# Studies on Non-Thiazolidinedione Antidiabetic Agents. 1. Discovery of Novel Oxyiminoacetic Acid Derivatives

Hiroshi IMOTO,* Eikoh IMAMIYA, Yu MOMOSE, Yasuo SUGIYAMA, Hiroyuki KIMURA, and Takashi SOHDA

*Takeda Chemical Industries, Ltd., Pharmaceutical Research Division; 2–17–85 Juso-Honmachi, Yodogawa-ku, Osaka 532–8686, Japan.* Received May 16, 2002; accepted August 2, 2002

**A novel series of oxyiminoacetic acid derivatives were synthesized in an effort to develop a potent antidiabetic agent, which does not contain the 2,4-thiazolidinedione moiety. These compounds were evaluated for glucose and lipid lowering effects in genetically obese and diabetic KKA$^y$ mice. Several of the compounds showed strong antidiabetic activity, including functional potency at peroxisome proliferator-activated receptor (PPAR)-$\gamma$. (*Z*)-2-[4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino]-2-(4-phenoxyphenyl)acetic acid (25) significantly reduced plasma glucose (33%, $p<0.01$) and plasma triglycelide levels (43%, $p<0.01$) even at a dosage of 0.001% in diet. Pharmacokinetic analyses of 25 are also reported.**

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

Type 2 diabetes is a multifactorial disease defined by a high plasma glucose level, and is characterized by both insulin resistance and impaired insulin secretion by pancreatic $\beta$-cells.[1] Clinical studies[2—5] indicate a direct relationship between hyperglycemia and long-term complications such as neuropathy, nephropathy, retinopathy, arteriosclerosis, and coronary artery disease. The disease is also associated with a high degree of morbidity and mortality. Therefore, it is important to control blood glucose levels in diabetics, especially during the early stage of the disease.[6]

The fundamental modes of treatment for type 2 diabetes are aerobic exercise and energy restriction, and these regimes increase insulin sensitivity.[7] However, few patients are able to achieve a satisfactory control of blood glucose. The most commonly used oral antidiabetic agents have been sulfonylureas. These agents increase insulin secretion from pancreatic $\beta$-cells, but sometimes induce severe hypoglycemia and weight gain,[8] and hyperinsulinemia is known to be a risk factor for ischemic heart disease.[9] In addition, high rates of both primary and secondary failure are observed with these drugs.[10—13] Therefore, drugs that ameliorate the insulin resistance without stimulating insulin release from $\beta$-cells have been developed for the treatment of type 2 diabetes.

The prototypical 2,4-thiazolidinedione, ciglitazone (**1**)[14] (Chart 1) was discovered by our company, and has antihyperglycemic activity in insulin-resistant animal models, KKA$^y$ mice[15] and Wistar fatty rats,[16] but no effect in insulin-deficient animal models of diabetes.[17,18] During structure–activity relationship studies on 2,4-thiazolidinediones and related compounds, we discovered highly potent compounds, such as pioglitazone (**2**),[19] and AD-5061 (**3**)[20] (Chart 1). Since the discovery of ciglitazone (**1**), a number of pharmaceutical companies have been evaluating new 2,4-thiazolidinedione analogs as agents for improving insulin resistance. Troglitazone (**4**)[21] was launched first in the market, but had been withdrawn because of liver toxicity and related deaths associated with the drug. Nowadays, two 2,4-thiazolidinedione class agents, pioglitazone (**2**) and rosiglitazone (**5**)[22] are clinically used. (Chart 1). Many companies are still endeavoring to find a new glucose lowering agent.[23—35] Although the precise mechanism of action of these drugs remains unknown, recent study suggests that antidiabetic thiazolidinediones interact with a family of nuclear receptors known as peroxisome proliferator-activated receptor (PPAR)-$\gamma$.[36] PPAR$\gamma$ is one of a subfamily of PPARs encoded by independent genes. Three human PPARs, designated PPAR$\alpha$, PPAR$\gamma$, and PPAR$\delta$, have been identified to date.[37—39] It was also observed that the potency for activation of PPAR$\gamma$ *in vitro* mirrored the *in vivo* glucose lowering activity in diabetic ob/ob mice.[40] This would indicate that the major mechanisms of action of 2,4-thiazolidinediones involve PPAR$\gamma$.

In the case of those 2,4-thiazolidinediones already on the market, several side effects, such as anemia, edema, and body weight gain, have been reported.[41] Naturally it occurs to us to find a new class of compounds with fewer side effects and a more advanced profile than known 2,4-thiazolidinediones. Thus, we focused on the search for a new series of non-thiazolidinedione compounds with potent antihyperglycemic activity in insulin-resistant animal models.

First, we selected (*Z*)-(4-chlorobenzyloxyimino)phenylacetic acid (**6**) (Fig. 1) as a seed compound. Compound (**6**) was found from our *in vivo* KKA$^y$ mice screening to search for novel glucose and lipid lowering agents. Although compound (**6**) has weak antihyperglycemic activity (data not

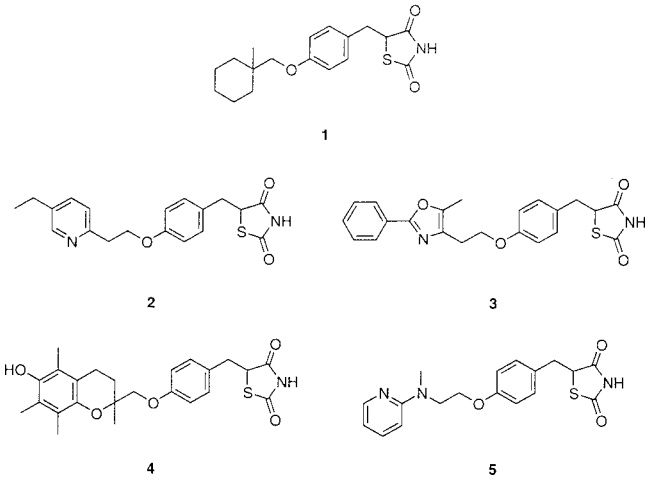



Chart 1

* To whom correspondence should be addressed. e-mail: Imoto_Hiroshi@takeda.co.jp

shown), we paid attention to its unique structure. There have been several reports of non-thiazolidine glucose and lipid lowering agents.[28—31,33] However, oxyiminoacetic acid derivatives as such agents have not been reported to our knowledge. For that reason, much effort was made to find more potent oxyiminoacetic acids. Compounds synthesized were evaluated first by *in vivo* KKA$^y$ mice screening. Although *in vivo* evaluation as first screening might not be efficient than *in vitro* evaluation in general, the screening using KKA$^y$ mice, which has been well established to develop pioglitazone (**2**),[19] takes only 4 d to evaluate compounds. In addition, compounds having poor pharmacokinetic properties would remove at the early stage of development.

Early in the modification, we found that replacement of the chloro moiety in **6** with the (5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy moiety enhanced the potency [compound (**7**), Fig. 1]. Encouraged by this result, we planned to synthesize a new series of oxyiminoacetic acids (structure A, Fig. 1) to investigate the effect of the phenyl group of **7**, which is positioned $\alpha$ to the carboxyl group, as antidiabetic agents. In this paper, we describe the synthesis, structure–activity relationships (SARs), and biological analysis of oxyiminoacetic acids.

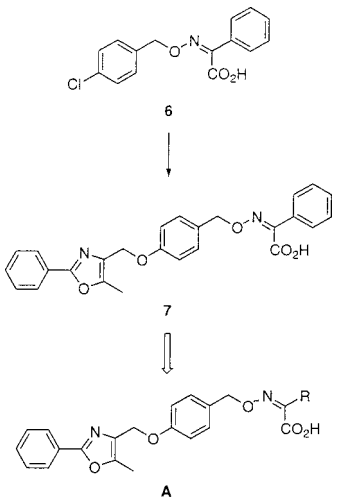



Fig. 1

## Chemistry

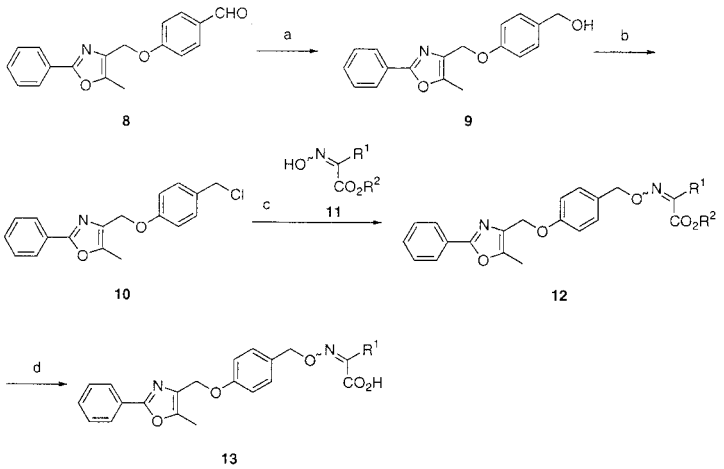
The general preparation procedure of oxyiminoacetic acids and their derivatives is outlined in Chart 2. The starting benzaldehyde (**8**) was reduced by sodium borohydride to give benzyl alcohol (**9**). Treatment of **9** with thionyl chloride gave benzyl chloride (**10**). Alkylation of oximes (**11**) with **10** gave alkoxyiminoacetates (**12**). Saponification of **12** with aqueous NaOH afforded acetic acid derivatives (**13**).

The methods for preparation of intermediates (**11**) in Chart 2 are shown in Charts 3—5. Friedel–Crafts acylation of substituted benzenes with ethyl oxalyl chloride gave phenylglyoxylates (**14**), which were treated with hydroxylamine to provide oximes (**11d**, **e**) as a mixture of *E*- and *Z*-isomers (Chart 3). These isomers were easily separated by column chromatography.

Several oximes were prepared by another method (Chart 4). Diethyl oxalate was converted into $\alpha$-ketoesters by a reaction with Grignard reagents (R=butyl, isopropyl, and 4-bromophenyl), or with ethyl phenylacetate in NaOEt/EtOH solution followed by de-ethoxycarbonylation (R=benzyl). The resultant ketoesters were treated with hydroxylamine to give oximes (**11b**, **h**—**j**), the isomers of which were separated by column chromatography.

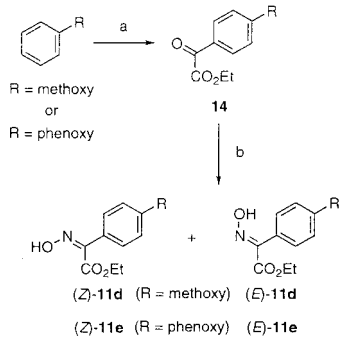
Chart 5 shows the method used for preparing ethyl (3-substitutedphenyl)glyoxylate oxime derivatives [**11c** (R=Br) and **11f** (R=phenoxy)]. Mesylation of 3-phenoxybenzyl alcohol (**16**) was followed by treatment with sodium iodide and a reaction with sodium cyanide to provide 3-phenoxybenzyl cyanide (**17b**). Benzyl cyanides [**17a** (R=Br: commercially available) and **17b** (R=phenoxy)] were reacted with isoamyl nitrite to give compounds (**18a**, **b**), which were treated with KOH and esterified subsequently to give the desired **11c** and **11f**. The *E*- and *Z*-isomers of **11c** and **11f** were also separated by column chromatography.

In case of aromatic R$^1$ in Fig. 2, the configuration of **11** was presumed by normal phase thin layer chromatography (TLC). Less polar isomer of **11** on TLC might have *Z* configuration, because the existence of hydrogen bonding between hydroxime hydrogen and carbonyl oxygen, which diminishes polarity, could be considered. With regard to methyl 2-(hydroxyimino)-2-phenylacetate (**11a**), the configurations were determined by $^1$H-NMR NOESY experiments (Fig. 3). A nu-



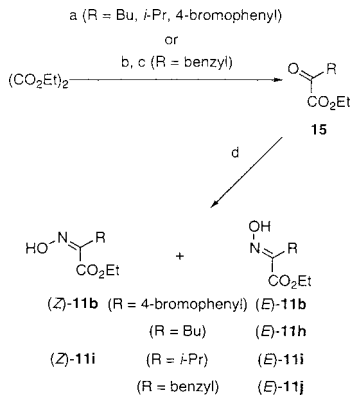

Reagents: (a) $NaBH_4$; (b) $SOCl_2$; (c) NaH; (d) aqueous NaOH.

Chart 2



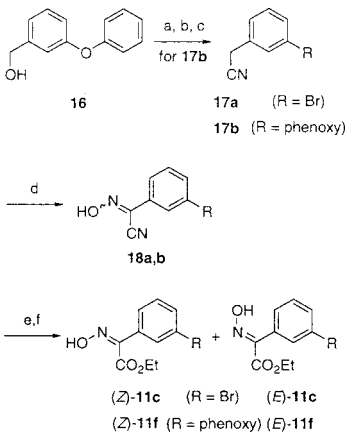

Reagents: (a) $ClCOCO_2Et$, $AlCl_3$; (b) $H_2NOH$, NaOAc.

Chart 3




Reagents: (a) RMgX; (b) Na, EtOH, then ethyl phenylacetate; (c) NaCl, DMSO, $H_2O$, heat; (d) $H_2NOH$, NaOAc.

Chart 4




Reagents: (a) MsCl, $Et_3N$; (b) NaI; (c) NaCN, DMSO; (d) isoamyl nitrite, Na, EtOH; (e) 4 M KOH; (f) $H_2SO_4$, EtOH.

Chart 5

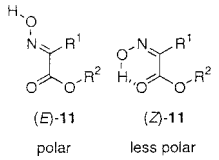



Fig. 2

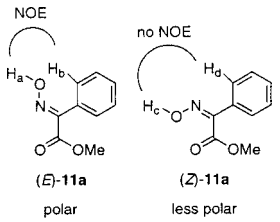
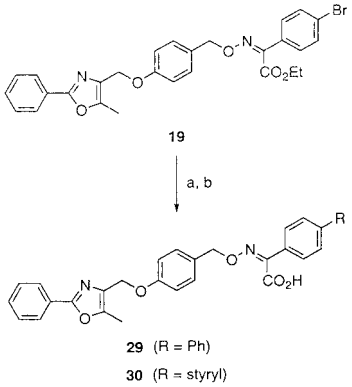



Fig. 3




Reagents: (a) $RB(OH)_2$, $Pd(PPh_3)_4$, $K_2CO_3$, heat; (b) aqueous NaOH.

Chart 6

clear Overhauser effect (NOE) was observed between $H_a$ and $H_b$ of the polar isomer of **11a**, which was proved to have *E* configuration. On the other hand, no NOE was observed between $H_c$ and $H_d$ of the less polar isomer of **11a**, which was turned out to have *Z* configuration. These results are considered to support the validity of the predictions of the configuration using TLC. In cases of **11h** and **11j**, which have aliphatic R in Chart 4 (**11h**, R=butyl; **11j**, R=benzyl), single isomers were obtained. The configuration is presumed as *E*, because **11i** (R=isopropyl) was obtained as a mixture of isomers probably by reason of steric repulsion between hydroxy group and bulky isopropyl group.

Compounds (**29**, **30**) were prepared by Suzuki coupling of the appropriate (phenyl or styryl) boronic acid with **19** and subsequent saponification with aqueous NaOH (Chart 6).

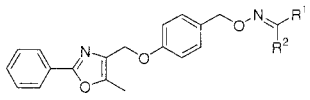
The analytical data of the synthesized oxyiminoacetic acids (**7**, **20**—**35**) are shown in Table 1.

## Results and Discussion

The biological activities of the compounds prepared (**7**, **20**—**35**) were tested using genetically obese and diabetic $KKA^y$ mice.[15] The results are shown in Table 2.

We initially examined the effect of introducing a functional group to the phenyl ring of **7**, which is positioned $\alpha$ to the carboxyl group. Introduction of a bromo group as an electron withdrawer at the *meta*- or *para*-position increased the potency *in vivo* (**21**, **23** *vs.* **7**). Introduction of a methoxy group as an electron donator at the *para*-position did not affect the activity (**24** *vs.* **7**), whereas introduction of a larger phenoxy group at the same position markedly increased activity. Compound (**25**) significantly reduced plasma glucose (33%, $p<0.01$) and plasma triglycelide levels (43%, $p<0.01$) even at a dosage of 0.001% in diet. Introduction of a phenyl group or a styryl group instead of a phenoxy group in **25** did

Table 1. Physical Data of Oxyiminoacetic Acids



| Entry | $R^1$ | $R^2$ | mp (°C) | Formula | *Anal.*[a] |
|---|---|---|---|---|---|
| **7** | Phenyl | $CO_2H$ | 171—172[b] | $C_{26}H_{22}N_2O_5$ | C,H,N |
| **20** | $CO_2H$ | Phenyl | 142—143[b] | $C_{26}H_{22}N_2O_5$ | C,H,N |
| **21** | 4-Bromophenyl | $CO_2H$ | 189—190[b] | $C_{26}H_{21}BrN_2O_5$ | C,H,N |
| **22** | $CO_2H$ | 4-Bromophenyl | 159—160[b] | $C_{26}H_{21}BrN_2O_5$ | C,H,N |
| **23** | 3-Bromophenyl | $CO_2H$ | 181—182[b] | $C_{26}H_{21}BrN_2O_5$ | C,H,N |
| **24** | 4-Methoxyphenyl | $CO_2H$ | 183—184[b] | $C_{27}H_{24}N_2O_6 \cdot 1/10H_2O$ | C,H,N |
| **25** | 4-Phenoxyphenyl | $CO_2H$ | 184—185[b] | $C_{32}H_{26}N_2O_6$ | C,H,N |
| **26** | $CO_2H$ | 4-Phenoxyphenyl | 152—153[b] | $C_{32}H_{26}N_2O_6 \cdot 1/4H_2O$ | C,H,N |
| **27** | 3-Phenoxyphenyl | $CO_2H$ | 173—174[b] | $C_{32}H_{26}N_2O_6$ | C,H,N |
| **28** | $CO_2H$ | 3-Phenoxyphenyl | Amorphous | $C_{32}H_{26}N_2O_6$ | C,H,N |
| **29** | 4-Biphenyl | $CO_2H$ | 193—194[b] | $C_{32}H_{26}N_2O_5 \cdot 1/4H_2O$ | C,H,N |
| **30** | 4-Styrylphenyl | $CO_2H$ | 194—195[b] | $C_{34}H_{28}N_2O_5 \cdot 1/4H_2O$ | C,H,N |
| **31** | $CO_2H$ | Methyl | 147—148 | $C_{21}H_{20}N_2O_5$ | C,H,N |
| **32** | $CO_2H$ | Butyl | 112—114 | $C_{24}H_{26}N_2O_5$ | C,H,N |
| **33** | Isopropyl | $CO_2H$ | 140—142 | $C_{23}H_{24}N_2O_5$ | C,H,N |
| **34** | $CO_2H$ | Isopropyl | 128—129 | $C_{23}H_{24}N_2O_5$ | C,H,N |
| **35** | $CO_2H$ | Benzyl | 143—144[b] | $C_{27}H_{24}N_2O_5$ | C,H,N |

*a*) Analytical results were within 0.4% of the theoretical value. *b*) Decomposed at the temperature.

Table 2. Glucose and Lipid Lowering Activities of Oxyiminoacetic Acids in KKA$^y$ Mice

| Entry | Glucose lowering activity[a—c] Dose (%) | | | Lipid lowering activity[a—c] Dose (%) | | |
|---|---|---|---|---|---|---|
| | 0.001 | 0.01 | 0.03 | 0.001 | 0.01 | 0.03 |
| **7** | | 17 | 32** | | L | 47** |
| **20** | | 15 | | | 20 | |
| **21** | | 44** | | | 44** | |
| **22** | | 28* | | | 24 | |
| **23** | | 40** | | | 27 | |
| **24** | | 21 | | | 24 | |
| **25** | 33** | 49** | | 43** | 82** | |
| **26** | | 30* | | | 12 | |
| **27** | | 26 | | | 32 | |
| **28** | | L | | | 16 | |
| **29** | | 19 | | | L | |
| **30** | | 26 | | | 34 | |
| **31** | | 30* | | | L | |
| **32** | | L | | | L | |
| **33** | | 38** | | | 66** | |
| **34** | | L | | | L | |
| **35** | | L | | | L | |
| **2** (Pioglitazone) | | 54**[d] | | | 47*[d] | |

*a*) Maximum reductions in plasma glucose and plasma triglyceride levels at a dosage of 0.001, 0.01, or 0.03% 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*) From reference 35.

Table 3. PPAR$\gamma$ Transcriptional Activity of Oxyiminoacetic Acids

| Entry | Transactivation[a] PPAR$\gamma$ $EC_{50}$ ($\mu$M) |
|---|---|
| **7** | 1.9 |
| **25** | 0.40 |
| **33** | 0.79 |
| **2** (Pioglitazone) | 0.69 |

*a*) $EC_{50}$, the concentration of test compound required to induce 50% of the maximum activity.

not increase potency (**29**, **30** *vs.* **25**). Attachment of a phenoxy group at the *meta*-position decreased potency (**27** *vs.* **25**). Those results indicate that an introduction of bulky, but not solid structure at the *para*-position of the phenyl group is important to increase *in vivo* potency.

Between the two regioisomers of oxime, the *Z*-configuration seemed to be more potent than the *E*-configuration (**21** *vs.* **22**; **25** *vs.* **26**; *etc.*), while compound (**26**), which has the *E*-configuration, caused a significant reduction in the plasma glucose level (30%, $p<0.05$) at a dosage of 0.01% in diet in KKA$^y$ mice. Therefore, it could be said that the recognition of the configuration of the oximes is somewhat loose for *in vivo* potency.

An exchange of the phenyl ring positioned $\alpha$ to the carboxyl group for alkyl moieties did not increase potency (**31**, **32**, **34**, **35**) except in **33**. Compound (**33**) significantly reduced of plasma glucose (38%, $p<0.01$) and plasma triglycelide levels (66%, $p<0.01$) at a dosage of 0.01% in diet. Taking into account the fact that only **33** has *Z*-configration among compounds (**31**—**35**), the results described above support our assumption that the *Z*-configration is more potent than the *E*-configuration.

To clarify whether the mechanisms of action of the oxyiminoacetic acid derivatives involved PPAR$\gamma$ or not, the functional potency at PPAR$\gamma$ of several compounds was investigated. Compounds (**7**, **25**, **33**) were selected on the basis of their activity in KKA$^y$ mice. As shown in Table 3, these three compounds possessed functional activity at PPAR$\gamma$. This means that the mechanisms of action of the oxyiminoacetic acid derivatives involve PPAR$\gamma$, at least in part. Compounds [**25** ($EC_{50}=0.40\,\mu$M) and **33** ($EC_{50}=0.79\,\mu$M)] had increased functional activity compared to **7** ($EC_{50}=1.9\,\mu$M), which paralleled the glucose and lipid lowering activity in diabetic KKA$^y$ mice.

Finally, we selected **25** for pharmacokinetic analysis. The

Table 4. Pharmacokinetic Parameters of Compound **25** in SD(IGS) Rats[a)]

| Pharmacokinetic parameter | *p.o.* | i.v. |
|---|---|---|
| Dose (mg/kg) | 10 | 1 |
| $AUC_{0—24\,h}$ ($\mu$g·h/ml) | 33.99±5.27 | 6.42±0.57 |
| $C_{5\,min}$ ($\mu$g/ml) | — | 9.08±0.90 |
| $C_{max}$ ($\mu$g/ml) | 7.08±1.99 | — |
| $T_{max}$ (h) | 1.00±0.00 | — |
| $T_{1/2}$ (h) | 2.47±0.07 | 2.32±0.53 |
| Bioavailability (%) | 53.0±9.5 | — |

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

results are shown in Table 4. The data revealed that **25** had desirable pharmacokinetic characteristics with good bioavailability (53.0±9.5%).

In summary, we demonstrated that a new series of oxyiminoacetic acid derivatives had potent antidiabetic activities in genetically obese and diabetic KKA$^y$ mice. (*Z*)-2-[4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino]-2-(4-phenoxyphenyl)acetic acid (**25**) showed particularly strong antidiabetic activity. Several selected compounds exhibited PPAR$\gamma$ transcriptional activity. This means that the mechanisms of action of the oxyiminoacetic acid derivatives involve PPAR$\gamma$, at least in part. Pharmacokinetic analysis showed that compound (**25**) possessed very good pharmacokinetic characteristics. Further structural modification of oxyiminoacetic acid and an expanded SAR study will be discussed in our next paper.

## Experimental

**Biological Procedures. (a) Glucose and Lipid Lowering Experiments** The glucose and lipid lowering activities of the compounds were tested using KKA$^y$ mice.[15)] 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 0.03, 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.

**(b) PPAR$\gamma$-Retinoid X Receptor $\alpha$ (RXR$\alpha$) Heterodimer Transactivation Assay** The full-length human PPAR$\gamma$1, full-length human RXR$\alpha$ 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 $2\times10^4$ cells/well, and cultured in a carbonate gas incubator at 37 °C overnight. The 96-well white plate was washed with PBS (phosphate-buffered saline), and 90 $\mu$l of HAM F12 medium containing 0.1% fatty acid-free bovine serum albumin (BSA) and 10 $\mu$l 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 $\mu$l 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 calculate the $EC_{50}$, the effective concentration of test compound required to induce 50% of the maximum activity.

**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, 24 h for the intravenous study; pre, 15, 30 min, 1, 2, 4, 8, 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:

$$[\text{bioavailability}]\ (\%)=[AUC_{0—24\,h}\ (p.o.)\times\text{dose (i.v.)}]/[AUC_{0—24\,h}\ (\text{i.v.})\times\text{dose}\ (p.o.)]\times100$$

**(b) Analysis of Plasma Samples** (i) Sample Preparation: Acetonitrile was added to each plasma sample (100 $\mu$l). 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 (55 : 45, v/v, 200 $\mu$l). 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 ($\phi$ 4.6×250 mm) was used for HPLC analysis. Analyses of compounds were carried out using acetonitrile–0.01 mol/l ammonium acetate (55 : 45, 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 **25** was 21.6 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 $\delta$ (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.

**(*E*)-2-(4-Bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)-methoxy]benzyloxyimino}acetic Acid (22)** (a) Sodium borohydride (4.31 g, 114 mmol) was added to a cold (0 °C) stirred solution of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzaldehyde (**8**, 33.42 g, 114 mmol) in MeOH (150 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 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol (**9**, 32.9 g, 98%) were isolated by filtration. Recrystallization from AcOEt–$Et_2O$ gave pale-yellow crystals. mp 128—129 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.67 (1H, br s), 2.43 (3H, s), 4.63 (2H, s), 4.99 (2H, s), 7.00 (2H, d, *J*=8.8 Hz), 7.31 (2H, d, *J*=8.8 Hz), 7.40—7.47 (3H, m), 7.98—8.04 (2H, m). IR (KBr) cm$^{-1}$: 3262, 1508, 1238, 1236, 1007, 718. *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.15; H, 5.85; N, 4.73.

(b) Thionyl chloride (1.85 ml, 25.4 mmol) was added to a solution of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol (**9**, 5.00 g, 16.9 mmol) in toluene (40 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-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**, 5.23 g, 99%) as crystals. Recrystallization from AcOEt–hexane gave colorless crystals. mp 108—109 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 2.44 (3H, s), 4.58 (2H, s), 5.00 (2H, s), 7.01 (2H, d, *J*=8.8 Hz), 7.33 (2H, d, *J*=8.8 Hz), 7.40—7.50 (3H, m), 7.98—8.05 (2H, m). IR (KBr) cm$^{-1}$: 1514, 1240, 1011, 835, 717, 654. *Anal.* Calcd for $C_{18}H_{16}NO_2Cl$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.91; H, 5.19; N, 4.36.

(c) A solution of 4-bromophenylmagnesium bromide, prepared from *p*-dibromobenzene (25.0 g, 106 mmol), magnesium (2.43 g, 100 mmol), and $Et_2O$ (250 ml), was added dropwise to a solution of diethyl oxalate (32.5 g, 223 mmol) in $Et_2O$ (250 ml) at −78 °C under nitrogen. After stirring at

−78 °C for 1 h, the reaction mixture was allowed to warm to 0 °C. To the mixture was added dil. HCl. The organic layer was separated, washed with 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 : 15, v/v) to leave an oil. The oil was dissolved in EtOH (100 ml), then hydroxylamine hydrochloride (4.17 g, 60.0 mmol) and sodium acetate (6.15 g, 75.0 mmol) were added to the mixture. The whole was refluxed for 18 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 recrystallized from $isoPr_2O$–hexane to give more polar ethyl (*E*)-2-(4-bromophenyl)-2-(hydroxyimino)acetate [(*E*)-**11b**, 4.31 g, 16%] as colorless crystals. The mother liquid was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 3, v/v) to give less polar (*Z*)-adduct [(*Z*)-**11b**, 5.31 g, 20%] as a colorless oil. The data for (*E*)-**11b**: mp 163—164 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.36 (3H, t, $J$=7.1 Hz), 4.35 (2H, q, $J$=7.1 Hz), 7.39 (2H, d, $J$=8.8 Hz), 7.59 (2H, d, $J$=8.8 Hz), 8.83 (1H, br s). IR (KBr) cm$^{-1}$: 3244, 1732, 1390, 1203, 1026, 1007, 766. *Anal.* Calcd for $C_{10}H_{10}NO_3Br$: C, 44.14; H, 3.70; N, 5.15. Found: C, 44.43; H, 3.78; N, 5.22. The data for (*Z*)-**11b**: $^1$H-NMR ($CDCl_3$) $\delta$: 1.40 (3H, t, $J$=7.1 Hz), 4.45 (2H, q, $J$=7.1 Hz), 7.43 (2H, d, $J$=8.6 Hz), 7.54 (2H, d, $J$=8.6 Hz), 8.47 (1H, s). IR (neat) cm$^{-1}$: 3419, 2983, 1736, 1491, 1319, 1217, 1036, 945, 829.

(d) Sodium hydride (60% in oil, 255 mg, 6.37 mmol) was added to a solution of ethyl (*E*)-2-(4-bromophenyl)-2-(hydroxyimino)acetate [(*E*)-**11b**, 1.73 g, 6.37 mmol] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**, 2.00 g, 6.37 mmol) in *N*,*N*-dimethylformamide (DMF) (20 ml) at room temperature under nitrogen. After stirring at room temperature for 1 h, the mixture was diluted with 1 M HCl (10 ml), 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 give ethyl (*E*)-2-(4-bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetate (2.54 g, 73%) as crystals. Recrystallization from AcOEt–hexane gave colorless crystals. mp 105—106 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.35 (3H, t, $J$=7.1 Hz), 2.43 (3H, s), 4.34 (2H, q, $J$=7.1 Hz), 4.99 (2H, s), 5.24 (2H, s), 7.00 (2H, d, $J$=8.6 Hz), 7.23—7.33 (4H, m), 7.39—7.54 (5H, m), 7.99—8.05 (2H, m). IR (KBr) cm$^{-1}$: 1724, 1514, 1252, 1209, 1066, 982, 822, 710. *Anal.* Calcd for $C_{28}H_{25}N_2O_5Br$: C, 61.21; H, 4.59; N, 5.10. Found: C, 61.24; H, 4.55; N, 5.09.

(e) Ethyl (*E*)-2-(4-bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetate (600 mg, 1.09 mmol) was dissolved in THF (6 ml)–MeOH (3 ml), and 1 M NaOH (3 ml) was added to the mixture. The whole was stirred at 40 °C for 1 h, then made acidic by addition of 1 M HCl (3.3 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 **22** (561 mg, 99%) as colorless crystals. mp 159—160 °C (dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 5.01 (2H, s), 5.16 (2H, s), 7.04 (2H, d, $J$=8.8 Hz), 7.29—7.38 (4H, m), 7.49—7.55 (3H, m), 7.62 (2H, d, $J$=8.8 Hz), 7.92—7.98 (2H, m). IR (KBr) cm$^{-1}$: 1711, 1514, 1240, 978, 831, 714, 690. *Anal.* Calcd for $C_{26}H_{21}N_2O_5Br$: C, 59.90; H, 4.06; N, 5.37. Found: C, 59.75; H, 4.10; N, 5.34.

**(*Z*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-phenylacetic Acid (7)** Using the procedures for preparation of **22**, steps b, d, and e, **7** (54% yield) was prepared from 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol (**9**) and ethyl (*Z*)-2-(hydroxyimino)-2-phenylacetate [(*Z*)-**11a**] as colorless crystals. mp 171—172 °C (AcOEt–hexane, dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 5.01 (2H, s), 5.16 (2H, s), 7.06 (2H, d, $J$=8.8 Hz), 7.36 (2H, d, $J$=8.8 Hz), 7.40—7.58 (8H, m), 7.91—7.98 (2H, m). IR (KBr) cm$^{-1}$: 2929, 1730, 1610, 1514, 1240, 995, 690. *Anal.* Calcd for $C_{26}H_{22}N_2O_5$: C, 70.58; H, 5.01; N, 6.33. Found: C, 70.49; H, 5.08; N, 6.16.

**(*E*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-phenylacetic Acid (20)** Using the procedures for preparation of **22**, steps d and e, **20** (70% yield) was prepared from methyl (*E*)-2-(hydroxyimino)-2-phenylacetate [(*E*)-**11a**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as colorless crystals. mp 142—143 °C (AcOEt–$isoPr_2O$, dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 5.01 (2H, s), 5.16 (2H, s), 7.04 (2H, d, $J$=8.8 Hz), 7.32 (2H, d, $J$=8.8 Hz), 7.40 (5H, s like), 7.48—7.56 (3H, m), 7.90—7.98 (2H, m). IR (KBr) cm$^{-1}$: 2939, 1714, 1514, 1242, 1211, 974, 706. *Anal.* Calcd for $C_{26}H_{22}N_2O_5$: C, 70.58; H, 5.01; N, 6.33. Found: C, 70.52; H, 5.14; N, 6.28.

**(*Z*)-2-(4-Bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetic Acid (21)** Using the procedures for preparation of **22**, steps d and e, **21** (81% yield) was prepared from ethyl (*Z*)-2-(4-bromophenyl)-2-(hydroxyimino)acetate [(*Z*)-**11b**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as colorless crystals. mp 189—190 °C (AcOEt, dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.50 (3H, s), 5.01 (2H, s), 5.17 (2H, s), 7.06 (2H, d, $J$=8.6 Hz), 7.36 (2H, d, $J$=8.6 Hz), 7.47 (2H, d, $J$=8.8 Hz), 7.48—7.57 (3H, m), 7.69 (2H, d, $J$=8.8 Hz), 7.90—7.98 (2H, m). IR (KBr) cm$^{-1}$: 1736, 1512, 1240, 1009, 831, 716. *Anal.* Calcd for $C_{26}H_{21}N_2O_5Br$: C, 59.90; H, 4.06; N, 5.37. Found: C, 59.81; H, 4.40; N, 5.01.

**(*Z*)-2-(3-Bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetic Acid (23)** (a) An EtOH (30 ml) solution of (3-bromophenyl)acetonitrile (**17a**, 17.8 g, 90.8 mmol) was added dropwise to a solution of NaOEt [prepared from Na (2.51 g, 109 mmol) and EtOH (40 ml)] at 0 °C under nitrogen. To this was added isoamyl nitrite (18.3 ml, 136 mmol) dropwise at 0 °C. The whole was stirred at room temperature for 18 h, then diluted with ether. The mixture was washed with 1 M HCl, 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 : 4, v/v) to give 2-(3-bromophenyl)-2-(hydroxyimino)acetonitrile (**18a**, 19.9 g, 97%) as orange slurry. Recrystallization from AcOEt–hexane gave orange crystals. mp 91—93 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 7.35 (1H, t, $J$=7.9 Hz), 7.63 (1H, br d, $J$=7.9 Hz), 7.73 (1H, br d, $J$=7.9 Hz), 7.97 (1H, br s), 8.71 (1H, br s). IR (KBr) cm$^{-1}$: 3302, 1593, 1475, 1423, 1277, 1074, 991, 793, 689. *Anal.* Calcd for $C_8H_5N_2OBr$: C, 42.70; H, 2.24; N, 12.45. Found: C, 42.92; H, 2.25; N, 12.24.

(b) A mixture of 2-(3-bromophenyl)-2-(hydroxyimino)acetonitrile (**18a**, 19.0 g, 84.4 mmol), 4 M KOH (100 ml) and 2-methoxyethanol (100 ml) was refluxed for 4 h. After cooling to room temperature, the mixture was made acidic by addition of 1 M 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 EtOH (200 ml), and conc. $H_2SO_4$ (catalytic amount) was added. The whole was refluxed for 48 h, then cooled to room temperature, diluted with 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 give less polar ethyl (*Z*)-2-(3-bromophenyl)-2-(hydroxyimino)acetate [(*Z*)-**11c**, 3.31 g, 14%] as a pale-brown oil and polar ethyl (*E*)-2-(3-bromophenyl)-2-(hydroxyimino)acetate as crystals. Recrystallization of (*E*)-adduct from AcOEt–hexane gave colorless crystals [(*E*)-**11c**, 1.52 g, 7%]. The data for (*Z*)-**11c**: $^1$H-NMR ($CDCl_3$) $\delta$: 1.41 (3H, t, $J$=7.1 Hz), 4.47 (2H, q, $J$=7.1 Hz), 7.23—7.32 (1H, m), 7.45—7.60 (2H, m), 7.72—7.75 (1H, m), 8.56 (1H, br s). IR (neat) cm$^{-1}$: 3377, 1730, 1560, 1317, 1215, 1039, 960, 789, 689. The data for (*E*)-**11c**: mp 113—114 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.36 (3H, t, $J$=7.1 Hz), 4.36 (2H, q, $J$=7.1 Hz), 7.28—7.47 (2H, m), 7.55—7.61 (1H, m), 7.65—7.68 (1H, m), 9.08 (1H, br s). IR (KBr) cm$^{-1}$: 3230, 1734, 1194, 1024, 754. *Anal.* Calcd for $C_{10}H_{10}NO_3Br$: C, 44.14; H, 3.70; N, 5.15. Found: C, 44.18; H, 3.71; N, 5.20.

(c) Using the procedure for preparation of **22**, step d, ethyl (*Z*)-2-(3-bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetate (48% yield) was prepared from ethyl (*Z*)-2-(3-bromophenyl)-2-(hydroxyimino)acetate [(*Z*)-**11c**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as a pale-yellow oil. $^1$H-NMR ($CDCl_3$) $\delta$: 1.33 (3H, t, $J$=7.1 Hz), 2.44 (3H, s), 4.41 (2H, q, $J$=7.1 Hz), 5.00 (2H, s), 5.20 (2H, s), 7.01 (2H, d, $J$=8.8 Hz), 7.20—7.56 (8H, m), 7.73—7.76 (1H, m), 7.99—8.06 (2H, m). IR (neat) cm$^{-1}$: 2933, 1738, 1610, 1512, 1221, 997, 692.

(d) Using the procedure for preparation of **22**, step e, **23** (91% yield) was prepared from ethyl (*Z*)-2-(3-bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetate as colorless crystals. mp 181—182 °C (AcOEt–hexane, dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 5.01 (2H, s), 5.18 (2H, s), 7.07 (2H, d, $J$=8.4 Hz), 7.32—7.58 (7H, m), 7.65—7.74 (2H, m), 7.90—7.98 (2H, m). IR (KBr) cm$^{-1}$: 1732, 1610, 1514, 1238, 997, 806, 716. *Anal.* Calcd for $C_{26}H_{21}N_2O_5Br$: C, 59.90; H, 4.06; N, 5.37. Found: C, 59.84; H, 4.07; N, 5.36.

**(*Z*)-2-(4-Methoxyphenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetic Acid (24)** (a) A mixture of ethyl 4-methoxyphenylglyoxylate (15.0 g, 72.0 mmol), hydroxylamine hydrochloride (6.00 g, 86.4 mmol), sodium acetate (8.86 g, 108 mmol), and EtOH (150 ml) was refluxed for 12 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 : 2, v/v) to give

less polar ethyl (*Z*)-2-(hydroxyimino)-2-(4-methoxyphenyl)acetate [(*Z*)-**11d**, 8.99 g, 56%] as crystals and polar ethyl (*E*)-2-(hydroxyimino)-2-(4-methoxyphenyl)acetate [(*E*)-**11d**, 4.97 g, 31%] as crystals. Recrystallization of (*Z*)-**11d** from AcOEt–hexane gave colorless crystals. Recrystallization of (*E*)-**11d** from AcOEt–hexane also gave colorless crystals. The data for (*Z*)-**11d**: mp 81—82 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.40 (3H, t, $J$=7.1 Hz), 3.83 (3H, s), 4.45 (2H, q, $J$=7.1 Hz), 6.91 (2H, d, $J$=9.2 Hz), 7.51 (2H, d, $J$=9.2 Hz), 8.43 (1H, br s). IR (KBr) cm$^{-1}$: 3304, 1701, 1516, 1248, 1039, 947, 829. *Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.15; H, 5.61; N, 6.25. The data for (*E*)-**11d**: mp 128—129 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.36 (3H, t, $J$=7.1 Hz), 3.85 (3H, s), 4.35 (2H, q, $J$=7.1 Hz), 6.96 (2H, d, $J$=9.0 Hz), 7.56 (2H, d, $J$=9.0 Hz), 9.33 (1H, br s). IR (KBr) cm$^{-1}$: 3259, 1730, 1614, 1292, 1178, 1024, 818, 797, 764. *Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.19; H, 5.65; N, 6.30.

(b) Using the procedure for preparation of **22**, step d, ethyl (*Z*)-2-(4-methoxyphenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetate (94% yield) was prepared from ethyl (*Z*)-2-(hydroxyimino)-2-(4-methoxyphenyl)acetate [(*Z*)-**11d**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) gave colorless crystals. mp 101—102 °C (AcOEt–hexane). $^1$H-NMR ($CDCl_3$) $\delta$: 1.33 (3H, t, $J$=7.1 Hz), 2.43 (3H, s), 3.82 (3H, s), 4.39 (2H, q, $J$=7.1 Hz), 4.99 (2H, s), 5.17 (2H, s), 6.89 (2H, d, $J$=8.8 Hz), 7.00 (2H, d, $J$=8.8 Hz), 7.32 (2H, d, $J$=8.8 Hz), 7.40—7.48 (3H, m), 7.50 (2H, d, $J$=8.8 Hz), 7.98—8.05 (2H, m). IR (KBr) cm$^{-1}$: 1731, 1512, 1223, 1169, 1024, 993, 924, 814, 692. *Anal.* Calcd for $C_{29}H_{28}N_2O_6$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.56; H, 5.64; N, 5.65.

(c) Using the procedure for preparation of **22**, step e, **24** (90% yield) was prepared from ethyl (*Z*)-2-(4-methoxyphenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetate as colorless crystals. mp 183—184 °C (AcOEt, dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 3.79 (3H, s), 5.01 (2H, s), 5.12 (2H, s), 7.02 (2H, d, $J$=8.8 Hz), 7.05 (2H, d, $J$=8.8 Hz), 7.36 (2H, d, $J$=8.8 Hz), 7.47 (2H, d, $J$=8.8 Hz), 7.48—7.56 (3H, m), 7.90—7.98 (2H, m). IR (KBr) cm$^{-1}$: 1726, 1610, 1512, 1238, 1176, 1028, 1003, 837. *Anal.* Calcd for $C_{27}H_{24}N_2O_6 \cdot 1/10H_2O$: C, 68.37; H, 5.14; N, 5.91. Found: C, 68.13; H, 5.35; N, 5.81.

**(*Z*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-(4-phenoxyphenyl)acetic Acid (25)** (a) Ethyl chloroglyoxylate (22.3 ml, 200 mmol) was added dropwise to a suspension of aluminum chloride (29.3 g, 220 mmol) in $CH_2Cl_2$ (250 ml) at 0 °C under nitrogen, and the mixture was stirred at 0 °C for 0.5 h. The mixture was added dropwise over a period of 0.5 h to diphenyl ether (63.5 ml, 400 mmol) at 0 °C. The whole was stirred at 0 °C for 2 h, then poured onto ice (250 g). After stirring at room temperature for 1 h, the organic layer was separated, washed with water and brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 10, v/v) to give ethyl (4-phenoxyphenyl)glyoxylate (38.0 g, 70%) as a colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 1.42 (3H, t, $J$=7.1 Hz), 4.44 (2H, q, $J$=7.1 Hz), 6.98—7.13 (4H, m), 7.20—7.29 (1H, m), 7.37—7.47 (2H, m), 8.01 (2H, d, $J$=9.0 Hz). IR (neat) cm$^{-1}$: 2983, 1734, 1682, 1585, 1489, 1250, 1200, 1161, 1020, 872, 750.

(b) A mixture of ethyl (4-phenoxyphenyl)glyoxylate (37.9 g, 140 mmol), hydroxylamine hydrochloride (11.7 g, 168 mmol), sodium acetate (17.3 g, 210 mmol), and EtOH (200 ml) was refluxed for 15 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 recrystallized from toluene–hexane to give ethyl (*E*)-2-(hydroxyimino)-2-(4-phenoxyphenyl)acetate [(*E*)-**11e**, 11.0 g, 28%] as crystals. The mother liquid was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4, v/v) to give ethyl (*Z*)-2-(hydroxyimino)-2-(4-phenoxyphenyl)acetate [(*Z*)-**11e**, 23.6 g, 59%] as a colorless oil. Recrystallization of (*E*)-**11e** from AcOEt–hexane gave colorless crystals. The data for (*E*)-**11e**: mp 131—132 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.37 (3H, t, $J$=7.1 Hz), 4.36 (2H, q, $J$=7.1 Hz), 6.99—7.22 (5H, m), 7.33—7.44 (2H, m), 7.55 (2H, d, $J$=9.0 Hz), 9.25 (1H, br s). IR (KBr) cm$^{-1}$: 3240, 1732, 1489, 1255, 1198, 1053, 1007, 764. *Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.42; H, 5.21; N, 4.93. The data for (*Z*)-**11e**: $^1$H-NMR ($CDCl_3$) $\delta$: 1.40 (3H, t, $J$=7.1 Hz), 4.46 (2H, q, $J$=7.1 Hz), 6.95—7.08 (4H, m), 7.11—7.20 (1H, m), 7.32—7.42 (2H, m), 7.53 (2H, d, $J$=8.8 Hz), 8.42—8.49 (1H, m). IR (neat) cm$^{-1}$: 3417, 1734, 1587, 1489, 1240, 1038, 943, 694.

(c) Using the procedures for preparation of **22**, steps d and e, **25** (89% yield) was prepared from ethyl (*Z*)-2-(hydroxyimino)-2-(4-phenoxyphenyl)-acetate [(*Z*)-**11e**] and 4-{[4-(chloromethyl)-phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as colorless crystals. mp 184—185 °C (AcOEt–hexane, dec.). $^1$H-NMR ($CDCl_3$) $\delta$: 2.44 (3H, s), 5.01 (2H, s), 5.15 (2H, s), 6.87—7.05 (6H, m), 7.09—7.18 (1H, m), 7.23—7.45 (7H, m), 7.58 (2H, d, $J$=8.8 Hz), 7.96—8.03 (2H, m). IR (KBr) cm$^{-1}$: 1730, 1537, 1489, 1236, 989, 916, 868, 694. *Anal.* Calcd for $C_{32}H_{26}N_2O_6$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.62; H, 4.98; N, 5.22.

**(*E*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-(4-phenoxyphenyl)acetic Acid (26)** Using the procedures for preparation of **22**, steps d and e, **26** (81% yield) was prepared from ethyl (*E*)-2-(hydroxyimino)-2-(4-phenoxyphenyl)acetate [(*E*)-**11e**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as colorless crystals. mp 152—153 °C (AcOEt–hexane, dec.). $^1$H-NMR ($CDCl_3$) $\delta$: 2.44 (3H, s), 5.01 (2H, s), 5.25 (2H, s), 6.94—7.09 (6H, m), 7.11—7.21 (1H, m), 7.28—7.48 (7H, m), 7.58 (2H, d, $J$=8.8 Hz), 7.98—8.05 (2H, m). IR (KBr) cm$^{-1}$: 1722, 1587, 1487, 1238, 978, 689. *Anal.* Calcd for $C_{32}H_{26}N_2O_6 \cdot 1/4H_2O$: C, 71.30; H, 4.95; N, 5.20. Found: C, 71.33; H, 4.94; N, 5.12.

**(*Z*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-(3-phenoxyphenyl)acetic Acid (27)** (a) Methanesulfonyl chloride (14.6 ml, 188 mmol) was added to a solution of 3-phenoxybenzyl alcohol (**16**, 25.0 g, 125 mmol) and triethylamine (26.3 ml, 188 mmol) in AcOEt (300 ml) at 0 °C, and the mixture was stirred for 1 h. The mixture was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in acetone (300 ml), then sodium iodide (37.5 g, 250 mmol) was added to the solution. The whole was stirred at room temperature for 1 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 dissolved in DMSO (100 ml), then sodium cyanide (7.35 g, 150 mmol) was added to the mixture. The whole was stirred at room temperature for 15 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 : 7, v/v) to give 2-(3-phenoxyphenyl)acetonitrile (**17b**, 8.36 g, 32%) as a pale-yellow oil. $^1$H-NMR ($CDCl_3$) $\delta$: 3.72 (2H, s), 6.90—7.20 (6H, m), 7.28—7.43 (3H, m). IR (neat) cm$^{-1}$: 3061, 2252, 1585, 1487, 1252, 1211, 775, 692.

(b) An EtOH (15 ml) solution of 2-(3-phenoxyphenyl)acetonitrile (**17b**, 8.30 g, 39.7 mmol) was added dropwise to a solution of NaOEt [prepared from Na (1.09 g, 47.6 mmol) and EtOH (20 ml)] at 0 °C under nitrogen. To this was added isoamyl nitrite (7.99 ml, 59.5 mmol) dropwise at 0 °C. The whole was stirred at room temperature for 15 h, then diluted with ether. The mixture was washed with 1 M HCl, 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 : 4, v/v) to give an oil. The oil was crystallized from AcOEt–hexane to give 2-(hydroxyimino)-2-(3-phenoxyphenyl)acetonitrile (**18b**, 4.25 g, 45%) as pale-yellow crystals. mp 124—125 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 7.01—7.20 (4H, m), 7.33—7.55 (5H, m), 8.75 (1H, br s). IR (KBr) cm$^{-1}$: 3290, 2247, 1591, 1487, 1288, 1228, 1072, 1001, 881, 696. *Anal.* Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.79; H, 4.10; N, 11.67.

(c) A solution of 2-(hydroxyimino)-2-(3-phenoxyphenyl)acetonitrile (**18b**, 3.00 g, 12.6 mmol) and KOH (3.40 g, 60.4 mmol) in EtOH (15 ml)–water (15 ml) was refluxed for 24 h. After cooling to room temperature, the mixture was made acidic by addition of 1 M 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 MeOH (30 ml), then conc. $H_2SO_4$ (catalytic amount) was added. The whole was refluxed for 24 h. After cooling to room temperature, the mixture was diluted with 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 : 2, v/v) to give less polar ethyl (*Z*)-2-(hydroxyimino)-2-(3-phenoxyphenyl)acetate [(*Z*)-**11f**, 1.14 g, 33%] as a yellow oil and polar ethyl (*E*)-2-(hydroxyimino)-2-(3-phenoxyphenyl)acetate [(*E*)-**11f**, 746 mg, 22%] as crystals. Recrystallization of (*E*)-**11f** from AcOEt–hexane gave colorless crystals. The data for (*Z*)-**11f**: $^1$H-NMR ($CDCl_3$) $\delta$: 3.95 (3H, s), 6.99—7.18 (4H, m), 7.21—7.28 (2H, m), 7.31—7.41 (3H, m), 8.33 (1H, s). IR (neat) cm$^{-1}$: 3415, 1741, 1578, 1489, 1435, 1246, 881, 694. The data for (*E*)-**11f**: mp 122—123 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 3.88 (3H, s), 7.02—7.24 (6H, m), 7.30—7.46 (3H, m), 8.83 (1H, br s). IR (KBr) cm$^{-1}$: 3217, 1738, 1491, 1244, 1012, 768. *Anal.* Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.29; H, 4.95; N, 5.21.

(d) Using the procedures for preparation of **22**, steps d and e, **27** (62% yield) was prepared from ethyl (*Z*)-2-(hydroxyimino)-2-(3-phenoxyphenyl)-acetate [(*Z*)-**11f**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-

phenyl-1,3-oxazole (**10**) as colorless crystals. mp 173—174 °C (AcOEt–hexane, dec.). $^1$H-NMR ($CDCl_3$) $\delta$: 2.44 (3H, s), 5.01 (2H, s), 5.16 (2H, s), 6.89 (2H, d, $J$=8.6 Hz), 6.97—7.15 (4H, m), 7.20—7.45 (10H, m), 7.97—8.03 (2H, m). IR (KBr) cm$^{-1}$: 2926, 1726, 1512, 1489, 1244, 999, 692. *Anal.* Calcd for $C_{32}H_{26}N_2O_6$: C, 71.90; H, 4.90; N, 5.24. Found: C, 72.05; H, 5.06; N, 5.00.

**(*E*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-(3-phenoxyphenyl)acetic Acid (28)** Using the procedures for preparation of **22**, steps d and e, **28** (62% yield) was prepared from ethyl (*E*)-2-(hydroxyimino)-2-(3-phenoxyphenyl)acetate [(*E*)-**11f**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as colorless amorphous. mp 55—65 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 2.45 (3H, s), 5.01 (2H, s), 5.22 (2H, s), 6.98—7.48 (16H, m), 7.98—8.05 (2H, m). IR (KBr) cm$^{-1}$: 1718, 1583, 1489, 1240, 993, 690. *Anal.* Calcd for $C_{32}H_{26}N_2O_6$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.63; H, 4.70; N, 5.04.

**(*Z*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-[(*E*)-4-styrylphenyl]acetic Acid (30)** A mixture of ethyl (*Z*)-2-(4-bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetate (**19**, 830 mg, 1.51 mmol), (*E*)-styrylboronic acid (268 mg, 1.81 mmol), potassium carbonate (626 mg, 4.53 mmol), toluene (20 ml), EtOH (2 ml), and water (2 ml) was stirred at room temperature under argon for 0.5 h. To this was added tetrakis(triphenylphosphine)palladium(0) (105 mg, 0.091 mmol), and the mixture was refluxed for 14 h. After cooling to room temperature, the mixture 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 (10 ml)–MeOH (5 ml), and 1 M NaOH (5 ml) was added to the mixture. The whole was stirred at 40 °C for 2 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 **30** (634 mg, 77%) as pale-yellow crystals. mp 194—195 °C (dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 5.01 (2H, s), 5.17 (2H, s), 7.07 (2H, d, $J$=8.8 Hz), 7.22—7.44 (7H, m), 7.47—7.58 (5H, m), 7.60—7.73 (4H, m), 7.90—7.98 (2H, m). IR (KBr) cm$^{-1}$: 1732, 1610, 1514, 1240, 1003, 690. *Anal.* Calcd for $C_{34}H_{28}N_2O_5 \cdot 1/4H_2O$: C, 74.37; H, 5.23; N, 5.10. Found: C, 74.29; H, 5.44; N, 4.94.

**(*Z*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-2-(4-biphenyl)acetic Acid (29)** Using the procedures for preparation of **30**, **29** (60% yield) was prepared from ethyl (*Z*)-2-(4-bromophenyl)-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}acetate (**19**) and phenylboronic acid as pale-yellow crystals. mp 193—194 °C (AcOEt–isoPr$_2$O, dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 5.02 (2H, s), 5.19 (2H, s), 7.07 (2H, d, $J$=8.8 Hz), 7.34—7.82 (14H, m), 7.90—7.98 (2H, m). IR (KBr) cm$^{-1}$: 1724, 1512, 1240, 993, 920, 806, 699. *Anal.* Calcd for $C_{32}H_{26}N_2O_5 \cdot 1/4H_2O$: C, 73.48; H, 5.11; N, 5.36. Found: C, 73.52; H, 5.00; N, 5.33.

**2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-propionic Acid (31)** Using the procedures for preparation of **22**, steps d and e, **31** (70% yield) was prepared from ethyl (*E*)-2-(hydroxyimino)-propanoate [(*E*)-**11g**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as colorless crystals. mp 147—148 °C (AcOEt–isoPr$_2$O). $^1$H-NMR ($CDCl_3$) $\delta$: 2.07 (3H, s), 2.44 (3H, s), 5.01 (2H, s), 5.21 (2H, s), 7.04 (2H, d, $J$=8.8 Hz), 7.32 (2H, d, $J$=8.8 Hz), 7.42—7.49 (3H, m), 7.99—8.05 (2H, m). IR (KBr) cm$^{-1}$: 2949, 1714, 1612, 1510, 1240, 1173, 1018, 984, 800, 689. *Anal.* Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.14; H, 5.26; N, 7.33.

**2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-hexanoic Acid (32)** (a) Butylmagnesium chloride (0.90 M solution in THF, 100 ml, 90 mmol) was added dropwise to a solution of diethyl oxalate (26.3 g, 180 mmol) in Et$_2$O (400 ml) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 1 h, then allowed to warm to 0 °C, and added dil. HCl. The organic layer was separated, washed with aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in EtOH (150 ml), then hydroxylamine hydrochloride (7.50 g, 108 mmol) and sodium acetate (11.1 g, 135 mmol) were added to the mixture. The whole was refluxed for 13 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*)-2-(hydroxyimino)hexanoate [(*E*)-**11h**, 11.0 g, 71%] as crystals. Recrystallization from hexane gave colorless crystals (8.26 g, 53%). mp 49—50 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 0.92 (3H, t, $J$=7.1 Hz), 1.27—1.60 (7H, m), 2.58—2.66 (2H, m), 4.31 (2H, q, $J$=7.1 Hz), 9.15—9.40 (1H, br). IR (KBr) cm$^{-1}$: 3232, 2956, 1726, 1446, 1174, 1020, 995, 762. *Anal.* Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.65; H, 8.54; N, 8.07.

(b) Using the procedures for preparation of **22**, steps d and e, **32** (68% yield) was prepared from ethyl (*E*)-2-(hydroxyimino)hexanoate [(*E*)-**11h**] and 4-{[4-(chloromethyl)phenoxy]-methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as colorless crystals. mp 112—114 °C (AcOEt–hexane). $^1$H-NMR ($CDCl_3$) $\delta$: 0.88 (3H, t, $J$=7.2 Hz), 1.21—1.55 (4H, m), 2.44 (3H, s), 2.53—2.61 (2H, m), 5.01 (2H, s), 5.19 (2H, s), 7.03 (2H, d, $J$=8.8 Hz), 7.30 (2H, d, $J$=8.8 Hz), 7.38—7.47 (3H, m), 7.98—8.05 (2H, m). IR (KBr) cm$^{-1}$: 3427, 2958, 1713, 1514, 1234, 1020, 982, 717. *Anal.* Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.25; H, 6.20; N, 6.66.

**(*Z*)-3-Methyl-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}butyric Acid (33)** (a) Isopropylmagnesium bromide (0.67 M solution in THF, 100 ml, 67 mmol) was added dropwise to a solution of diethyl oxalate (19.6 g, 134 mmol) in Et$_2$O (400 ml) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 1 h, then allowed to warm to 0 °C, and added dil. HCl. The organic layer was separated, washed with aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in EtOH (100 ml), then hydroxylamine hydrochloride (5.59 g, 80.4 mmol) and sodium acetate (8.24 g, 101 mmol) were added to the mixture. 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 2-(hydroxyimino)-3-methylbutyrate (**11i**, 7.74 g, 73%, mixture of isomers, $E:Z=ca.$ 3 : 1) as slurry. Recrystallization from hexane gave colorless crystals of (*E*)-**11i** (1.91 g, 18%). Concentration of the mother liquid gave a mixture of isomers (5.69 g, 53%, $E:Z$=2.3 : 1) as slurry. The data for (*E*)-**11i**: mp 54—55 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.24 (6H, d, $J$=7.0 Hz), 1.35 (3H, t, $J$=7.1 Hz), 3.49 (1H, sept, $J$=7.0 Hz), 4.29 (2H, q, $J$=7.1 Hz), 9.79 (1H, br s). IR (KBr) cm$^{-1}$: 3269, 2985, 1732, 1431, 1186, 1018, 771. *Anal.* Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.72; H, 7.96; N, 8.72. The data for (*Z*)-**11i**: $^1$H-NMR ($CDCl_3$) $\delta$: 1.17 (6H, d, $J$=6.6 Hz), 1.36 (3H, t, $J$=7.1 Hz), 2.80 (1H, sept, $J$=6.6 Hz), 4.36 (2H, q, $J$=7.1 Hz), 9.75 (1H, br s).

(b) Sodium hydride (60% in oil, 255 mg, 6.37 mmol) was added to a solution of ethyl 2-(hydroxyimino)-3-methylbutyrate (**11i**, $E:Z$=2.3 : 1, 1.01 g, 6.37 mmol) and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**, 2.00 g, 6.37 mmol) in DMF (20 ml) at room temperature under nitrogen. The mixture was stirred at room temperature for 1 h, then diluted with 1 M HCl (10 ml), 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–$CH_2Cl_2$ (1 : 10 : 10, v/v) to give less polar ethyl (*Z*)-3-methyl-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}butyrate (640 mg, 23%) as a colorless oil and polar ethyl (*E*)-3-methyl-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}butyrate (1.34 g, 48%) as a colorless oil. The data for (*Z*)-adduct: $^1$H-NMR ($CDCl_3$) $\delta$: 1.14 (6H, d, $J$=6.8 Hz), 1.28 (3H, t, $J$=7.1 Hz), 2.43 (3H, s), 2.70 (1H, sept, $J$=6.8 Hz), 4.29 (2H, q, $J$=7.1 Hz), 4.99 (2H, s), 5.03 (2H, s), 6.98 (2H, d, $J$=8.8 Hz), 7.27 (2H, d, $J$=8.8 Hz), 7.41—7.49 (3H, m), 7.97—8.05 (2H, m). IR (neat) cm$^{-1}$: 2972, 1734, 1512, 1238, 1190, 1018, 714. The data for (*E*)-adduct: $^1$H-NMR ($CDCl_3$) $\delta$: 1.17 (6H, d, $J$=7.0 Hz), 1.35 (3H, t, $J$=7.1 Hz), 2.44 (3H, s), 3.40 (1H, sept, $J$=7.0 Hz), 4.30 (2H, q, $J$=7.1 Hz), 5.00 (2H, s), 5.17 (2H, s), 7.01 (2H, d, $J$=8.8 Hz), 7.32 (2H, d, $J$=8.8 Hz), 7.40—7.48 (3H, m), 7.97—8.05 (2H, m). IR (neat) cm$^{-1}$: 2968, 1722, 1512, 1302, 1240, 1186, 997, 777.

(c) Using the procedure for preparation of **22**, step e, **33** (96% yield) was prepared from ethyl (*Z*)-3-methyl-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}butyrate as colorless crystals. mp 140—142 °C (AcOEt–hexane). $^1$H-NMR ($CDCl_3$) $\delta$: 1.15 (6H, d, $J$=7.0 Hz), 2.44 (3H, s), 2.93 (1H, sept, $J$=7.0 Hz), 5.00 (2H, s), 5.14 (2H, s), 6.98 (2H, d, $J$=8.8 Hz), 7.29 (2H, d, $J$=8.8 Hz), 7.40—7.48 (3H, m), 7.97—8.04 (2H, m). IR (KBr) cm$^{-1}$: 2974, 1722, 1514, 1244, 1005, 935, 878, 716. *Anal.* Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.79; H, 5.86; N, 6.83.

**(*E*)-3-Methyl-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}butyric Acid (34)** Using the procedure for preparation of **22**, step e, **34** (85% yield) was prepared from ethyl (*E*)-3-methyl-2-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}butyrate as colorless crystals. mp 128—129 °C (AcOEt–hexane). $^1$H-NMR ($CDCl_3$) $\delta$:

1.22 (6H, d, $J$=7.0 Hz), 2.44 (3H, s), 3.41 (1H, sept, $J$=7.0 Hz), 5.01 (2H, s), 5.17 (2H, s), 7.03 (2H, d, $J$=8.8 Hz), 7.29 (2H, d, $J$=8.8 Hz), 7.40—7.48 (3H, m), 7.98—8.05 (2H, m). IR (KBr) $cm^{-1}$: 2935, 1711, 1514, 1257, 1188, 985, 833, 714. *Anal.* Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.86; H, 5.94; N, 6.94.

**(*E*)-2-{4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyloxyimino}-3-phenylpropionic Acid (35)** (a) Ethyl phenylacetate (25.8 g, 157 mmol) and diethyl oxalate (45.9 g, 314 mmol) were added to a solution of NaOEt [prepared from Na (7.22 g, 314 mmol) and EtOH (400 ml)]. The mixture was heated at 70 °C for 1.5 h with continuous removal of EtOH. The residue was partitioned between 1 M HCl (350 ml) and AcOEt (500 ml), and the two layers were separated. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to leave an oil. The oil was dissolved in DMSO (150 ml)–water (15 ml), then NaCl (9.18 g, 157 mmol) was added to the mixture. The whole was heated at 130 °C for 1.5 h, then poured into 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 EtOH (100 ml), then hydroxylamine hydrochloride (3.34 g, 48.0 mmol) and sodium acetate (4.92 g, 60.0 mmol) were added to the solution. The whole was refluxed for 17 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 ethyl (*E*)-2-(hydroxyimino)-3-phenylpropionate [(*E*)-**11j**, 6.94 g, 21%] as crystals. Recrystallization from AcOEt–hexane gave colorless crystals. mp 54—55 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 1.32 (3H, t, $J$=7.1 Hz), 3.99 (2H, s), 4.28 (2H, q, $J$=7.1 Hz), 7.15—7.35 (5H, m), 9.58 (1H, br s). IR (KBr) $cm^{-1}$: 3365, 1730, 1452, 1213, 1132, 1024, 719. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.21; N, 7.06.

(b) Using the procedures for preparation of **22**, steps d and e, **35** (58% yield) was prepared from ethyl (*E*)-2-(hydroxyimino)-3-phenylpropionate [(*E*)-**11j**] and 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-2-phenyl-1,3-oxazole (**10**) as colorless crystals. mp 143—144 °C (AcOEt–isoPr$_2$O, dec.). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.45 (3H, s), 3.81 (2H, s), 5.02 (2H, s), 5.20 (2H, s), 7.04 (2H, d, $J$=8.8 Hz), 7.10—7.33 (7H, m), 7.48—7.55 (3H, m), 7.91—7.98 (2H, m). IR (KBr) $cm^{-1}$: 2935, 1716, 1514, 1238, 993, 833, 694. *Anal.* Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 70.96; H, 5.19; N, 6.06.

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