 (2H, q, J=7.1 Hz), 7.43 (1H, dd, J=4.8, 8.0 Hz), 8.23—8.30 (1H, m), 8.80 (1H, dd, J=1.6, 4.8 Hz), 9.22 (1H, d, J=2.2 Hz). IR (neat) cm^{-1}: 2983, 1732, 1698, 1587, 1223, 1174, 1028, 706.

(b) Using the procedure for preparation of **26**, step c, ethyl 4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-(3-pyridyl)butyrate (73% yield, E : Z=*ca.* 4 : 1) was prepared from 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**) and ethyl 4-oxo-4-(3-pyridyl)butyrate (**11i**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.30 (3H, m), 2.44 (3H, s), 2.51—2.64 (2H, m), 2.86 (0.4H, t, J=6.9 Hz), 3.05 (1.6H, t, J=7.9 Hz), 4.02—4.18 (2H, m), 5.00 (2.4H, s like), 5.18 (1.6H, s), 6.95—7.06 (2H, m), 7.23—7.48 (6H, m), 7.71—7.78 (0.2H, m), 7.91—8.05 (2.8H, m), 8.53—8.61 (1H, m), 8.66—8.69 (0.2H, m), 8.85—8.88 (0.8H, m). IR (neat) cm^{-1}: 2929, 1732, 1512, 1238, 1011, 712.

(c) Using the procedure for preparation of **29**, step e, **40** (77% yield) was prepared from ethyl 4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-benzyloxyimino}-4-(3-pyridyl)butyrate as colorless crystals. mp 158—159 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.63 (2H, t, J=7.5 Hz), 3.07 (2H, t, J=7.5 Hz), 5.00 (2H, s), 5.18 (2H, s), 7.01 (2H, d, J=8.6 Hz), 7.23—7.50 (6H, m), 7.97—8.09 (3H, m), 8.52—8.56 (1H, m), 8.91—8.93 (1H, m). IR (KBr) cm^{-1}: 2933, 1705, 1610, 1516, 1254, 1018, 939, 712. *Anal.* Calcd for $C_{27}H_{25}N_3O_5$: C, 68.78; H, 5.34; N, 8.91. Found: C, 68.43; H, 5.49; N, 8.67.

(*E*)-4-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-(4-pyridyl)butyric Acid (41) (a) Using the procedure for preparation of **39**, step a, ethyl 4-oxo-4-(4-pyridyl)butyrate (**11j**, 31% yield) was prepared from 4-pyridinecarboxylic acid as a pale-brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.1 Hz), 2.78 (2H, t, J=6.5 Hz), 3.30 (2H, t, J=6.5 Hz), 4.17 (2H, q, J=7.1 Hz), 7.76 (2H, d, J=6.2 Hz), 8.83 (2H, d, J=6.2 Hz). IR (neat) cm^{-1}: 2981, 1734, 1701, 1408, 1223, 1174, 1030, 814.

(b) Using the procedure for preparation of **26**, step c, ethyl 4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-4-(4-pyridyl)butyrate (92% yield, E : Z=*ca.* 3 : 1) was prepared from 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**) and ethyl 4-oxo-4-(4-pyridyl)butyrate (**11j**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.31 (3H, m), 2.44 (3H, s), 2.48—4.63 (2H, m), 2.77—2.86 (0.5H, m), 3.02 (1.5H, t, J=7.9 Hz), 4.02—4.18 (2H, m), 5.00 (2.5H, s like), 5.20 (1.5H, s), 6.95—7.22 (2H, m), 7.20—7.56 (7H, m), 7.99—8.05 (2H, m), 8.59—8.66 (2H, m). IR (neat) cm^{-1}: 2929, 1734, 1512, 1238, 1176, 1011, 824, 714.

(c) Using the procedure for preparation of **29**, step e, **41** (75% yield) was prepared from ethyl 4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-benzyloxyimino}-4-(4-pyridyl)butyrate as colorless crystals. mp 161—162 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.58 (2H, t, J=7.5 Hz), 3.05 (2H, t, J=7.5 Hz), 5.00 (2H, s), 5.20 (2H, s), 7.02 (2H, d, J=8.8 Hz), 7.35 (2H, d, J=8.8 Hz), 7.38—7.46 (3H, m), 7.58 (2H, d, J=6.2 Hz), 7.98—8.04 (2H, m), 8.51 (2H, d, J=6.2 Hz). IR (KBr) cm^{-1}: 2929, 1730, 1610, 1512, 1236, 1018, 837, 714. *Anal.* Calcd for $C_{27}H_{25}N_3O_5$: C, 68.78; H, 5.34; N, 8.91. Found: C, 68.85; H, 5.32; N, 8.74.

(*Z*)-3-(2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-phenylacetoamido)propionic Acid (42) (a) Triethylamine (0.222 ml, 1.58 mmol) was added to a solution of β-alanine ethyl ester hydrochloride (243 mg, 1.58 mmol) in DMF (7 ml). The mixture was stirred room temperature for 0.5 h. To this was added (*Z*)-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}phenylacetic acid (**2**, 700 mg, 1.58 mmol), WSC (303 mg, 1.58 mmol), and HOBt (242 mg, 1.58 mmol). The whole was stirred at room temperature for 18 h, then diluted with AcOEt. The mixture was washed with diluted HCl, aqueous potassium carbonate, and brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 3, v/v) to give ethyl (*Z*)-3-(2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-2-phenylacetoamido)propionate (**24**, 829 mg, 97%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.1 Hz), 2.44 (3H, s), 2.60 (2H, d, J=6.0 Hz), 3.63—3.74 (2H, m), 4.10 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.16 (2H, s), 6.48—6.60 (1H, m), 7.01 (2H, d, J=8.8 Hz), 7.29—7.48 (8H, m), 7.58—7.65 (2H, m), 7.97—8.05 (2H, m). IR (neat) cm^{-1}: 2931, 1732, 1664, 1514, 1240, 1178, 1007, 692.

(b) Ethyl (*Z*)-3-(2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-phenylacetoamido)propionate (**24**, 720 mg, 1.33 mmol) was dissolved in THF (6 ml), water (4 ml), and MeOH (4 ml), then lithium hydroxide monohydrate (167 mg, 3.99 mmol) was added. The whole was stirred at room temperature for 1.5 h, then made acidic by addition of 1 M HCl (4.1 ml) and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to give **42** (661 mg, 97%) as colorless crystals. mp 121—122 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.38—2.47 (5H, m), 3.50—3.60 (2H, m), 5.02 (2H, s), 5.18 (2H, s), 6.10—6.20 (1H, m), 6.98 (2H, d, J=8.8 Hz), 7.27—7.50 (8H, m), 7.61—7.69 (2H, m), 7.92—7.99 (2H, m). IR (KBr) cm^{-1}: 3319, 2935, 1711, 1666, 1514, 1250, 991, 689. *Anal.* Calcd for C29H27N3O6: C, 67.83; H, 5.30; N, 8.18. Found: C, 67.51; H, 5.28; N, 8.10.

(*E*)-2-(3-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-3-phenylpropanamido)acetic Acid (43) (a) Using the procedure for preparation of **42**, step a, ethyl (*E*)-2-(3-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-3-phenylpropanamido)acetate (**25**, 86% yield) was prepared from (*E*)-3-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-3-phenylpropionic acid (**26**) and glycine ethyl ester hydrochloride as colorless crystals. mp 144—145 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.1 Hz), 2.44 (3H, s), 3.78 (2H, s), 3.88 (2H, d, J=5.2 Hz), 4.16 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.28 (2H, s), 6.65—6.80 (1H, br), 7.02 (2H, d, J=8.8 Hz), 7.32—7.47 (8H, m), 7.74—7.81 (2H, m), 7.98—8.04 (2H, m). IR (KBr) cm^{-1}: 3296, 1730, 1645, 1238, 1009, 690. *Anal.* Calcd for $C_{31}H_{31}N_3O_6$: C, 68.75; H, 5.77; N, 7.76. Found: C, 68.62; H, 5.63; N, 7.84.

(b) Using the procedure for preparation of **42**, step b, **43** (92% yield) was prepared from ethyl (*E*)-2-(3-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}-3-phenylpropanamido)acetate (**25**) as colorless crystals. mp 176—177 °C (THF–hexane). ^{1}H-NMR (DMSO-d_6) δ: 2.45 (3H,

s), 3.70—3.80 (4H, m), 5.00 (2H, s), 5.14 (2H, s), 7.03 (2H, d, J=8.4 Hz), 7.34—7.40 (5H, m), 7.47—7.57 (3H, m), 7.59—7.67 (2H, m), 7.92—7.98 (2H, m), 8.28—8.35 (1H, m). IR (KBr) cm^{-1}: 3296, 1728, 1643, 1514, 1236, 1014, 692. *Anal.* Calcd for $C_{29}H_{27}N_3O_6$: C, 67.83; H, 5.30; N, 8.18. Found: C, 67.60; H, 5.41; N, 7.96.

(*E*)-2,2-Dimethyl-6-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-benzyloxyimino}-6-phenylhexanoic Acid (44) (a) To a suspension of lithium aluminum hydride (949 mg, 25.0 mmol) in Et_2O (30 ml) was added an Et_2O (15 ml) solution of 2-[2-(methoxycarbonyl)ethyl]-2-phenyl-1,3-dioxolane[41] (**21**, 5.00 g, 21.1 mmol) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 0.5 h. The reaction was quenched by addition of water, and the precipitate was removed by filtration. The filtrate was extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 3, v/v) to give 2-(3-hydroxypropyl)-2-phenyl-1,3-dioxolane (**22**, 3.81 g, 87%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.61—1.72 (2H, m), 2.02 (2H, t, J=6.4 Hz), 3.63 (2H, t, J=6.3 Hz), 3.74—3.87 (2H, m), 3.95—4.08 (2H, m), 7.24—7.49 (5H, m). IR (neat) cm^{-1}: 3390, 2954, 1446, 1190, 1045, 957, 704.

(b) Methanesulfonyl chloride (1.81 ml, 23.4 mmol) was added to a solution of 2-(3-hydroxypropyl)-2-phenyl-1,3-dioxolane (**22**, 3.75 g, 18.0 mmol) and triethylamine (5.05 ml, 36.0 mmol) in AcOEt (100 ml) at 0 °C. The mixture was stirred for 0.5 h, then washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in acetone (100 ml), then sodium iodide (5.40 g, 36.0 mmol) was added to the solution. The whole was stirred at 60 °C for 2 h. After evaporation of the solvent, the residue was dissolved in water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give 2-(3-iodopropyl)-2-phenyl-1,3-dioxolane (**23**, 5.41 g, 94%) as crystals. Recrystallization from AcOEt–hexane gave colorless crystals. mp 71—73 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.83—2.05 (4H, m), 3.17 (2H, t, J=6.7 Hz), 3.69—3.86 (2H, m), 3.93—4.11 (2H, m), 7.28—7.48 (5H, m). IR (KBr) cm^{-1}: 2885, 1444, 1227, 1039, 899, 704. *Anal.* Calcd for $C_{12}H_{15}O_2I$: C, 45.30; H, 4.75. Found: C, 45.39; H, 4.74.

(c) *n*-Butyllithium (1.6 M solution in hexane, 2.16 ml, 3.46 mmol) was added dropwise to a cold (−20 °C) stirred solution of diisopropylamine (0.529 ml, 3.77 mmol) in THF (5 ml), and the mixture was stirred for 20 min. The mixture was cooled to −78 °C, and a THF (5 ml) solution of methyl isobutyrate (0.397 ml, 3.46 mmol) was added dropwise over a period of 0.5 h. The whole was stirred at −78 °C for 20 min, then 2-(3-iodopropyl)-2-phenyl-1,3-dioxolane (**23**, 1.00 g, 3.14 mmol) and HMPA (0.602 ml, 3.46 mmol) were added. The mixture was stirred at −40 °C for 3 h. The reaction was quenched by addition of dil. HCl and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in acetone (30 ml), then 1 M H_2SO_4 (10 ml) was added to the solution. The whole was refluxed for 3 h, then diluted with AcOEt, washed with water, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 7, v/v) to give methyl 2,2-dimethyl-6-oxo-6-phenylhexanoate (**11k**, 350 mg, 45%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, s), 1.55—1.80 (4H, m), 2.96 (2H, t, J=6.8 Hz), 3.65 (3H, s), 7.41—7.61 (3H, m), 7.92—8.02 (2H, m). IR (neat) cm^{-1}: 2951, 1732, 1687, 1449, 1244, 1047, 692.

(d) Using the procedure for preparation of **26**, step c, methyl (*E*)-2,2-dimethyl-6-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-6-phenylhexanoate (47% yield) was prepared from 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**) and methyl 2,2-dimethyl-6-oxo-6-phenylhexanoate (**11k**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (6H, s), 1.35—1.65 (4H, m), 2.44 (3H, s), 2.73 (2H, t, J=7.3 Hz), 3.55 (3H, s), 5.00 (2H, s), 5.15 (2H, s), 7.02 (2H, d, J=8.8 Hz), 7.33—7.48 (8H, m), 7.57—7.63 (2H, m), 7.99—8.05 (2H, m). IR (neat) cm^{-1}: 2947, 1732, 1512, 1240, 1009, 694.

(e) Methyl (*E*)-2,2-dimethyl-6-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-6-phenylhexanoate (340 mg, 0.629 mmol) was dissolved in THF (5 ml)–MeOH (5 ml), then 4 M KOH (5 ml) was added. The whole was refluxed for 1.5 h. After cooling to room temperature, the mixture was made acidic by addition of dil. HCl and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 1, v/v) to give **44** (275 mg, 83%) as crystals. Recrystallization from AcOEt–hexane gave colorless crystals. mp 111—112 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (6H, s), 1.35—1.55 (4H, m), 2.44 (3H, s), 2.73 (2H, t, J=6.6 Hz), 5.02 (2H, s), 5.15 (2H, s), 7.01 (2H, d, J=8.8 Hz), 7.32—7.47 (8H, m), 7.56—7.62 (2H, m), 7.98—8.04 (2H, m). IR (KBr) cm^{-1}: 1714, 1516, 1248, 1171, 1034, 985, 690. *Anal.* Calcd for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32. Found: C, 73.02; H, 6.37; N, 5.10.

(*E*)-3-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxy-imino}-1-indancarboxylic Acid (45) Using the procedure for preparation of **26**, step c, **45** (69% yield) was prepared from 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyamine (**10a**) and 3-oxo-1-indancarboxylic acid (**11l**) as colorless crystals. mp 148—149 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.11 (1H, dd, J=8.6, 19.0 Hz), 3.31 (1H, dd, J=4.4, 19.0 Hz), 4.12—4.20 (1H, m), 5.00 (2H, s), 5.16 (2H, s), 7.00 (2H, d, J=8.6 Hz), 7.28—7.46 (7H, m), 7.50—7.57 (1H, m), 7.68—7.74 (1H, m), 7.96—8.04 (2H, m). IR (KBr) cm^{-1}: 2922, 1722, 1514, 1240, 1007, 916, 760, 716. *Anal.* Calcd for $C_{28}H_{24}N_2O_5$: C, 71.78; H, 5.16; N, 5.98. Found: C, 71.71; H, 5.19; N, 5.75.

(*E*)-4-Phenyl-4-{4-[(2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxy-imino}butyric Acid (46) (a) Chloromethyl methyl ether (34.2 ml, 450 mmol) was added dropwise to a cold (0 °C) stirred suspension of 4-hydroxybenzaldehyde (50.0 g, 409 mmol), potassium carbonate (84.9 g, 614 mmol), and DMF (150 ml). The whole was stirred at 0 °C for 1 h and at room temperature for additional 11 h, then diluted with water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in THF (300 ml) and MeOH (50 ml). The solution was cooled to 0 °C, then sodium borohydride (7.76 g, 205 mmol) was added portionwise. The whole was stirred at 0 °C for 0.5 h, then quenched by addition of water carefully and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 3, v/v) to give 4-(methoxymethoxy)-benzyl alcohol (**14a**, 56.7 g, 82%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s), 4.63 (2H, s), 5.18 (2H, s), 7.03 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.8 Hz). IR (neat) cm^{-1}: 3388, 2899, 1612, 1512, 1232, 1151, 1078, 1003, 922, 818.

(b) Diethyl azodicarboxylate (40% in toluene, 142 g, 325 mmol) was added dropwise to a stirred solution of 4-(methoxymethoxy)benzyl alcohol (**14a**, 50.0 g, 297 mmol), *N*-hydroxyphthalimide (44.1 g, 270 mmol), and triphenylphosphine (83.7 g, 319 mmol) in THF (900 ml) at room temperature under nitrogen. The reaction was completed within 1 h. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt–hexane (1 : 1, v/v) to remove triphenylphosphine oxide. The obtained crystals were washed with solvent (AcOEt : hexane = 1 : 5). The crystals were dissolved in EtOH (50 ml) and THF (200 ml), then hydrazine monohydrate (33.7 ml, 694 mmol) was added dropwise. The whole was refluxed for 3 h, then cooled to room temperature, diluted with aqueous potassium carbonate and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. To the residue was added cold (0 °C) $isoPr_2O$, and the crystals were removed by filtration. The filtrate was concentrated *in vacuo* to give crude [4-(methoxymethoxy)benzyloxy]-amine (**16a**, 28.9 g, 58%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s), 4.63 (2H, s), 5.18 (2H, s), 7.04 (2H, d, J=8.6 Hz), 7.30 (2H, d, J=8.6 Hz). IR (neat) cm^{-1}: 3315, 2902, 1612, 1508, 1232, 1151, 1078, 1001, 846.

(c) A mixture of crude [4-(methoxymethoxy)benzyloxy]amine (**16a**, 4.99 g, 27.2 mmol), methyl 4-oxo-4-phenylbutyrate (**11b**, 5.71 g, 29.7 mmol), acetic acid (5.10 ml, 89.1 mmol), sodium acetate (4.87 g, 59.4 mmol), and MeOH (200 ml) was refluxed for 15 h. After evaporation of the half of the solvent, the mixture was diluted with AcOEt, washed with dil. HCl, brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in MeOH (5 ml) and THF (50 ml), then 1 M HCl (10 ml) was added. The whole was refluxed for 3 h. After cooling to room temperature, the mixture was diluted with water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 5, v/v) to give methyl (*E*)-4-[(4-hydroxybenzyloxy)imino]-4-phenylbutyrate (**17a**, 4.24 g, 50%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.59 (2H, m), 3.01—3.10 (2H, m), 3.63 (3H, s), 4.97—5.05 (1H, m), 5.14 (2H, s), 6.82 (2H, d, J=8.8 Hz), 7.25—7.38 (5H, m), 7.59—7.65 (2H, m). IR (neat) cm^{-1}: 3404, 1738, 1714, 1516, 1443, 1211, 1020, 694.

(d) A mixture of 4-(chloromethyl)-2-phenyl-1,3-oxazole (250 mg, 1.29 mmol), methyl (*E*)-4-[(4-hydroxybenzyloxy)imino]-4-phenylbutyrate (**17a**, 369 mg, 1.18 mmol), potassium carbonate (325 mg, 2.35 mmol), and DMF (7 ml) was stirred at room temperature for 17 h, then diluted with water and extracted with AcOEt. The extract was washed with water, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 9, v/v) to give methyl (*E*)-4-phenyl-4-{4-[(2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-

butyrate (320 mg, 58%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.60 (2H, m), 3.02—3.11 (2H, m), 3.62 (3H, s), 5.10 (2H, s), 5.17 (2H, s), 7.01 (2H, d, J=8.8 Hz), 7.32—7.40 (5H, m), 7.41—7.49 (3H, m), 7.60—7.66 (2H, m), 7.74 (1H, s), 8.03—8.09 (2H, m). IR (neat) cm^{-1}: 2949, 1738, 1512, 1246, 1024, 716, 692.

(e) Using the procedure for preparation of **42**, step b, **46** (87% yield) was prepared from methyl (*E*)-4-phenyl-4-{4-[(2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}butyrate as colorless crystals. mp 144—145 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.55—2.64 (2H, m), 3.02—3.11 (2H, m), 5.09 (2H, s), 5.17 (2H, s), 7.01 (2H, d, J=8.4 Hz), 7.33—7.40 (5H, m), 7.42—7.48 (3H, m), 7.60—7.66 (2H, m), 7.73 (1H, s), 8.02—8.08 (2H, m). IR (KBr) cm^{-1}: 2931, 1720, 1610, 1512, 1252, 1180, 1018, 984, 714. *Anal.* Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.01; H, 5.33; N, 6.17.

(*E*)-4-Phenyl-4-{4-[(2-phenyl-1,3-thiazol-4-yl)methoxy]benzyloxyimino}butyric Acid (47) (a) Using the procedure for preparation of **46**, step d, methyl (*E*)-4-phenyl-4-{4-[(2-phenyl-1,3-thiazol-4-yl)methoxy]benzyloxyimino}butyrate (63% yield) was prepared from 4-(chloromethyl)-2-phenyl-1,3-thiazole and methyl (*E*)-4-[(4-hydroxybenzyloxy)imino]-4-phenylbutyrate (**17a**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.60 (2H, m), 3.02—3.11 (2H, m), 3.62 (3H, s), 5.17 (2H, s), 5.28 (2H, s), 7.02 (2H, d, J=8.8 Hz), 7.31—7.49 (9H, m), 7.59—7.65 (2H, m), 7.93—7.99 (2H, m). IR (neat) cm^{-1}: 2949, 1738, 1610, 1512, 1242, 1003, 766, 692.

(b) Using the procedure for preparation of **42**, step b, **47** (90% yield) was prepared from methyl (*E*)-4-phenyl-4-{4-[(2-phenyl-1,3-thiazol-4-yl)-methoxy]benzyloxyimino}butyrate as colorless crystals. mp 104—105 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.55—2.64 (2H, m), 3.02—3.11 (2H, m), 5.17 (2H, s), 5.28 (2H, s), 7.02 (2H, d, J=8.8 Hz), 7.24—7.51 (9H, m), 7.58—7.66 (2H, m), 7.91—7.99 (2H, m). IR (KBr) cm^{-1}: 2929, 1726, 1610, 1514, 1250, 1016, 980, 762, 694. *Anal.* Calcd for $C_{27}H_{24}N_2O_4S$: C, 68.62; H, 5.12; N, 5.93. Found: C, 68.49; H, 5.09; N, 5.76.

(*E*)-4-Phenyl-4-{4-[(3-phenylisoxazol-5-yl)methoxy]benzyloxyimino}-butyric Acid (48) (a) Using the procedure for preparation of **46**, step d, methyl (*E*)-4-phenyl-4-{4-[(3-phenylisoxazol-5-yl)methoxy]benzyloxyimino}butyrate (62% yield) was prepared from 5-(chloromethyl)-3-phenylisoxazole and methyl (*E*)-4-[(4-hydroxybenzyloxy)imino]-4-phenylbutyrate (**17a**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.60 (2H, m), 3.02—3.11 (2H, m), 3.62 (3H, s), 5.17 (2H, s), 5.22 (2H, s), 6.66 (1H, s), 6.99 (2H, d, J=8.8 Hz), 7.34—7.49 (8H, m), 7.59—7.65 (2H, m), 7.78—7.84 (2H, m). IR (neat) cm^{-1}: 2949, 1738, 1612, 1508, 1240, 1026, 770, 694.

(b) Using the procedure for preparation of **42**, step b, **48** (97% yield) was prepared from methyl (*E*)-4-phenyl-4-{4-[(3-phenylisoxazol-5-yl)methoxy]-benzyloxyimino}butyrate as colorless crystals. mp 96—97 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.55—2.64 (2H, m), 3.02—3.11 (2H, m), 5.17 (2H, s), 5.21 (2H, s), 6.65 (1H, s), 6.99 (2H, d, J=8.8 Hz), 7.29—7.48 (8H, m), 7.59—7.65 (2H, m), 7.77—7.84 (2H, m). IR (KBr) cm^{-1}: 2927, 1707, 1614, 1512, 1244, 1011, 768, 694. *Anal.* Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.18; H, 5.31; N, 6.00.

(*E*)-4-Phenyl-4-{4-[(5-phenylisoxazol-3-yl)methoxy]benzyloxyimino}-butyric Acid (49) (a) Using the procedure for preparation of **46**, step d, methyl (*E*)-4-phenyl-4-{4-[(5-phenylisoxazol-3-yl)methoxy]benzyloxyimino}butyrate (63% yield) was prepared from 3-(chloromethyl)-5-phenylisoxazole and methyl (*E*)-4-[(4-hydroxybenzyloxy)imino]-4-phenylbutyrate (**17a**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.59 (2H, m), 3.01—3.11 (2H, m), 3.62 (3H, s), 5.16 (2H, s), 5.21 (2H, s), 6.66 (1H, s), 7.01 (2H, d, J=8.8 Hz), 7.34—7.53 (8H, m), 7.57—7.65 (2H, m), 7.74—7.82 (2H, m). IR (neat) cm^{-1}: 2949, 1738, 1612, 1512, 1242, 1020, 766, 692.

(b) Using the procedure for preparation of **42**, step b, **49** (80% yield) was prepared from methyl (*E*)-4-phenyl-4-{4-[(5-phenylisoxazol-3-yl)methoxy]-benzyloxyimino}butyrate as colorless crystals. mp 100—101 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.54—2.64 (2H, m), 3.02—3.11 (2H, m), 5.17 (2H, s), 5.21 (2H, s), 6.65 (1H, s), 7.01 (2H, d, J=8.8 Hz), 7.32—7.50 (8H, m), 7.57—7.66 (2H, m), 7.75—7.81 (2H, m). IR (KBr) cm^{-1}: 2927, 1701, 1610, 1514, 1454, 1234, 1012, 766, 690. *Anal.* Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 70.99; H, 5.22; N, 6.13.

(*E*)-4-{4-[(5-Methyl-2-phenyl-1,3-thiazol-4-yl)methoxy]benzyloxyimino}-4-phenylbutyric Acid (50) (a) Using the procedure for preparation of **46**, step d, methyl (*E*)-4-{4-[(5-methyl-2-phenyl-1,3-thiazol-4-yl)-methoxy]benzyloxyimino}-4-phenylbutyrate (71% yield) was prepared from 4-(chloromethyl)-5-methyl-2-phenyl-1,3-thiazole and methyl (*E*)-4-[(4-hydroxybenzyloxy)imino]-4-phenylbutyrate (**17a**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.60 (5H, m), 3.02—3.11 (2H, m), 3.62 (3H, s), 5.17 (2H, s), 5.18 (2H, s), 7.04 (2H, d, J=8.6 Hz), 7.33—7.51 (8H, m), 7.58—7.66 (2H, m), 7.85—7.93 (2H, m). IR (neat) cm^{-1}: 2949, 1738, 1612, 1512, 1236, 1011, 764, 692.

(b) Using the procedure for preparation of **42**, step b, **50** (75% yield) was prepared from methyl (*E*)-4-{4-[(5-methyl-2-phenyl-1,3-thiazol-4-yl)-methoxy]benzyloxyimino}-4-phenylbutyrate as colorless crystals. mp 99—100 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s), 2.54—2.63 (2H, m), 3.01—3.11 (2H, m), 5.17 (2H, s), 5.18 (2H, s), 7.04 (2H, d, J=8.8 Hz), 7.32—7.45 (8H, m), 7.60—7.66 (2H, m), 7.86—7.92 (2H, m). IR (KBr) cm^{-1}: 2926, 1716, 1610, 1514, 1240, 1020, 926, 760, 692. *Anal.* Calcd for $C_{28}H_{26}N_2O_4S$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.97; H, 5.42; N, 5.65.

(*E*)-4-(4-{[2-(2-Furyl)-5-methyl-1,3-oxazol-4-yl]methoxy}benzyloxyimino)-4-phenylbutyric Acid (51) (a) Using the procedure for preparation of **46**, step d, methyl (*E*)-4-(4-{[2-(2-furyl)-5-methyl-1,3-oxazol-4-yl]-methoxy}benzyloxyimino)-4-phenylbutyrate (67% yield) was prepared from 4-(chloromethyl)-2-(2-furyl)-5-methyl-1,3-oxazole and methyl (*E*)-4-[(4-hydroxybenzyloxy)imino]-4-phenylbutyrate (**17a**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.50—2.59 (2H, m), 3.01—3.11 (2H, m), 3.62 (3H, s), 5.00 (2H, s), 5.16 (2H, s), 6.51—6.54 (1H, m), 6.95—7.02 (3H, m), 7.28—7.40 (5H, m), 7.52—7.55 (1H, m), 7.59—7.66 (2H, m). IR (neat) cm^{-1}: 2951, 1738, 1512, 1238, 1012, 754.

(b) Using the procedure for preparation of **42**, step b, **51** (79% yield) was prepared from methyl (*E*)-4-(4-{[2-(2-furyl)-5-methyl-1,3-oxazol-4-yl]-methoxy}benzyloxyimino)-4-phenylbutyrate as colorless crystals. mp 124—125 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.54—2.63 (2H, m), 3.01—3.10 (2H, m), 4.99 (2H, s), 5.16 (2H, s), 6.50—6.54 (1H, m), 6.96—7.03 (3H, m), 7.30—7.40 (5H, m), 7.52—7.54 (1H, m), 7.60—7.65 (2H, m). IR (KBr) cm^{-1}: 2929, 1724, 1612, 1512, 1250, 1018, 982, 750. *Anal.* Calcd for $C_{26}H_{24}N_2O_6$: C, 67.82; H, 5.25; N, 6.08. Found: C, 67.67; H, 5.29; N, 5.97.

(*E*)-4-(4-{[5-Methyl-2-(2-thienyl)-1,3-oxazol-4-yl]methoxy}benzyloxyimino)-4-phenylbutyric Acid (52) (a) Using the procedure for preparation of **46**, step d, methyl (*E*)-4-(4-{[5-methyl-2-(2-thienyl)-1,3-oxazol-4-yl]-methoxy}benzyloxyimino)-4-phenylbutyrate (63% yield) was prepared from 4-(chloromethyl)-5-methyl-2-(2-thienyl)-1,3-oxazole and methyl (*E*)-4-[(4-hydroxybenzyloxy)imino]-4-phenylbutyrate (**17a**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.50—2.60 (2H, m), 3.02—3.11 (2H, m), 3.63 (3H, s), 4.98 (2H, s), 5.16 (2H, s), 6.99 (2H, d, J=8.8 Hz), 7.10 (1H, dd, J=3.6, 5.0 Hz), 7.32—7.42 (6H, m), 7.59—7.66 (3H, m). IR (neat) cm^{-1}: 2949, 1738, 1512, 1238, 1174, 1011, 725, 696.

(b) Using the procedure for preparation of **42**, step b, **52** (88% yield) was prepared from methyl (*E*)-4-(4-{[5-methyl-2-(2-thienyl)-1,3-oxazol-4-yl]methoxy}benzyloxyimino)-4-phenylbutyrate as colorless crystals. mp 142—143 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.54—2.63 (2H, m), 3.01—3.10 (2H, m), 4.97 (2H, s), 5.16 (2H, s), 6.99 (2H, d, J=8.8 Hz), 7.09 (1H, dd, J=3.6, 5.0 Hz), 7.32—7.42 (6H, m), 7.60—7.65 (3H, m). IR (KBr) cm^{-1}: 2929, 1724, 1512, 1248, 982, 723. *Anal.* Calcd for $C_{26}H_{24}N_2O_5S$: C, 65.53; H, 5.08; N, 5.88. Found: C, 65.56; H, 4.91; N, 5.75.

(*E*)-4-{4-[2-(Methyl-2-pyridylamino)ethoxy]benzyloxyimino}-4-phenylbutyric Acid (53) (a) Using the procedure for preparation of **29**, step b, 4-[2-(methyl-2-pyridylamino)ethoxy]benzyl alcohol (**5c**, 94% yield) was prepared from 4-[2-(methyl-2-pyridylamino)ethoxy]benzaldehyde (**4c**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.15 (3H, s), 3.98 (2H, t, J=5.5 Hz), 4.19 (2H, t, J=5.5 Hz), 4.61 (2H, d, J=5.4 Hz), 6.50—6.59 (2H, m), 6.89 (2H, d, J=8.8 Hz), 7.27 (2H, d, J=8.8 Hz), 7.40—7.50 (1H, m), 8.13—8.18 (1H, m). IR (neat) cm^{-1}: 3325, 2931, 1601, 1504, 1246, 1007, 770.

(b) Using the procedures for preparation of **29**, steps c, d, and e, **53** (41% yield) was prepared from 4-[2-(methyl-2-pyridylamino)ethoxy]benzyl alcohol (**5c**) and (*E*)-4-(hydroxyimino)-4-phenylbutyrate [(*E*)-**7a**] as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.51—2.62 (2H, m), 3.00—3.09 (2H, m), 3.13 (3H, s), 3.97 (2H, t, J=5.6 Hz), 4.19 (2H, t, J=5.6 Hz), 5.14 (2H, s), 6.50—6.59 (2H, m), 6.87 (2H, d, J=8.8 Hz), 7.24—7.51 (6H, m), 7.59—7.65 (2H, m), 8.13—8.18 (1H, m). IR (neat) cm^{-1}: 2929, 1732, 1608, 1504, 1423, 1246, 770. *Anal.* Calcd for $C_{25}H_{27}N_3O_4$–3/4AcOEt: C, 67.32; H, 6.66; N, 8.41. Found: C, 67.20; H, 6.63; N, 8.59.

(*E*)-4-{4-[2-(Methyl-2-pyrimydylamino)ethoxy]benzyloxyimino}-4-phenylbutyric Acid (54) (a) Using the procedure for preparation of **29**, step b, 4-[2-(methyl-2-pyrimidylamino)ethoxy]benzyl alcohol (**5d**, 91% yield) was prepared from 4-[2-(methyl-2-pyrimidylamino)ethoxy]benzaldehyde (**4d**) as colorless crystals. mp 73—74 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 3.29 (3H, s), 3.98—4.05 (2H, m), 4.17—4.24 (2H, m), 4.61 (2H, d, J=6.0 Hz), 6.48 (1H, t, J=4.8 Hz), 6.90 (2H, d, J=8.6 Hz), 7.27 (2H, d, J=8.6 Hz), 8.31 (2H, d, J=4.8 Hz). IR (KBr) cm^{-1}: 2938, 1587, 1529, 1410, 1240, 1036, 797. *Anal.* Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 65.09; H, 6.32; N, 16.09.

(b) Using the procedures for preparation of **29**, steps c and d, methyl (*E*)-

4-{4-[2-(methyl-2-pyrimydylamino)ethoxy]benzyloxyimino}-4-phenylbutyrate (51% yield) was prepared from 4-[2-(methyl-2-pyrimidylamino)-ethoxy]benzyl alcohol (**5d**) and methyl (*E*)-4-(hydroxyimino)-4-phenylbutyrate [(*E*)-**7a**] as a dark-red oil. ^{1}H-NMR ($CDCl_3$) δ: 2.49—2.58 (2H, m), 3.00—3.09 (2H, m), 3.30 (3H, s), 3.62 (3H, s), 4.02 (2H, t, J=5.7 Hz), 4.21 (2H, t, J=5.7 Hz), 5.14 (2H, s), 6.48 (1H, t, J=4.8 Hz), 6.90 (2H, d, J=8.4 Hz), 7.29—7.38 (5H, m), 7.59—7.65 (2H, m), 8.31 (2H, d, J=4.8 Hz). IR (neat) cm^{-1}: 2949, 1738, 1589, 1514, 1408, 1248, 1026, 800, 694.

(c) Using the procedure for preparation of **29**, step e, **54** (92% yield) was prepared from methyl (*E*)-4-{4-[2-(methyl-2-pyrimydylamino)ethoxy]benzyloxyimino}-4-phenylbutyrate as colorless crystals. mp 72—73 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.52—2.61 (2H, m), 3.00—3.09 (2H, m), 3.25 (3H, s), 4.01 (2H, t, J=5.5 Hz), 4.22 (2H, t, J=5.5 Hz), 5.14 (2H, s), 6.49 (1H, t, J=4.8 Hz), 6.88 (2H, d, J=8.4 Hz), 7.28—7.38 (5H, m), 7.59—7.65 (2H, m), 8.33 (2H, d, J=4.8 Hz). IR (KBr) cm^{-1}: 2935, 1713, 1593, 1556, 1514, 1410, 1250, 984, 797. *Anal.* Calcd for $C_{24}H_{26}N_4O_4$: C, 66.34; H, 6.03; N, 12.89. Found: C, 66.49; H, 6.20; N, 12.70.

(*E*)-4-{4-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyloxyimino}-4-phenylbutyric Acid (55) (a) Sodium hydride (60% in oil, 649 mg, 16.2 mmol) was added portionwise to a solution of 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethanol (3.00 g, 14.8 mmol) in DMF (60 ml) at room temperature under nitrogen. The mixture was stirred at room temperature for 1 h. A DMF (15 ml) solution of 4-fluorobenzaldehyde (2.02 g, 16.2 mmol) was added dropwise to the mixture. The whole was stirred at room temperature for 12 h. The mixture was poured onto ice (50 g), then the solvent was evaporated *in vacuo*. The residue was diluted with AcOEt, washed with water, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4, v/v) to leave an oil. The oil was dissolved in THF (20 ml)–MeOH (20 ml), then sodium borohydride (321 mg, 8.49 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h, then quenched by addition of water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was dissolved in toluene (20 ml), then thionyl chloride (0.888 ml, 12.2 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h, and the solvent was evaporated *in vacuo* to give 4-{2-[4-(chloromethyl)phenoxy]ethyl}-5-methyl-2-phenyl-1,3-oxazole (**6d**, 2.51 g, 52%) as crystals. Recrystallization from AcOEt–hexane gave pale-yellow crystals. mp 93—94 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.98 (2H, d, J=6.7 Hz), 4.25 (2H, d, J=6.7 Hz), 4.56 (2H, s), 6.88 (2H, d, J=8.8 Hz), 7.29 (2H, d, J=8.8 Hz), 7.40—7.49 (3H, m), 7.95—8.02 (2H, m). IR (KBr) cm^{-1}: 1608, 1516, 1248, 1180, 1026, 710, 689, 667. *Anal.* Calcd for $C_{19}H_{18}NO_2Cl$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.69; H, 5.61; N, 4.36.

(b) Using the procedure for preparation of **29**, step d, methyl (*E*)-4-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyloxyimino}-4-phenylbutyrate (26% yield) was prepared from methyl (*E*)-4-(hydroxyimino)-4-phenylbutyrate [(*E*)-**7a**] and 4-{2-[4-(chloromethyl)phenoxy]ethyl}-5-methyl-2-phenyl-1,3-oxazole (**6d**) as colorless crystals. mp 73—74 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.49—2.58 (2H, m), 2.95—3.09 (4H, m), 3.61 (3H, s), 4.25 (2H, t, J=6.7 Hz), 5.14 (2H, s), 6.90 (2H, d, J=8.6 Hz), 7.27—7.46 (8H, m), 7.59—7.65 (2H, m), 7.95—8.00 (2H, m). IR (KBr) cm^{-1}: 1734, 1514, 1254, 1020, 984, 710, 690. *Anal.* Calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 72.24; H, 5.93; N, 5.62.

(c) Using the procedure for preparation of **29**, step e, **55** (99% yield) was prepared from methyl (*E*)-4-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-ethoxy]benzyloxyimino}-4-phenylbutyrate as colorless crystals. mp 106—107 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.53—2.62 (2H, m), 2.94—3.09 (4H, m), 4.24 (2H, t, J=6.8 Hz), 5.14 (2H, s), 6.89 (2H, d, J=8.4 Hz), 7.29—7.45 (8H, m), 7.59—7.65 (2H, m), 7.94—8.00 (2H, m). IR (KBr) cm^{-1}: 2924, 1728, 1512, 1244, 1026, 775, 690. *Anal.* Calcd for $C_{29}H_{28}N_2O_5$: C, 71.88; H, 5.82; N, 5.78. Found: C, 71.84; H, 5.89; N, 5.64.

(*E*)-6-(4-{[2-(2-Furyl)-5-methyl-1,3-oxazol-4-yl]methoxy}benzyloxyimino)-6-phenylhexanoic Acid (56) (a) *tert*-Butyldimethylsilyl chloride (24.1 g, 160 mmol) was added to a stirred mixture of 4-hydroxybenzaldehyde (17.8 g, 145 mmol), imidazole (19.8 g, 292 mmol), and DMF (100 ml). The whole was stirred at room temperature for 1.5 h, then diluted with water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in THF (300 ml) and MeOH (40 ml). The solution was cooled to 0 °C, then sodium borohydride (11.1 g, 292 mmol) was added portionwise. The whole was stirred at 0 °C for 0.5 h, then quenched by addition of water carefully and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4, v/v) to give 4-(*tert*-butyldimethylsilyloxy)benzyl alcohol (**14b**, 27.7 g, 79%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.19 (6H, s), 0.98 (9H, s), 4.61 (2H, s), 6.83 (2H, d, J=8.4 Hz), 7.23 (2H, d, J=8.4 Hz). IR (neat) cm^{-1}: 3323, 2930, 1610, 1510, 1261, 916, 839, 781.

(b) Diethyl azodicarboxylate (40% in toluene, 54.0 g, 113 mmol) was added dropwise to a stirred solution of 4-(*tert*-butyldimethylsilyloxy)benzyl alcohol (**14b**, 27.5 g, 113 mmol), *N*-hydroxyphthalimide (16.8 g, 103 mmol), and triphenylphosphine (31.1 g, 118 mmol) in THF (450 ml) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 18 h. After evaporation of the solvent, the residue was diluted with isoPr$_2$O (200 ml). The precipitate was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane–toluene (1 : 10 : 10, v/v) to give *N*-[4-(*tert*-butyldimethylsilyloxy)benzyloxy]phthalimide (**15a**, 17.4 g, 43%) as crystals. Recrystallization from AcOEt–hexane gave colorless crystals. mp 76—77 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.17 (6H, s), 0.96 (9H, s), 5.14 (2H, s), 6.83 (2H, d, J=8.6 Hz), 7.40 (2H, d, J=8.6 Hz), 7.70—7.84 (4H, m). IR (KBr) cm^{-1}: 2927, 1722, 1512, 1257, 912, 698. *Anal.* Calcd for $C_{21}H_{25}NO_4Si$: C, 65.77; H, 6.57; N, 3.65. Found: C, 65.89; H, 6.48; N, 3.91.

(c) Hydrazine monohydrate (1.25 ml, 25.8 mmol) was added dropwise to a solution of *N*-[4-(*tert*-butyldimethylsilyloxy)benzyloxy]phthalimide (**15a**, 5.00 g, 12.9 mmol) in THF (40 ml) and EtOH (10 ml) at room temperature. The whole was heated at 60 °C for 1 h, then cooled to room temperature, diluted with aqueous potassium carbonate and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give crude [4-(*tert*-butyldimethylsilyloxy)benzyloxy]amine (**16b**, 3.15 g, 95%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.19 (6H, s), 0.98 (9H, s), 4.62 (2H, s), 5.20—5.50 (2H, br), 6.83 (2H, d, J=8.6 Hz), 7.24 (2H, d, J=8.6 Hz). IR (neat) cm^{-1}: 2930, 1608, 1512, 1261, 916, 841, 781.

(d) A mixture of crude [4-(*tert*-butyldimethylsilyloxy)benzyloxy]amine (**16b**, 5.31 g, 20.6 mmol), ethyl 6-oxo-6-phenylhexanoate (**11d**, 6.76 g, 28.9 mmol), acetic acid (3.54 ml, 61.8 mmol), sodium acetate (3.38 g, 41.2 mmol), and EtOH (150 ml) was refluxed for 18 h. After evaporation of the solvent, the mixture was diluted with AcOEt, washed with dil. HCl and brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in THF (100 ml), then tetrabutylammonium fluoride trihydrate (6.89 g, 21.8 mmol) was added. The whole was stirred at room temperature for 1 h, then added water and extracted with AcOEt. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 7, v/v) to give ethyl (*E*)-6-[(4-hydroxybenzyloxy)imino]-6-phenylhexanoate (**17b**, 5.64 g, 77%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.1 Hz), 1.45—1.75 (4H, m), 2.23—2.31 (2H, m), 2.73—2.81 (2H, m), 4.09 (2H, q, J=7.1 Hz), 5.04 (1H, s), 5.13 (2H, s), 6.82 (2H, d, J=8.2 Hz), 7.25—7.38 (5H, m), 7.58—7.64 (2H, m). IR (neat) cm^{-1}: 3390, 2935, 1708, 1518, 1213, 1024, 766, 696.

(e) Using the procedure for preparation of **46**, step d, ethyl (*E*)-6-(4-{[2-(2-furyl)-5-methyl-1,3-oxazol-4-yl]methoxy}benzyloxyimino)-6-phenylhexanoate (88% yield) was prepared from 4-(chloromethyl)-2-(2-furyl)-5-methyl-1,3-oxazole and ethyl (*E*)-6-[(4-hydroxybenzyloxy)imino]-6-phenylhexanoate (**17b**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.1 Hz), 1.45—1.75 (4H, m), 2.28 (2H, t, J=7.1 Hz), 2.42 (3H, s), 2.73—2.82 (2H, m), 4.09 (2H, q, J=7.1 Hz), 5.00 (2H, s), 5.15 (2H, s), 6.51—6.54 (1H, m), 6.95—7.03 (3H, m), 7.30—7.39 (5H, m), 7.53—7.64 (3H, m). IR (neat) cm^{-1}: 2931, 1732, 1512, 1238, 1012, 730.

(f) Using the procedure for preparation of **42**, step b, **56** (98% yield) was prepared from ethyl (*E*)-6-(4-{[2-(2-furyl)-5-methyl-1,3-oxazol-4-yl]-methoxy}benzyloxyimino)-6-phenylhexanoate as colorless crystals. mp 112—113 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.55 (4H, m), 2.15—2.23 (2H, m), 2.43 (3H, s), 2.74—2.82 (2H, m), 5.01 (2H, s), 5.15 (2H, s), 6.49—6.53 (1H, m), 6.94—7.01 (3H, m), 7.33—7.39 (5H, m), 7.52—7.55 (1H, m), 7.57—7.63 (2H, m). IR (KBr) cm^{-1}: 2970, 1713, 1514, 1240, 1022, 939, 758. *Anal.* Calcd for $C_{28}H_{28}N_2O_6$: C, 68.84; H, 5.78; N, 5.73. Found: C, 68.58; H, 5.82; N, 5.75.

(*E*)-6-(4-{[5-Methyl-2-(2-thienyl)-1,3-oxazol-4-yl]methoxy}benzyloxyimino)-6-phenylhexanoic Acid (57) (a) Using the procedure for preparation of **46**, step d, ethyl (*E*)-6-(4-{[5-methyl-2-(2-thienyl)-1,3-oxazol-4-yl]-methoxy}benzyloxyimino)-6-phenylhexanoate (95% yield) was prepared from 4-(chloromethyl)-5-methyl-2-(2-thienyl)-1,3-oxazole and ethyl (*E*)-6-[(4-hydroxybenzyloxy)imino]-6-phenylhexanoate (**17b**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.1 Hz), 1.45—1.75 (4H, m), 2.28 (2H, t, J=7.1 Hz), 2.41 (3H, s), 2.77 (2H, t, J=7.4 Hz), 4.09 (2H, q, J=7.1 Hz), 4.98 (2H, s), 5.15 (2H, s), 6.99 (2H, d, J=8.8 Hz), 7.09 (1H, dd, J=3.6,

5.0 Hz), 7.31—7.42 (6H, m), 7.58—7.65 (3H, m). IR (neat) cm^{-1}: 2931, 1732, 1512, 1238, 1024, 725, 696.

(b) Using the procedure for preparation of **42**, step b, **57** (92% yield) was prepared from ethyl (*E*)-6-(4-{[5-methyl-2-(2-thienyl)-1,3-oxazol-4-yl]-methoxy}benzyloxyimino)-6-phenylhexanoate as colorless crystals. mp 101—102 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.55 (4H, m), 2.15—2.24 (2H, m), 2.42 (3H, s), 2.74—2.82 (2H, m), 5.00 (2H, s), 5.16 (2H, s), 6.98 (2H, d, J=8.6 Hz), 7.09 (1H, dd, J=3.6, 5.0 Hz), 7.31—7.42 (6H, m), 7.57—7.67 (3H, m). IR (KBr) cm^{-1}: 2929, 1713, 1514, 1240, 1022, 937, 729, 690. *Anal.* Calcd for $C_{28}H_{28}N_2O_5S$: C, 66.65; H, 5.59; N, 5.55. Found: C, 66.52; H, 5.66; N, 5.64.

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