Novel 5-Substituted-1*H*-tetrazole Derivatives as Potent Glucose and Lipid Lowering Agents

Yu Momose,*[,a] Tsuyoshi Maekawa,[a] Hiroyuki Odaka,[b] Hitoshi Ikeda,[c] and Takashi Sohda[d]

Medicinal Chemistry Research Laboratories II,[a] Pharmacology Research Laboratories II,[b] Product Planning, Strategic Product Planning Department, Takeda Chemical Industries, Ltd., 4–1–1 Doshomachi, Chuo-ku, Osaka 540–8645, Japan,[c] and Strategic Research Planning,[d] Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 2–17–85 Jusohonmachi, Yodogawa-ku, Osaka 532–8686, Japan. Received September 20, 2001; accepted November 2, 2001

A series of 5-(4-alkoxyphenylalkyl)-1*H*-tetrazole derivatives, containing an oxazole-based group at the alkoxy moiety, was prepared and their antidiabetic effects were evaluated in two genetically obese and diabetic animal models, KKA^y mice and Wistar fatty rats. Syntheses were performed by cyclization of the corresponding nitriles reacting with azide compounds. A large number of the 5-(4-alkoxyphenylalkyl)-1*H*-tetrazoles showed potent glucose and lipid lowering activities in KKA^y mice. In particular, 5-[3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propyl]-1*H*-tetrazole had potent glucose lowering activity (ED_{25}=0.0839 mg·kg^{-1}·d^{-1}), being 72 times more active than pioglitazone hydrochloride (ED_{25}=6.0 mg·kg^{-1}·d^{-1}). This compound also showed strong glucose lowering (ED_{25}=0.0873 mg·kg^{-1}·d^{-1}) and lipid lowering effects (ED_{25}=0.0277 mg·kg^{-1}·d^{-1}) in Wistar fatty rats. The antidiabetic effects of this compound are considered to be due to its potent agonistic activity for peroxisome proliferator-activated receptor γ (PPARγ) (EC_{50}=6.75 nM).

Key words antidiabetic agent; 5-(4-alkoxyphenylalkyl)-1*H*-tetrazole; Wistar fatty rat; glucose lowering effect; lipid lowering effect; KKA^y mouse

Type 2 diabetes is a complex, chronic and metabolic disorder typically characterized by insulin resistance in the liver and peripheral tissues together with a pancreatic β-cell defect.[1)] Treatment for type 2 diabetes is currently performed with a combination of exercise and restriction of caloric intake,[2)] or drug therapy. The most commonly used oral hypoglycemics for the disease are sulfonylureas. These agents, however, induce serious hypoglycemia[3)] and exhibit primary or secondary failure, which is presumably due to their characteristics as insulin secretagogues. Thus, use of the non-sulfonylurea class of hypoglycemics which do not increase insulin secretion but enhance the action of insulin (insulin sensitizers) is required.[4)] In the course of developing novel therapeutic agents for the treatment of type 2 diabetes, we discovered the prototypical 2,4-thiazolidinedione compound, ciglitazone (**1**)[5)] (Chart 1), which has antihyperglycemic activity in two insulin-resistant animal models, KKA^y mice[6)] and Wistar fatty rats,[7)] but does not show the effect in type 1 diabetic or nondiabetic animals.[8)] Efforts to find more potent antidiabetic 5-benzyl-2,4-thiazolidinedione derivatives[9)] resulted in the discovery of pioglitazone (**2**)[9b–f)] (Chart 1), which has a 2-(5-ethyl-2-pyridyl)ethoxy group at the *p*-position of the 5-benzyl substituent and is currently in clinical use. After that, we identified a series of potent 5-benzyl-2,4-thiazolidinediones with a 4-linked oxazole or thiazole moiety, leading to the discovery of AD-5061 (**3**) and AD-5075 (**4**) (Chart 1) as optimized analogues within the azole series.[10)] Since our discovery of ciglitazone, a substantial effort has been made in the pharmaceutical industry to develop new types of drugs for type 2 diabetes, particularly insulin sensitizers possessing 2,4-thiazolidinedione[11)] or analogous acidic 5-membered heterocycles.[12)] A series of perfluoroamides represented by Wy-49,322 (**5**) (Chart 1) was the first hypoglycemic agent having a tetrazole ring as an acidic heterocycle.[12a)] It appeared, however, that the lipophilic perfluorocarbon chain was the component critical for the activity, and unfavorable side-effects prohibited further development of these compounds.[13)]

We describe in this paper the syntheses and biological activities of a series of 5-substituted-1*H*-tetrazoles, including the finding that use of a tri- or tetramethylene unit as a spacer between the tetrazole and the phenyl or pyridyl moiety is better than that of the methylene group which was previously considered as the optimal spacer for use in the series of 2,4-thiazolidinediones.

Chemistry

Most of the 5-substituted-1*H*-tetrazoles **8**, **9** in Table 1 were synthesized from the corresponding nitriles **6**, **7** as shown in Chart 2. Conversion of the nitriles into final products was carried out in *N*,*N*-dimethylformamide (DMF) by treatment with sodium azide and ammonium chloride (method A). Some of the 5-alkyl-1*H*-tetrazoles **8** were obtained from the 5-alkenyl-1*H*-tetrazoles **9** by catalytic hydrogenation (method B).

The requisite nitriles were prepared as shown in Chart 3. The alkoxyphenylacetonitriles **12** were obtained starting with the corresponding benzaldehydes **10** *via* a three-step sequence: reduction with sodium borohydride and chlorination

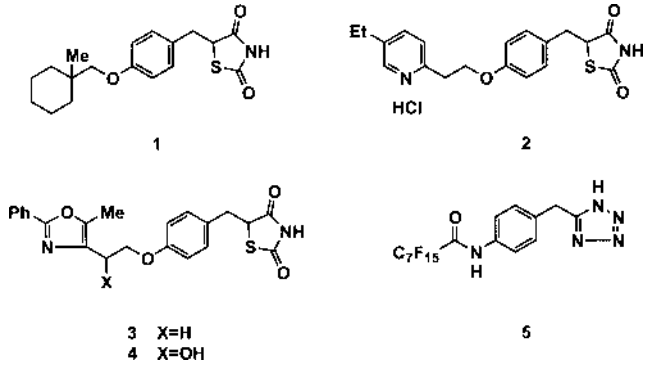
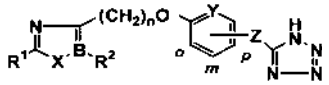
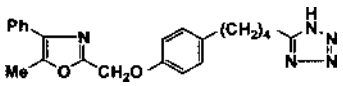


Chart 1

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

Table 1. Physical Data and Yields of 5-Substituted-1*H*-tetrazoles



Compd.	R^1	B–R^2	X	*n*	Y	Substituted position	Z	Prep. method[a]	Yield[b] (%)	mp (°C)	Recryst. solvent[c]
29	Ph	C–Me	O	3	CH	*p*	CH_2	A	58	138—139	AC–H
30	Ph	C–Me	O	2	CH	*p*	CH_2	A	56	173—174	ME
31	Ph	C–Me	O	2	CH	*p*	$(CH_2)_2$	A	48	143—144	AC–H
32	Ph	C–Me	O	2	CH	*p*	$(CH_2)_3$	A	56	124—125	AC–H
33	Ph	C–Me	O	2	CH	*p*	$(CH_2)_4$	A	80	118—119	A–IP
34	Ph	C–Me	O	2	CH	*p*	CH=CH	A	63	154—155	AC
35	Me	C–Me	O	2	CH	*p*	$(CH_2)_2$	A	45	225—226[d]	ME–E
36	Cyclohexyl	C–Me	O	2	CH	*p*	$(CH_2)_2$	A	81	80—81	D–IP
37	3-(Me)C_6H_4	C–Me	O	2	CH	*p*	$(CH_2)_2$	A	89	141—142	D–AC
38	2-(Cl)C_6H_4	C–Me	O	2	CH	*p*	$(CH_2)_2$	A	43	124—125	D–AC
39	2-Thienyl	C–Me	O	2	CH	*p*	$(CH_2)_2$	A	47	143—144	ME
40	Ph	C–Me	O	2	N	*p*	$(CH_2)_2$	A	44	143—144	ET
41	Ph	C–Me	O	1	CH	*p*	CH_2	A	83	163—164	ET
42	Ph	C–Me	O	1	CH	*p*	$(CH_2)_2$	B	81	203—204	C–ME
43	Ph	C–Me	O	1	CH	*p*	$(CH_2)_3$	A	25	107—108	AC–H
44	Ph	C–Me	O	1	CH	*p*	$(CH_2)_4$	B	67	116—117	AC–H
45	Ph	C–Me	O	1	CH	*p*	$(CH_2)_5$	A	46	129—130	AC–H
46	Ph	C–Me	O	1	CH	*p*	$(CH=CH)_2$	A	57	203—204	ME
47	2-Naphthyl	C–Me	O	1	CH	*p*	$(CH_2)_3$	A	29	156—157	D–E
48	2-Furyl	C–Me	O	1	CH	*p*	$(CH_2)_3$	A	44	133—134	D–IP
49	2-Benzofuranyl	C–Me	O	1	CH	*p*	$(CH_2)_3$	A	46	121—122	D–IP
50	Ph	C–Me	O	1	CF	*p*	$(CH_2)_4$	A	57	114—115	D–IP
51	Ph	C–Me	O	1	COMe	*p*	$(CH_2)_4$	B	13[e]	110—112	D–E
52	Ph	C–Me	O	1	N	*p*	$(CH_2)_3$	A	45	137—138	ME–AC
53	Ph	C–Me	O	1	N	*p*	$(CH_2)_4$	A	46	104—105	AC–H
54	Ph	C–Me	S	1	CH	*p*	$(CH_2)_3$	A	68	124—125	A–IP
55	Ph	N	NMe	1	CH	*p*	$(CH_2)_3$	A	83	159—160	D–ME
56	Ph	C–Me	O	1	CH	*m*	$(CH_2)_4$	B	81	94—95	AC–H
57	Ph	C–Me	O	1	CH	*o*	$(CH_2)_4$	B	55	148—149	D–ME
58								A	13	126—127	C–IP
59	Ph	C–Me	O	1	CH	*p*	CH=CH	A	85	214—215	C–ME
60	Ph	C–Me	O	1	CH	*m*	$(CH=CH)_2$	A	52[f]	201—202	ME
61	Ph	C–Me	O	1	CH	*o*	$(CH=CH)_2$	A	40	192—193	D–ME

a) A=from the corresponding nitriles **6** or **7**, B=from the corresponding 5-alkenyl-1*H*-tetrazoles **9**. *b*) Yield based on **6**, **7** (method A) or **9** (method B). *c*) A=acetone, AC=ethyl acetate, C=chloroform, D=dichloromethane, E=diethyl ether, ET=ethanol, H=hexane, IP=isopropyl ether, ME=methanol. *d*) Sodium salt. *e*) Yield from **17b**. *f*) Yield from **15e**.

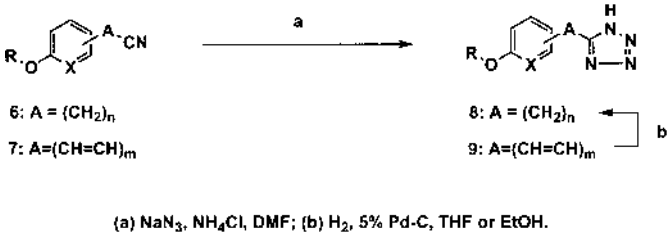
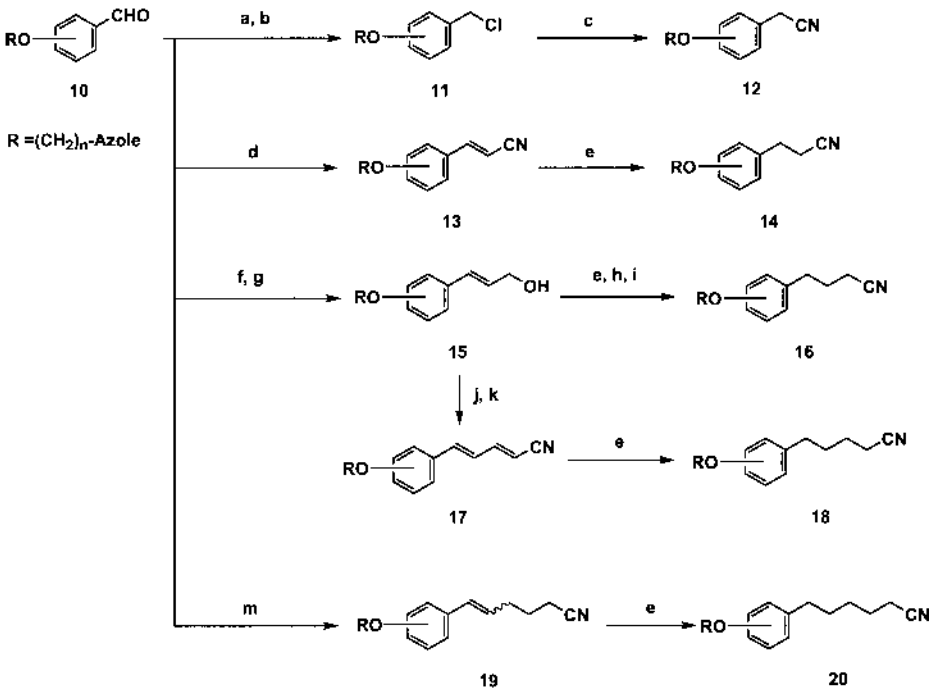


Chart 2

with thionyl chloride to give the benzyl chlorides **11**, followed by cyanation with potassium cyanide. Treatment of the benzaldehydes **10** with diethyl cyanomethylphosphonate gave the cinnamonitriles **13** which were converted into the 3-phenylpropionitriles **14** by catalytic hydrogenation. Synthesis of the 4-phenylbutyronitriles **16** required a five-step sequence. The Horner–Emmons reaction of the benzaldehydes **10** yielded the cinnamates, which were reduced with diisobutylaluminium hydride (DIBAL-H) to provide the cinnamyl alcohols **15**. Catalytic hydrogenation of the intermediates **15** furnished 3-phenylpropanols, which were sequentially treated with phosphorous tribromide and potassium cyanide to yield the desired products **16**. Oxidation of the cinnamyl alcohols **15** with activated manganese dioxide gave cinnamoaldehydes, which were transformed into the 5-phenyvaleronitriles **18** *via* the unsaturated nitriles **17** by the same reactions described for the synthesis of the propionitriles **14**. Treatment of the aldehydes **10** under the Wittig reaction conditions with phosphonium ylide generated the intermediates **19**. Catalytic hydrogenation of **19** yielded the 6-phenylhexanenitriles **20**. The prepared nitriles are listed in Table 2.

The starting 4-alkoxybenzaldehydes **10** were readily prepared by a method described previously.[9f,10]

The pyridyl analogues **23**, **26**, **28** were synthesized as indicated in Chart 4. Coupling of 2-chloro-5-nitropyridine with the corresponding alkoxides gave 2-alkoxy-5-nitropyridines which were reduced by catalytic hydrogenation to obtain 2-alkoxy-5-aminopyridines **21**. Diazotization of **21** followed by



(a) $NaBH_4$; (b) $SOCl_2$; (c) KCN; (d) $(EtO)_2P(O)CH_2CN$, NaH; (e) H_2, 5% Pd-C; (f) NaH, $(EtO)_2P(O)CH_2CO_2R^1$; (g) DIBAL-H; (h) PBr_3; (i) KCN; (j) MnO_2; (k) $(EtO)_2P(O)CH_2CN$, NaH; (m) $Ph_3P^+(CH_2)_4CN\ Br^-$, NaH.

Chart 3

treatment with acrylonitrile (Meerwein arylation) gave the 2-bromopropionitriles **22** which were debrominated under catalytic hydrogenation conditions to yield the 3-(6-alkoxy-3-pyridyl)propionitriles **23**. The Meerwein arylation of **21** with methyl acrylate gave the 2-bromopropionates **24** which were treated with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) followed by reduction with DIBAL-H to obtain 3-pyridyl-2-propen-1-ols **25**. The ω-(6-alkoxy-3-pyridyl)butyro- and valeronitriles **26**, **28** were derived from **25** by using the general procedures described in Chart 3. The 2- or 4-functionalized azoles used above were prepared by the procedure reported by Meguro and co-researchers.[14)]

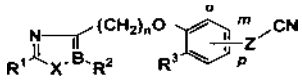
Biology

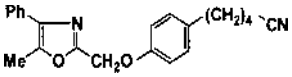
In Vitro. **Peroxisome Proliferator-Activated Receptor γ (PPARγ)–Retinoid X Receptor α (RXRα) Heterodimer Transactivation Assay** PPARγ : RXRα : PPRE×4/CHO-K1 cells were cultured in HAM F12 medium (Nissui Seiyaku, Japan) containing 10% fetal bovine serum (Life Technologies, Inc., U.S.A.) and then inoculated 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. After the washing of the white plate with PBS (phosphate-buffered saline), 90 μl of HAM F12 medium containing 0.1% fatty acid-free bovine serum albumin (BSA) and 10 μl of the test substance were added to the plate, which was then cultured in a carbonate gas incubator at 37 °C for 48 h. After removal of the medium, 40 μl of PICAGENE 7.5 (Wako Pure Chemical Ind., Osaka, Japan) was added, and after stirring, luciferase activity was determined using Lumistar (BMG Labtechnologies GmbH, Germany). A fold induction was calculated based on the luciferase activity of each test substance with the luciferase activity in the non-treatment group being regarded as 1. The values of the test substance concentration and the fold induction were analyzed using PRISM 2.01 (GraphPad Software Inc., U.S.A.) to calculate the EC_{50}, the effective concentration of a compound for the induction of 50% of maximum activity.

In Vivo The glucose and lipid lowering activities of the compounds prepared were tested using KKA^y mice[6)] and Wistar fatty rats.[7)]

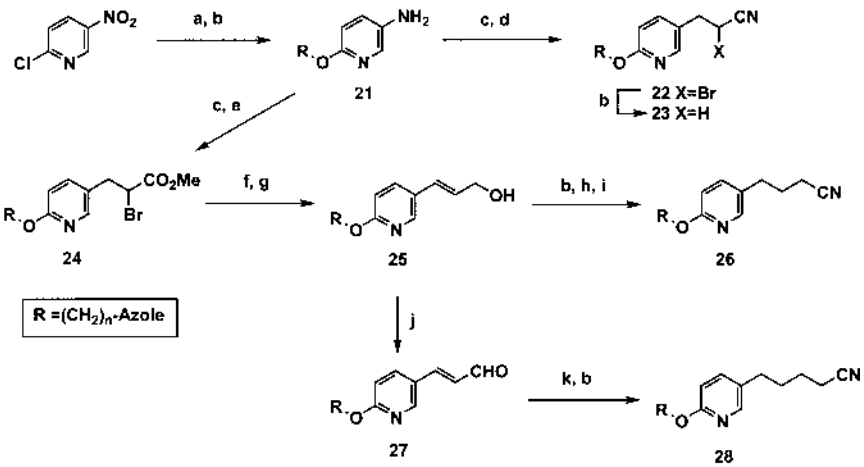
KKA^y Mice (9—13 Weeks Old): After being fed a powdered laboratory chow (CE-2, Clea Japan Inc., Tokyo, Japan) for 3 d, the mice were divided into experimental groups of five animals each based on their blood glucose levels. The test compounds were given as a dietary admixture at 0.01, 0.005, or 0.001% 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 and plasma triglyceride levels were determined by enzyme methods using the Iatrochem-GLU(A) and Iatro-MA701 TG kits (Iatron Laboratories, Inc., Tokyo, Japan), respectively. The respective values are shown as percent reduction from the control value. The effective dose to reduce plasma glucose and triglyceride levels by 25% (ED_{25}) was determined using results of an experiment in which three different doses were tested. The doses were selected in accordance with the potency of the compound. The dosages of test compounds ($mg\cdot kg^{-1}\cdot d^{-1}$) were calculated from food intake and body

Table 2. Physical Data and Yields of ω-Phenylalk(en)ylnitriles



Compd.	R^1	B–R^2	R^3	X	Substituted position	*n*	Z	Yield (%)	mp (°c)	Recryst. solvent[g)]
12a	Ph	C–Me	H	O	*p*	2	CH_2	81[a)]	109—110	AC–H
12b	Ph	C–Me	H	O	*p*	1	CH_2	88[a)]	98—99	A–IP
12c	Ph	C–Me	H	O	*p*	3	CH_2	87[b)]	79—80	AC–IP
13a	Ph	C–Me	H	O	*p*	2	(*E*)-CH=CH	85[b)]	112—113	AC–H
13b	Me	C–Me	H	O	*p*	2	CH=CH (*E* : *Z*=*ca.* 5 : 3)	87[b)]	Oil	—
13c	Cyclohexyl	C–Me	H	O	*p*	2	CH=CH (*E* : *Z*=*ca.* 3 : 1)	79[b)]	Oil	—
13d	3-(Me)C_6H_4	C–Me	H	O	*p*	2	(*E*)-CH=CH	49[b)]	97—98	D–IP
13e	2-(Cl)C_6H_4	C–Me	H	O	*p*	2	(*E*)-CH=CH	67[b)]	121—122	AC–H
13f	2-Thienyl	C–Me	H	O	*p*	2	(*E*)-CH=CH	48[b)]	146—147	D–IP
13g	Ph	C–Me	H	O	*p*	1	(*E*)-CH=CH	76[b)]	97—98	AC–H
14a	Ph	C–Me	H	O	*p*	2	$(CH_2)_2$	93[c)]	109—110	AC–H
14b	Me	C–Me	H	O	*p*	2	$(CH_2)_2$	100[c)]	62—63	A–H
14c	Cyclohexyl	C–Me	H	O	*p*	2	$(CH_2)_2$	79[c)]	Oil	—
14d	3-(Me)C_6H_4	C–Me	H	O	*p*	2	$(CH_2)_2$	93[c)]	79—80	E–H
14e	2-(Cl)C_6H_4	C–Me	H	O	*p*	2	$(CH_2)_2$	65[c)]	85—86	ET
14f	2-Thienyl	C–Me	H	O	*p*	2	$(CH_2)_2$	77[c)]	116—117	D–IP
16a	Ph	C–Me	H	O	*p*	2	$(CH_2)_3$	26[d)]	69—70	ET–H
16b	Ph	C–Me	H	O	*p*	1	$(CH_2)_3$	47[d)]	73—74	AC–H
16c	2-Naphthyl	C–Me	H	O	*p*	1	$(CH_2)_3$	44[e)]	149—151	C–E
16d	2-Furyl	C–Me	H	O	*p*	1	$(CH_2)_3$	63[e)]	Oil	—
16e	2-Benzofuranyl	C–Me	H	O	*p*	1	$(CH_2)_3$	67[e)]	118—119	D–IP
16f	Ph	C–Me	H	S	*p*	1	$(CH_2)_3$	80[e)]	91—92	A–IP
16g	Ph	N	H	NMe	*p*	1	$(CH_2)_3$	91[e)]	106—107	D–IP
17a	Ph	C–Me	H	O	*p*	1	$(CH=CH)_2$[f)]	48[d)]	120—121	AC–H
17b	Ph	C–Me	OMe	O	*p*	1	(*E*,*E*)-$(CH=CH)_2$	76[d)]	158—160	AC–E
17c	Ph	C–Me	H	O	*o*	1	(*E*,*E*)-$(CH=CH)_2$	52[d)]	128—129	ET–C
18a	Ph	C–Me	H	O	*p*	2	$(CH_2)_4$	86[d)]	56—57	E–IP
18b	Ph	C–Me	F	O	*p*	1	$(CH_2)_4$	89[d)]	68—69	E–H
18c								64[d)]	65—66	E–H
20a	Ph	C–Me	H	O	*p*	1	$(CH_2)_5$	68[b)]	76—77	E–H

a) Yield based on **11**. *b*) Yield based on **10**. *c*) Yield based on **13**. *d*) Yield based on **15**. *e*) Yield based on 4-(4-hydroxyphenyl)butyronitrile. *f*) A mixture of (2*E*,4*E*) and (2*Z*,4*E*) isomers (*ca.* 5 : 2). *g*) See footnote *c*) in Table 1.



(a) ROH, NaH; (b) H_2, 5% Pd-C; (c) HBr, $NaNO_2$; (d) CH_2=CHCN, Cu_2O; (e) CH_2=$CHCO_2Me$, Cu_2O; (f) DBU; (g) DIBAL-H; (h) MsCl, NEt_3; (i) NaCN; (j) MnO_2; (k) $(EtO)_2P(O)CH_2CN$, NaH.

Chart 4

Table 3. Glucose and Lipid Lowering Activities of 5-Substituted-1*H*-tetrazoles in KKA^y Mice

Compd.		Glucose lowering activity[a]				Lipid lowering activity[a]			
		Dose (%)			ED_{25}[b]	Dose (%)			ED_{25}[b]
		0.001	0.005	0.01		0.001	0.005	0.01	
29				29				25	
30				L[c]				L	
31			27*[d]	45**	10.7			28	
32				36**				37*	
33				33*				L	
34				L				L	
35				L				L	
36				26**				L	
37				31*				33	
38				L				22	
39				38**				32*	
40				22**				L	
41			L				L		
42				L				L	
43			53**	60**	1.89		74**	74**	1.85
44			43**	62**	2.01		48**	71**	5.63
45				30*				L	
46				L				L	
47			46**				85**		
48			48**				41**		
49			46**				57**		
50			22				L		
51			L				24		
52		47**	45**		0.0839	81**	89**		0.13
53		20	55**		1.36	L	36*		>1.6
54			L				L		
55			L				28*		
56				L				26	
57				20				24*	
58				L				24**	
1	Ciglitazone				31				25
2	Pioglitazone·HCl				6.0				6.0
5	Wy-49,322			42**[e]				45**[e]	

a) Maximum reductions in plasma glucose and plasma triglyceride levels at a dosage of 0.001, 0.005 or 0.01% in the diet were calculated as percent reduction with respect to the control value. *b*) Effective dose ($mg \cdot kg^{-1} \cdot d^{-1}$) for 25% reduction, estimated from a dose–response curve for three doses. *c*) Less than 20% reduction at this dosage. *d*) Statistically significant at (*) $p<0.05$, (**) $p<0.01$ by Dunnett's test. *e*) Compound was given as a dietary admixture at 0.02% in the diet.

weight. The ED_{25} ($mg \cdot kg^{-1} \cdot d^{-1}$) was then derived by linear regression analysis.

Wistar Fatty Rats (10—15 Weeks Old): The rats were divided into experimental groups of five animals each based on their plasma glucose and triglyceride levels. They were orally administered the compounds suspended in 0.5% methyl cellulose (Wako Pure Chemical Ind., Osaka, Japan) at three different concentrations once per day for 6 d *via* a stomach tube. They were fed a CE-2 pellet diet and water *ad libitum*. Blood samples were taken from a tail vein. Plasma glucose and triglyceride levels were measured and the ED_{25} was estimated in the same fashion as described above.

Results and Discussion

Antidiabetic activities were initially determined for KKA^y mice. As noted in our previous paper on the 5-(4-alkoxybenzyl)-2,4-thiazolidinedione series of compounds, two-carbon units between the azole ring and oxygen atom at the 4-position of the benzyl group were the most effective in eliciting the biological activity.[10] Based on this finding, we began our study with 5-alkyl-1*H*-tetrazoles possessing a 4-[2-(4-oxazolyl)ethoxy]phenyl moiety at the ω-position of the 5-alkyl chain, and found that compound **31** (Table 3) had glucose lowering activity. Structure–activity relationship (SAR) studies on the 5-substituted-1*H*-tetrazoles related to **31** initially focused on the length of the carbon chain between the tetrazole ring and the benzene ring. Studies of variation of the polymethylene unit [$(CH_2)_n$: $n=1$—4] showed that ethylene ($n=2$) was the best spacer (**31** *vs.* **30**, **32**, **33**). Derivative **34** with an unsaturated two-carbon unit was less potent than the corresponding saturated compound **31**. With regard to the effect of a substituent at the 2-position of the oxazole ring, an alkyl group was inferior to an aryl or a heteroaryl group (**35**, **36** *vs.* **31**, **39**), as was also the case for the 2,4-thiazolidinedione derivatives.[10] Introduction of a substituent into the benzene ring at the 2-position of the oxazole ring of **31** resulted in a decrease in activity (**31** *vs.* **37**, **38**). As regards the central benzene ring, conversion into the pyridine ring reduced the antihyperglycemic activity (**31** *vs.* **40**). Thus, considerable activity was observed for compounds with a 2-(4-oxazolyl)ethoxy moiety (**31**—**33**, **36**, **37**, **39**, **40**), but these tetrazole derivatives were less active than pioglitazone **2**. We found that antidiabetic activity was increased by extending the spacer between the tetrazole ring and the benzene ring from methylene (**30**: $-(CH_2)-$) to ethylene (**31**: $-(CH_2)_2-$).

Considering the effect of the distance between the oxazole

Table 4. Glucose and Lipid Lowering Activities in Wistar Fatty Rats and Transcriptional Activities of PPARγ of 5-Substituted-1*H*-tetrazoles

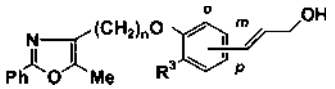
Compd.	Glucose lowering activity	Lipid lowering activity	Transcriptional activity of PPARγ
	ED_{25}[a)]	ED_{25}[a)]	EC_{50} (nM)[c)]
43	0.146	ND[b)]	22.3
44	0.167	ND[b)]	87.7
52	0.0873	0.0277	6.75
53	0.175	0.124	83.0
2 Pioglitazone·HCl	0.45	0.47	490[d)]

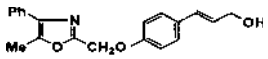
a) See footnote *b*) in Table 3. *b*) Not determined. *c*) Concentration required to induce 50% of the maximum luciferase activity. *d*) COS-1 cells were utilized.[16)]

and the tetrazole moieties on activity, our attention was next directed toward a series of compounds with a (4-oxazolyl)-methoxy moiety (**41**—**58**). These derivatives, especially those with a tri- or tetramethylene moiety as the spacer between the central benzene ring and the tetrazole ring (**43**, **44**, **47**—**49**, **52**, **53**), demonstrated much more activity than the above-mentioned compounds with a 2-(4-oxazolyl)ethoxy moiety. However, compound **46** with an unsaturated carbon chain as the spacer between the central benzene ring and the tetrazole ring was less active than the corresponding saturated compound **44**. Exchange of both alkyl spacers on the central benzene ring in compound **43** (–CH_2–, –$(CH_2)_3$–) resulted in compound **29** with less potent activity. Altering the substitution pattern on the benzene ring also resulted in compounds with less antidiabetic activity (**44** *vs.* **56**, **57**). These findings suggested that the spatial configuration of three aromatic rings (oxazole, central benzene, tetrazole) connected by two alkyl spacers (–$(CH_2)_n$– and Z (Table 1)) plays an important role in determining activity. Derivatives with a 2-naphthyl, 2-furyl, or 2-benzofuranyl group at the 2-position of the oxazole ring were equipotent to the 2-phenyl derivative (**47**—**49** *vs.* **43**). Substitution of a thiazole or a triazole for the oxazole ring, or shifting the side chain from the 4- to the 2-position of the oxazole ring, significantly reduced potency (**43** *vs.* **54**, **55**; **44** *vs.* **58**). These findings contrast with our previous results for the 2,4-thiazolidinediones,[10)] for which no significant difference was observed between the activities of the oxazole and thiazole derivatives, and of the 4-oxazolyl- and 2-oxazolyl derivatives. Introduction of an additional substituent into the central benzene ring also resulted in compounds with less antidiabetic activity (**44** *vs.* **50**, **51**). The pyridyl analogues had activities either stronger than or comparable to those of the parent compounds (**43** *vs.* **52**; **44** *vs.* **53**). In particular, compound **52** (ED_{25}=0.0839 mg·kg^{-1}·d^{-1}) exhibited an approximately 70-fold increase in antihyperglycemic activity over pioglitazone hydrochloride (**2**: ED_{25}=6.0 mg·kg^{-1}·d^{-1}).[9b)] These findings were quite different from the result of compound **40** with a 2-(4-oxazolyl)ethoxy moiety on the central pyridine ring as discussed above. These results confirmed us that the spatial configuration of three aromatic rings (oxazole, central benzene (central pyridine), tetrazole) is very important to appear the potent activity and the pyridine ring, especially, among three aromatic rings plays the most crucial role in increasing antidiabetic effect. Wy-49,322 (**5**),[12a)] reported as a novel hypoglycemic tetrazole derivative, was less potent than the typical tetrazoles (**43**, **52**) in this model.

A number of potent analogues, **43**, **44**, **52**, and **53**, were tested for their glucose and lipid lowering activities in Wistar fatty rats.[7)] As shown in Table 4, SARs for these compounds were almost the same as those in KK^y mice. The pyridyl analogue **52** had the most potent glucose lowering activity (ED_{25}=0.0873 mg·kg^{-1}·d^{-1}), and was about 5 times more active than pioglitazone hydrochloride (**2**, ED_{25}=0.5 mg·kg^{-1}·d^{-1}).[9d)] Moreover, these compounds were also evaluated in the transactivation assay of PPARγ as shown in Table 4. A correlation between the *in vitro* transcriptional activity of PPARγ and the *in vivo* glucose lowering activity in two genetically obese and diabetic animal models, KK^y mice and Wistar fatty rats, was demonstrated as expected.[15)]

Table 5. Physical Data and Yields of (*E*)-3-(Azolylalkoxy)phenyl-2-propen-1-ols



Compd.	R^3	Substituted position	*n*	Yield[a)] (%)	mp (°C)	Recryst. solvent[b)]
15a	H	*p*	2	79	127—128	AC
15b	H	*p*	1	93	133—134	AC–H
15c	F	*p*	1	80[c)]	134—135	D–IP
15d	OMe	*p*	1	61	137—138	AC–E
15e	H	*m*	1	75	120—121	AC
15f	H	*o*	1	76	128—129	AC–IP
15g			1	27	154—155	C–IP

a) Yield based on **10**. *b*) See footnote *c*) in Table 1. *c*) Yield from 3,4-difluoronitrobenzene. (See Experimental section.)

In summary, we showed that a series of 5-substituted-1*H*-tetrazoles had potent antidiabetic activities in KK^y mice and Wistar fatty rats, that were genetically obese and diabetic animal models. The tetrazole moiety suitably functioned as a bioisostere for the acidic 2,4-thiazolidinedione ring. The results of the SAR studies identified that the spatial configuration of three aromatic rings (oxazole, central benzene, tetrazole) connected by two alkyl spacers plays an important role in determining the activity. Compound **52**, the most potent derivative in this series, and some of its congeners, enhanced the remarkable PPARγ transcriptional activity, suggesting that this series of compounds act *via* the same mechanism reported for 2,4-thiazolidinedione-type insulin sensitizers.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. The ^{1}H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as an internal standard, and coupling constants (*J*) are given in hertz. Elemental Analyses were performed by

Takeda Analytical Research Laboratories, Ltd. and results obtained were within ±0.4% of the theoretical values. Column chromatography was performed using SiO_2 (Merck Kieselgel 60, 70—230 mesh).

General Procedure for Method A. 5-[2-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]ethyl]-1*H*-tetrazole (31) A mixture of 3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionitrile (**14a**, 700 mg, 2.1 mmol), sodium azide (411 mg, 6.3 mmol), ammonium chloride (337 mg, 6.3 mmol), and DMF (15 ml) was stirred at 120 °C for 24 h, poured into water and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**31**, 380 mg, 48%). ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 2.8—3.2 (6H, m), 4.15 (2H, t, J=6.5 Hz), 6.65 (2H, d, J=8.5 Hz), 6.85 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.52; H, 5.40; N, 18.98. Compounds **29**, **30**, **32**—**41**, **43**, **45**—**50**, **52**—**55**, and **58**—**61** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 1. **29**; ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 2.85—3.0 (4H, m), 3.12 (2H, t, J=7 Hz), 4.15 (2H, t, J=6.5 Hz), 6.65 (2H, d, J=8.5 Hz), 6.85 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.85—8.0 (2H, m). *Anal.* Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.11; H, 5.62; N, 18.56. **30**; ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.13 (2H, m), 2.30 (3H, s), 2.56—2.70 (2H, m), 3.87—3.96 (2H, m), 4.16 (2H, s), 6.60—6.72 (2H, m), 6.96—7.06 (2H, m), 7.34—7.46 (3H, m), 7.80—7.92 (2H, m). *Anal.* Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.09; H, 5.72; N, 18.43. **32**; ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m), 2.40 (3H, s), 2.51 (2H, t, J=7.5 Hz), 2.74 (2H, t, J=7.5 Hz), 2.98 (2H, t, J=6.5 Hz), 4.20 (2H, t, J=6.5 Hz), 6.69 (2H, d, J=8.5 Hz), 6.90 (2H, d, J=8.5 Hz), 7.35—7.45 (3H, m), 7.85—8.0 (2H, m). *Anal.* Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 67.60; H, 6.03; N, 17.74. **33**; ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.6 (4H, m), 2.40 (3H, s), 2.46 (2H, t, J=6.5 Hz), 2.78 (2H, t, J=7.5 Hz), 2.98 (2H, t, J=6.5 Hz), 4.20 (2H, t, J=6.5 Hz), 6.67 (2H, d, J=8.5 Hz), 6.90 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.85—8.0 (2H, m). *Anal.* Calcd for $C_{23}H_{25}N_5O_2$: C, 68.47; H, 6.25; N, 17.36. Found: C, 68.54; H, 6.26; N, 17.15. **34**; ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.99 (2H, t, J=6.5 Hz), 4.20 (2H, t, J=6.5 Hz), 6.77 (2H, d, J=9 Hz), 6.96 (1H, d, J=16.5 Hz), 7.31 (2H, d, J=9 Hz), 7.35—7.5 (3H, m), 7.65 (2H, d, J=16.5 Hz), 7.9—8.05 (2H, m). *Anal.* Calcd for $C_{21}H_{19}N_5O_2$: C, 67.55; H, 5.13; N, 18.75. Found: C, 67.20; H, 5.21; N, 18.19. **35**; ^{1}H-NMR ($CDCl_3$) δ: 2.22 (3H, s), 2.36 (3H, s), 2.82 (2H, t, J=6.5 Hz), 2.85—3.15 (4H, m), 4.11 (2H, t, J=6.5 Hz), 6.77 (2H, d, J=8.5 Hz), 7.09 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{16}H_{18}N_5O_2Na\cdot 1/2H_2O$: C, 55.81; H, 5.56; N, 20.34. Found: C, 56.01; H, 5.82; N, 20.68. **36**; ^{1}H-NMR ($CDCl_3$) δ: 1.15—2.1 (10H, m), 2.26 (3H, s), 2.71 (1H, tt, J=11, 3.5 Hz), 2.85 (2H, t, J=6.5 Hz), 2.95—3.3 (4H, m), 4.04 (2H, t, J=6.5 Hz), 6.64 (2H, d, J=8.5 Hz), 6.93 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{21}H_{27}N_5O_2$: C, 66.12; H, 7.13; N, 18.36. Found: C, 66.14; H, 7.41; N, 18.39. **37**; ^{1}H-NMR ($CDCl_3$) δ: 2.38 (6H, s), 2.8—3.2 (6H, m), 4.15 (2H, t, J=6.5 Hz), 6.64 (2H, d, J=9 Hz), 6.84 (2H, d, J=9 Hz), 7.23 (1H, br d, J=8 Hz), 7.31 (1H, t, J=7.5 Hz), 7.7—7.8 (2H, m). *Anal.* Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.97. Found: C, 68.13; H, 6.14; N, 18.26. **38**; ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.8—3.2 (6H, m), 4.16 (2H, t, J=6.5 Hz), 6.67 (2H, d, J=8.5 Hz), 6.87 (2H, d, J=8.5 Hz), 7.25—7.5 (3H, m), 7.8—7.9 (2H, m). *Anal.* Calcd for $C_{21}H_{20}ClN_5O_2$: C, 61.54; H, 4.92; N, 17.09. Found: C, 61.53; H, 4.89; N, 17.24. **39**; ^{1}H-NMR (DMSO-d_6) δ: 2.32 (3H, s), 2.8—3.2 (6H, m), 4.14 (2H, t, J=6.5 Hz), 6.82 (2H, d, J=8.5 Hz), 7.09 (2H, d, J=8.5 Hz), 7.19 (1H, dd, J=5, 3.5 Hz), 7.58 (1H, dd, J=3.5, 1 Hz), 7.70 (1H, dd, J=5, 1 Hz). *Anal.* Calcd for $C_{19}H_{19}N_5O_2S$: C, 59.83; H, 5.02; N, 18.36. Found: C, 59.78; H, 4.96; N, 18.18. **40**; ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.85—3.05 (4H, m), 3.18 (2H, t, J=7 Hz), 4.43 (2H, t, J=6.5 Hz), 6.52 (1H, d, J=8.5 Hz), 7.23 (1H, dd, J=8.5, 2.5 Hz), 7.35—7.5 (3H, m), 7.79 (1H, d, J=2.5 Hz), 7.85—8.0 (2H, m). *Anal.* Calcd for $C_{20}H_{20}N_5O_2S$: C, 63.82; H, 5.36; N, 22.33. Found: C, 63.53; H, 5.33; N, 22.23. **41**; ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 4.17 (2H, s), 4.87 (2H, s), 6.74 (2H, d, J=8.5 Hz), 7.04 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{19}H_{17}N_5O_2$: C, 65.70; H, 4.93; N, 20.16. Found: C, 65.65; H, 4.77; N, 20.18. **43**; ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.35 (2H, m), 1.45—1.85 (4H, m), 2.46 (3H, s), 2.48 (2H, t, J=7.5 Hz), 2.92 (2H, t, J=7.5 Hz), 4.96 (2H, s), 6.81 (2H, d, J=8.5 Hz), 6.98 (2H, d, J=8.5 Hz), 7.4—7.5 (3H, m), 7.95—8.05 (2H, m). *Anal.* Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.15; H, 5.96; N, 18.56. **45**; ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.15 (2H, m), 2.47 (3H, s), 2.57 (2H, t, J=7 Hz), 2.83 (2H, t, J=8 Hz), 4.93 (2H, s), 6.74 (2H, d, J=9 Hz), 6.92 (2H, d, J=9 Hz), 7.4—7.5 (3H, m), 7.9—8.05 (2H, m). *Anal.* Calcd for $C_{23}H_{25}N_5O_2$: C, 68.47; H, 6.25; N, 17.36. Found: C, 68.36; H, 6.34; N, 17.50. **46**; ^{1}H-NMR ($CDCl_3$) δ: 2.49 (3H, s), 4.99 (2H, s), 6.45—6.75 (3H, m), 6.94 (2H, d, J=9 Hz), 7.34 (2H, d, J=9 Hz), 7.4—7.55 (4H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.53; H, 4.96; N, 18.11. **47**; ^{1}H-NMR (dimethyl sulfoxide (DMSO)-d_6) δ: 1.9—2.1 (2H, m), 2.49 (3H, s), 2.59 (2H, t, J=7.5 Hz), 2.87 (2H, t, J=7.5 Hz), 5.01 (2H, s), 6.99 (2H, d, J=8.5 Hz), 7.16 (2H, d, J=8.5 Hz), 7.55—7.7 (2H, m), 7.9—8.15 (4H, m), 8.54 (1H, s). *Anal.* Calcd for $C_{25}H_{23}N_5O_2$: C, 70.57; H, 5.44; N, 16.46. Found: C, 70.38; H, 5.41; N, 16.59. **48**; ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.15 (2H, m), 2.45 (3H, s), 2.58 (2H, t, J=7 Hz), 2.86 (2H, t, J=8 Hz), 4.93 (2H, s), 6.53 (1H, dd, J=3, 1.5 Hz), 6.74 (2H, d, J=8.5 Hz), 6.93 (2H, d, J=8.5 Hz), 7.00 (1H, d, J=3 Hz), 7.48 (1H, d, J=1.5 Hz). *Anal.* Calcd for $C_{19}H_{19}N_5O_3\cdot 1/4H_2O$: C, 61.70; H, 5.31; N, 18.93. Found: C, 61.86; H, 5.22; N, 19.07. **49**; ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.2 (2H, m), 2.50 (3H, s), 2.59 (2H, t, J=7 Hz), 2.90 (2H, t, J=7.5 Hz), 4.97 (2H, s), 6.74 (2H, d, J=8.5 Hz), 6.93 (2H, d, J=8.5 Hz), 7.25—7.7 (5H, m). *Anal.* Calcd for $C_{23}H_{21}N_5O_3\cdot 1/4H_2O$: C, 65.78; H, 5.16; N, 16.68. Found: C, 65.75; H, 5.28; N, 16.82. **50**; ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (4H, m), 2.46 (3H, s), 2.50 (2H, t, J=7 Hz), 2.94 (2H, t, J=7.5 Hz), 5.02 (2H, s), 6.65—6.8 (2H, m), 6.89 (1H, t, J=8.5 Hz), 7.35—7.5 (3H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{22}H_{22}FN_5O_2$: C, 64.85; H, 5.44; N, 17.19. Found: C, 64.67; H, 5.16; N, 17.21. **52**; ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.15 (2H, m), 2.49 (3H, s), 2.54 (2H, t, J=7 Hz), 2.89 (2H, t, J=7.5 Hz), 5.26 (2H, s), 6.55 (1H, d, J=8.5 Hz), 7.25 (1H, dd, J=8.5, 2 Hz), 7.35—7.5 (3H, m), 7.79 (1H, d, J=2 Hz), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{20}H_{20}N_6O_2$: C, 63.82; H, 5.36; N, 22.33. Found: C, 63.75; H, 5.35; N, 22.56. **53**; ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (4H, m), 2.47 (2H, t, J=6.5 Hz), 2.49 (3H, s), 2.96 (2H, t, J=7.5 Hz), 5.26 (2H, s), 6.55 (1H, d, J=8.5 Hz), 7.23 (1H, dd, J=8.5, 2 Hz), 7.35—7.5 (3H, m), 7.79 (1H, d, J=2 Hz), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{21}H_{22}N_6O_2$: C, 64.60; H, 5.68; N, 21.52. Found: C, 64.42; H, 5.47; N, 21.57. **54**; ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.1 (2H, m), 2.53 (2H, t, J=7 Hz), 2.56 (3H, s), 2.77 (2H, t, J=7.5 Hz), 5.10 (2H, s), 6.77 (2H, d, J=9 Hz), 6.90 (2H, d, J=9 Hz), 7.35—7.5 (3H, m), 7.75—7.9 (2H, m). *Anal.* Calcd for $C_{21}H_{21}N_5O_2S$: C, 64.43; H, 5.41; N, 17.89. Found: C, 64.24; H, 5.40; N, 17.74. **55**; ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.1 (2H, m), 2.54 (2H, t, J=7 Hz), 2.82 (2H, t, J=7.5 Hz), 4.02 (3H, s), 5.23 (2H, s), 6.79 (2H, d, J=8.5 Hz), 6.94 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{21}N_7O$: C, 63.98; H, 5.64; N, 26.12. Found: C, 63.87; H, 5.52; N, 26.03. **58**; ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.75 (4H, m), 2.50 (2H, t, J=7 Hz), 2.56 (3H, s), 2.80 (2H, t, J=7 Hz), 5.14 (2H, s), 6.5—6.6 (2H, m), 6.81 (2H, d, J=8.5 Hz), 6.95 (2H, d, J=8.5 Hz), 7.3—7.45 (3H, m), 7.55—7.65 (2H, m). *Anal.* Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 67.51; H, 5.99; N, 17.79. **59**; ^{1}H-NMR (DMSO-d_6) δ: 2.48 (3H, s), 5.08 (2H, s), 7.12 (2H, d, J=8.5 Hz), 7.16 (1H, d, J=16.5 Hz), 7.45—7.55 (3H, m), 7.61 (1H, d, J=16.5 Hz), 7.68 (2H, d, J=8.5 Hz), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.50; H, 4.75; N, 19.46. **60**; ^{1}H-NMR (DMSO-d_6) δ: 2.48 (3H, s), 5.06 (2H, s), 6.75—7.05 (3H, m), 7.15—7.55 (8H, m), 7.9-8.0 (2H, m). *Anal.* Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.24; H, 4.64; N, 17.99. **61**; ^{1}H-NMR (DMSO-d_6) δ: 2.46 (3H, s), 5.11 (2H, s), 6.72 (1H, d, J=15.5 Hz), 6.95—7.7 (10H, m), 7.9—8.05 (2H, m). *Anal.* Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.25; H, 4.91; N, 18.33.

General Procedure for Method B. 5-[2-[4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)phenyl]ethyl]-1*H*-tetrazole (42) A mixture of 5-[2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]vinyl]-1*H*-tetrazole (**59**, 1.00 g, 2.8 mmol), 5% Pd–C (50% wet, 0.50 g), and 1,4-dioxane (100 ml) was hydrogenated at 1 atm. After removal of the catalyst by filtration and the filtrate was concentrated *in vacuo* to give the title compound (**42**, 810 mg, 81%). ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 2.95—3.3 (4H, m), 4.93 (2H, s), 6.82 (2H, d, J=8.5 Hz), 6.96 (2H, d, J=8.5 Hz), 7.4—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.30; H, 5.33; N, 19.25. Compounds **44**, **51**, **56**, and **57** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 1. **44**; ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (4H, m), 2.45 (3H, s), 2.49 (2H, t, J=7 Hz), 2.91 (2H, t, J=7.5 Hz), 4.92 (2H, s), 6.75 (2H, d, J=8.5 Hz), 6.93 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.9—8.05 (2H, m). *Anal.* Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 67.39; H, 5.80; N, 17.70. **51**; ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.85 (4H, m), 2.44 (3H, s), 2.50 (2H, t, J=7.5 Hz), 2.91 (2H, t, J=7.5 Hz), 3.73 (3H, s), 4.98 (2H, s), 6.5—6.6 (2H, m), 6.80 (1H, d, J=8 Hz), 7.35—7.5 (3H, m), 7.85—8.05 (2H, m). *Anal.* Calcd for $C_{23}H_{25}N_5O_3$: C, 65.86; H, 6.01; N, 16.70. Found: C, 65.59; H, 5.92; N, 16.73. **56**; ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (4H, m), 2.46 (3H, s), 2.50 (2H, t, J=6.5 Hz), 2.92 (2H, t, J=7.5 Hz), 4.94 (2H, s), 6.53 (1H, br t, J=1.5 Hz), 6.65—6.8 (2H, m), 7.13 (1H, t, J=8 Hz), 7.4—7.5 (3H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 67.58; H, 6.07; N, 17.99. **57**; ^{1}H-NMR (DMSO-d_6) δ: 1.45—1.8

(4H, m), 2.42 (3H, s), 2.59 (2H, t, J=7 Hz), 2.86 (2H, t, J=7 Hz), 5.02 (2H, s), 6.8—6.95 (1H, m), 7.05—7.25 (3H, m), 7.45—7.6 (3H, m), 7.85—8.0 (2H, m). *Anal.* Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 67.65; H, 5.79; N, 18.18.

The starting aldehydes (**10a**—**h**) were prepared following the procedure reported previously by Sohda *et al.*[9f,10]

4-[2-(2,5-Dimethyl-4-oxazolyl)ethoxy]benzaldehyde (10a) ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.38 (3H, s), 2.89 (2H, t, J=6.5 Hz), 4.26 (2H, t, J=6.5 Hz), 6.98 (2H, d, J=9 Hz), 7.81 (2H, d, J=9 Hz), 9.87 (1H, s).

4-[2-(2-Cyclohexyl-5-methyl-4-oxazolyl)ethoxy]benzaldehyde (10b) ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.1 (10H, m), 2.25 (3H, s), 2.69 (1H, tt, J=11, 3.5 Hz), 2.91 (2H, t, J=6.5 Hz), 4.26 (2H, t, J=6.5 Hz), 6.98 (2H, d, J=9 Hz), 7.81 (2H, d, J=9 Hz), 9.87 (1H, s).

4-[2-[5-Methyl-2-(3-methylphenyl)-4-oxazolyl]ethoxy]benzaldehyde (10c) mp 81—82 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.40 (3H, s), 3.01 (2H, t, J=6.5 Hz), 4.34 (2H, t, J=6.5 Hz), 7.00 (2H, d, J=9 Hz), 7.22 (1H, br d, J=7.5 Hz), 7.32 (1H, t, J=7.5 Hz), 7.7—7.85 (4H, m), 9.87 (1H, s). *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.55; H, 5.87; N, 4.31.

4-[2-[2-(2-Chlorophenyl)-5-methyl-4-oxazolyl]ethoxy]benzaldehyde (10d) mp 74—75 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.05 (2H, t, J=6.5 Hz), 4.36 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.5 Hz), 7.3—7.5 (3H, m), 7.82 (2H, d, J=8.5 Hz), 7.85—7.95 (1H, m), 9.87 (1H, s). *Anal.* Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 67.06; H, 4.64; N, 4.04.

4-[2-[5-Methyl-2-(2-thienyl)-4-oxazolyl]ethoxy]benzaldehyde (10e) mp 96—97 °C (CH_2Cl_2–$isoPr_2O$). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.99 (2H, t, J=6.5 Hz), 4.32 (2H, t, J=6.5 Hz), 6.99 (2H, d, J=8.5 Hz), 7.08 (1H, dd, J=5, 3.5 Hz), 7.37 (1H, dd, J=5, 1.5 Hz), 7.59 (1H, dd, J=3.5, 1.5 Hz), 7.81 (2H, d, J=8.5 Hz), 9.87 (1H, s). *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47. Found: C, 64.98; H, 4.98; N, 4.57.

2-(5-Methyl-2-phenyl-4-oxazolylmethoxy)benzaldehyde (10f) mp 95—96 °C (AcOEt–Et_2O). ^{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.

3-Methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzaldehyde (10g) mp 126—127 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 3.93 (3H, s), 5.15 (2H, s), 7.22 (1H, d, J=7.5 Hz), 7.35—7.55 (5H, m), 7.9—8.1 (2H, m), 9.86 (1H, s). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.51; H, 5.26; N, 4.21.

4-(5-Methyl-4-phenyl-2-oxazolylmethoxy)benzaldehyde (10h) mp 90—91 °C (AcOEt–$isoPr_2O$). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s), 5.22 (2H, s), 7.17 (2H, d, J=8.5 Hz), 7.25—7.5 (3H, m), 7.6—7.7 (2H, m), 7.8—7.9 (2H, m), 9.90 (1H, s). *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.58; H, 5.08; N, 4.73.

4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl Chloride (11a) Sodium borohydride (473 mg, 12.5 mmol) was added to an ice-cooled mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (7.7 g, 25 mmol) and MeOH (100 ml). The mixture was stirred at room temperature for 2 h, quenched with acetic acid (2 ml), concentrated *in vacuo*, and treated with water to give 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl alcohol (6.9 g, 88%). mp 109—110 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.64 (1H, t, J=6 Hz), 2.38 (3H, s), 2.98 (2H, t, J=6.5 Hz), 4.24 (2H, t, J=6.5 Hz), 4.61 (2H, d, J=6 Hz), 6.89 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.78; H, 6.27; N, 4.45.

Thionyl chloride (3.1 g, 26 mmol) was added to a stirred solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl alcohol (6.8 g, 22 mmol) in $CHCl_3$ (100 ml). After stirring for 1 h, the reaction mixture was washed successively with aqueous sodium bicarbonate and brine. The organic layer was separated, dried ($MgSO_4$), and concentrated to give the title compound (**11a**, 6.5 g, 79%). mp 93—94 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.98 (2H, t, J=6.5 Hz), 4.25 (2H, t, J=6.5 Hz), 4.56 (2H, s), 6.88 (2H, d, J=8.5 Hz), 7.29 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.90; H, 5.54; N, 4.23.

4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)benzyl chloride (**11b**) was prepared similarly. yield 92%. mp 108—109 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 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). *Anal.* Calcd for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.91; H, 5.19; N, 4.36.

4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]phenylacetonitrile (12a) A mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl chloride (**11a**, 6.4 g, 20 mmol), potassium cyanide (4.0 g, 61 mmol), and DMF (50 ml) was stirred at 60 °C for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**12a**, 5.2 g, 81%). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.98 (2H, t, J=6.5 Hz), 3.68 (2H, s), 4.25 (2H, t, J=6.5 Hz), 6.90 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.52; H, 5.77; N, 8.73.

4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)phenylacetonitrile (**12b**) and 4-[3-(5-methyl-2-phenyl-4-oxazolyl)propoxy]phenylacetonitrile (**12c**) were prepared similarly. The yields, recrystallization solvents, and melting points were listed in Table 2. **12b**; ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 3.70 (2H, s), 5.00 (2H, s), 7.03 (2H, d, J=9 Hz), 7.26 (2H, d, J=9 Hz), 7.4—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.77; H, 5.25; N, 9.04. **12c**; ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.23 (2H, m), 2.28 (3H, s), 2.70 (2H, t, J=7.2 Hz), 3.68 (2H, s), 3.98 (2H, t, J=6.0 Hz), 6.86—6.95 (2H, m), 7.16—7.26 (2H, m), 7.38—7.48 (3H, m), 7.94—8.02 (2H, m). *Anal.* Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.81; H, 6.24; N, 8.29.

General Procedure for (*E*)-4-(Azolylalkoxy)cinnamonitriles (13). (*E*)-4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]cinnamonitrile (13a) An ice-cooled solution of diethyl cyanomethylphosphonate (8.2 g, 47 mmol) in tetrahydrofuran (THF, 150 ml) was treated with sodium hydride (60% in oil, 2.0 g, 50 mmol) for 15 min, and then 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (13.0 g, 42 mmol) was added to the mixture. The resultant was stirred for 30 min, poured into water, and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**13a**, 11.8 g, 85%). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 3.00 (2H, t, J=6.5 Hz), 4.29 (2H, t, J=6.5 Hz), 5.71 (1H, d, J=16.5 Hz), 6.91 (2H, d, J=9 Hz), 7.33 (1H, d, J=16.5 Hz), 7.3—7.5 (5H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.04; H, 5.55; N, 8.27. Compounds **13b**—**g** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 2. **13b** (E : Z=*ca.* 5 : 3); ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 2.38 (3H, s), 2.88 (2H, t, J=7 Hz), 4.21 (major, t, J=7 Hz) and 4.23 (minor, t, J=7 Hz) total 2H, 5.28 (minor, d, J=12 Hz) and 5.71 (major, d, J=16.5 Hz) total 1H, 6.89 (major, d, J=9 Hz) and 6.93 (minor, d, J=9 Hz) total 2H, 7.02 (minor, d, J=12 Hz) and 7.32 (major, d, J=16.5 Hz) total 1H, 7.37 (major, d, J=9 Hz) and 7.77 (minor, d, J=9 Hz) total 2H. **13c** (E : Z=*ca.* 3 : 1); ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.1 (10H, m), 2.24 (3H, s), 2.6—2.8 (1H, m), 2.89 (2H, t, J=7 Hz), 4.20 (major, t, J=7 Hz) and 4.21 (minor, t, J=7 Hz) total 2H, 5.28 (minor, d, J=12 Hz) and 5.70 (major, d, J=16.5 Hz) total 1H, 6.88 (major, d, J=9 Hz) and 6.91 (minor, d, J=9 Hz) total 2H, 7.02 (minor, d, J=12 Hz) and 7.32 (major, d, J=16.5 Hz) total 1H, 7.37 (major, d, J=9 Hz) and 7.76 (minor, d, J=9 Hz) total 2H. **13d**; ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.40 (3H, s), 2.99 (2H, t, J=6.5 Hz), 4.28 (2H, t, J=6.5 Hz), 5.70 (1H, d, J=16.5 Hz), 6.90 (2H, d, J=9 Hz), 7.15—7.4 (5H, m), 7.5—7.85 (2H, m). *Anal.* Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.48; H, 5.88; N, 8.09. **13e**; ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.03 (2H, t, J=6.5 Hz), 4.31 (2H, t, J=6.5 Hz), 5.71 (1H, d, J=16.5 Hz), 6.92 (2H, d, J=9 Hz), 7.2—7.55 (6H, m), 7.85—7.95 (1H, m). *Anal.* Calcd for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68. Found: C, 69.11; H, 4.69; N, 7.65. **13f**; ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.97 (2H, t, J=6.5 Hz), 4.26 (2H, t, J=6.5 Hz), 5.70 (1H, d, J=16.5 Hz), 6.89 (2H, d, J=8.5 Hz), 7.08 (1H, dd, J=5, 4 Hz), 7.3—7.45 (4H, m), 7.58 (1H, dd, J=4, 1 Hz). *Anal.* Calcd for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33. Found: C, 67.68; H, 4.80; N, 8.38. **13g**; ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 5.03 (2H, s), 5.73 (1H, d, J=16.5 Hz), 7.04 (2H, d, J=9 Hz), 7.34 (1H, d, J=16.5 Hz), 7.35—7.5 (5H, m), 7.95—8.05 (2H, m). *Anal.* Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.77; H, 5.14; N, 8.94.

General Procedure for 3-[4-(Azolylalkoxy)phenyl]propionitriles (14). 3-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionitrile (14a) A mixture of (*E*)-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]cinnamonitrile (**13a**, 4.0 g, 12 mmol), 5% Pd–C (50% wet, 0.5 g), and AcOEt (50 ml) was hydrogenated at 1 atm. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give the title compound (**14a**, 3.7 g, 93%). ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.56 (2H, t, J=7.5 Hz), 2.89 (2H, t, J=7.5 Hz), 2.98 (2H, t, J=7 Hz), 4.24 (2H, t, J=7 Hz), 6.87 (2H, d, J=8.5 Hz), 7.13 (2H, d, J=8.5 Hz), 7.85—8.0 (3H, m), 7.9—8.05 (2H, m). *Anal.* Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.83; H, 6.19; N, 8.28. Compounds **14b**—**f** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 2. **14b**; ^{1}H-NMR

($CDCl_3$) δ: 2.24 (3H, s), 2.37 (3H, s), 2.57 (2H, t, J=7 Hz), 2.8—2.95 (4H, m), 4.16 (2H, t, J=7 Hz), 6.85 (2H, d, J=8.5 Hz), 7.13 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.99; H, 6.93; N, 10.64. **14c**; ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.1 (10H, m), 2.24 (3H, s), 2.57 (2H, t, J=7.5 Hz), 2.69 (1H, tt, J=11.5, 3.5 Hz), 2.87 (2H, t, J=7 Hz), 2.89 (2H, t, J=7.5 Hz), 4.14 (2H, t, J=7 Hz), 6.84 (2H, d, J=8.5 Hz), 7.12 (2H, d, J=8.5 Hz). **14d**; ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s), 2.40 (3H, s), 2.56 (2H, t, J=7.5 Hz), 2.89 (2H, t, J=7.5 Hz), 2.97 (2H, t, J=7 Hz), 4.23 (2H, t, J=7 Hz), 6.86 (2H, d, J=8.5 Hz), 7.12 (2H, d, J=8.5 Hz), 7.21 (1H, br d, J=8 Hz), 7.31 (1H, t, J=7.5 Hz), 7.7—7.85 (2H, m). *Anal.* Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.43; H, 6.55; N, 8.02. **14e**; ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 2.57 (2H, t, J=7.5 Hz), 2.88 (2H, t, J=7.5 Hz), 3.00 (2H, t, J=6.5 Hz), 4.24 (2H, t, J=6.5 Hz), 6.87 (2H, d, J=8.5 Hz), 7.12 (2H, d, J=8.5 Hz), 7.25—7.5 (3H, m), 7.85—8.0 (1H, m). **14f**; ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.57 (2H, t, J=7.5 Hz), 2.89 (2H, t, J=7.5 Hz), 2.95 (2H, t, J=6.5 Hz), 4.21 (2H, t, J=6.5 Hz), 6.85 (2H, d, J=8.5 Hz), 7.08(1H, dd, J=5, 3.5 Hz), 7.12 (2H, d, J=8.5 Hz), 7.36 (1H, dd, J=5, 1 Hz), 7.58 (1H, dd, J=3.5, 1 Hz). *Anal.* Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.37; H, 5.27; N, 8.33.

General Procedure for (*E*)-3-[4-(Azolylalkoxy)phenyl]-2-propen-1-ols (15). (*E*)-3-[4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-propen-1-ol (15b) A stirred and ice-cooled solution of triethyl phosphonoacetate (3.3 g, 15 mmol) in THF (100 ml) was treated with sodium hydride (60% in oil, 620 mg, 16 mmol) for 15 min. 4-(5-Methyl-2-phenyl-4-oxazolymethoxy)-benzaldehyde (3.9 g, 13 mmol) was added to the mixture, and the resultant was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give ethyl (*E*)-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamate (4.5 g, 96%). mp 145—146 °C (AcOEt–hexane). ^{1}H-NHR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz), 2.45 (3H, s), 4.26 (2H, q, J=7 Hz), 5.03 (2H, s), 6.32 (1H, d, J=16 Hz), 7.03 (2H, d, J=9 Hz), 7.4—7.55 (5H, m), 7.65 (1H, d, J=16 Hz), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.78; H, 5.85; N, 3.88.

DIBAL-H (1.5 M in toluene, 16 ml, 24 mmol) was added dropwise to a stirred and ice-cooled solution of ethyl (*E*)-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamate (4.4 g, 12 mmol) in CH_2Cl_2 (80 ml). After stirring for 1 h, 2 N HCl (50 ml) was added to the mixture with cooling, and then the resultant was stirred at room temperature for 1 h. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**15b**, 3.8 g, 93%). ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 4.25—4.35 (2H, m), 5.00 (2H, s), 6.25 (1H, dt, J=16, 6 Hz), 6.57 (1H, d, J=16 Hz), 6.98 (2H, d, J=9 Hz), 7.34 (2H, d, J=9 Hz), 7.35—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{19}NO_3 \cdot 1/4H_2O$: C, 73.72; H, 6.03; N, 4.30. Found: C, 73.60; H, 6.01; N, 4.23. Compounds **15a** and **15d**—**g** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 5. **15a**; ^{1}H-NMR ($CDCl_3$) δ: 1.42 (1H, t, J=6 Hz), 2.27 (3H, s), 2.98 (2H, t, J=6.5 Hz), 4.25 (2H, t, J=6.5 Hz), 4.25—4.35 (2H, m), 6.22 (1H, dt, J=16, 6 Hz), 6.55 (1H, d, J=16 Hz), 6.86 (2H, d, J=9 Hz), 7.30 (2H, d, J=9 Hz), 7.35—7.5 (3H, m), 7.9—8.05 (2H, m). *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 74.84; H, 6.27; N, 4.17. **15d**; ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 3.88 (3H, s), 4.25—4.4 (2H, m), 5.06 (2H, s), 6.25 (1H, dt, J=16, 6 Hz), 6.55 (1H, d, J=16 Hz), 6.85—7.05 (3H, m), 7.35—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.60; H, 6.05; N, 3.71. **15e**; ^{1}H-NMR ($CDCl_3$) δ: 1.49 (1H, t, J=6 Hz), 2.44 (3H, s), 4.25—4.4 (2H, m), 5.01 (2H, s), 6.37 (1H, dt, J=16, 5.5 Hz), 6.60 (1H, d, J=16 Hz), 6.85—7.1 (3H, m), 7.25 (1H, t, J=8 Hz), 7.4—7.55 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.78; H, 5.76; N, 4.39. **15f**; ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 4.25—4.4 (2H, m), 5.02 (2H, s), 6.37 (1H, dt, J=16, 6 Hz), 6.9—7.1 (3H, m), 7.15—7.3 (1H, m), 7.4—7.5 (4H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.37; H, 6.06; N, 4.47. **15g**; ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, s), 4.25—4.4 (2H, m), 5.14 (2H, s), 6.25 (1H, dt, J=16, 6 Hz), 6.56 (1H, d, J=16 Hz), 7.00 (2H, d, J=9 Hz), 7.25—7.5 (5H, m), 7.6—7.7 (2H, m). *Anal.* Calcd for $C_{20}H_{19}NO_3 \cdot 1/4H_2O$: C, 73.72; H, 6.03; N, 4.30. Found: C, 73.74; H, 5.99; N, 4.01.

(*E*)-3-[3-Fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-propen-1-ol (15c) Sodium hydride (60% in oil, 2.22 g, 55.5 mmol) was added gradually to a mixture of 5-methyl-2-phenyl-4-oxazolemethanol (10.0 g, 52.9 mmol), 3,4-difluoronitrobenzene (8.83 g, 55.5 mmol), and DMF (100 ml) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was poured onto ice-H_2O and acidified with 2 N HCl to give crystals. Recrystallization from CH_2Cl_2–MeOH gave 4-(2-fluoro-4-nitrophenoxymethyl)-5-methyl-2-phenyloxazole (14.0 g, 81%) as colorless prisms. mp 155—156 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 5.19 (2H, s), 7.33 (1H, dd, J=9, 8 Hz), 7.4—7.5 (3H, m), 7.95—8.05 (3H, m), 8.07 (1H, ddd, J=9, 3, 1.5 Hz). *Anal.* Calcd for $C_{17}H_{13}FN_2O_4$: C, 62.20; H, 3.99; N, 8.53. Found: C, 61.79; H, 3.92; N, 8.46.

A solution of 4-(2-fluoro-4-nitrophenoxymethyl)-5-methyl-2-phenyloxazole (13.6 g, 41.4 mmol) in THF (200 ml) was hydrogenated on 5% Pd–C (50% wet, 2.00 g) at 1 atm. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give 3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)aniline (12.3 g, quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 3.53 (2H, br s), 4.96 (2H, s), 6.35 (1H, ddd, J=8.5, 3, 1.5 Hz), 6.46 (1H, dd, J=12.5, 3 Hz), 6.91 (1H, t, J=9 Hz), 7.35—7.5 (3H, m), 7.95—8.1 (2H, m).

A solution of sodium nitrite (3.13 g, 45.4 mmol) in water (5 ml) was added dropwise to a stirred and ice-cooled mixture of 3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)aniline (12.3 g, 41.2 mmol), hydrobromic acid (47%, 28.4 g, 164 mmol), MeOH (50 ml), and acetone (150 ml) below 5 °C. After stirring for 15 min, methyl acrylate (21.3 g, 247 mmol) was added and the temperature was raised to 35 °C. Powdered copper(I) oxide (50 mg) was added gradually to the vigorously stirred mixture. After a nitrogen gas evolution had ceased, the reaction mixture was concentrated *in vacuo.* The residue was diluted with ammonia solution (25% in water) and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated to leave an oil which was purified by column chromatography on SiO_2 (200 g) with AcOEt–hexane (1 : 4, v/v) to give methyl 2-bromo-3-[3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propionate (14.2 g, 75%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 3.16 (1H, dd, J=14, 7 Hz), 3.39 (1H, dd, J=14, 8.5 Hz), 3.73 (3H, s), 4.34 (1H, dd, J=8.5, 7 Hz), 5.05 (2H, s), 6.85—7.0 (2H, m), 7.07 (1H, t, J=8.5 Hz), 7.35—7.5 (3H, m), 7.95—8.05 (2H, m).

A mixture of methyl 2-bromo-3-[3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propionate (14.2 g, 31.7 mmol), DBU (4.83 g, 31.7 mmol), and toluene (150 ml) was stirred at 80—90 °C for 2 h. The reaction mixture was diluted with 2 N HCl and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give ethyl (*E*)-3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamate (10.0 g, 86%) as crystals. mp 167—168 °C (CH_2Cl_2–MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 3.80 (3H, s), 5.11 (2H, s), 6.30 (1H, d, J=16 Hz), 7.1—7.35 (3H, m), 7.4—7.5 (3H, m), 7.59 (1H, d, J=16 Hz), 7.95—8.05 (2H, m). *Anal.* Calcd for $C_{21}H_{18}FNO_4$: C, 68.66; H, 4.94; N, 3.81. Found: C, 68.62; H, 4.66; N, 3.85.

DIBAL-H (1.5 M in toluene, 37.2 ml, 55.8 mmol) was added dropwide to a stirred solution of ethyl (*E*)-3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamate (9.30 g, 25.3 mmol) in CH_2Cl_2 (200 ml) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with 2 N HCl and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 (200 g) with AcOEt–$CHCl_3$ (1 : 5, v/v) to give the title compound (**15c**, 6.85 g, 80%). mp 134—135 °C (CH_2Cl_2–isoPr$_2$O). ^{1}H-NMR ($CDCl_3$) δ: 1.53 (1H, br s), 2.43 (3H, s), 4.25—4.35 (2H, m), 5.07 (2H, s), 6.23 (1H, dt, J=16, 5.5 Hz), 6.52 (1H, d, J=16 Hz), 7.0—7.2 (3H, m), 7.35—7.5 (3H, m), 7.95—8.05 (2H, m). *Anal.* Calcd for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13. Found: C, 70.56; H, 5.31; N, 4.15.

General Procedure for 4-[4-(Azolylalkoxy)phenyl]butyronitriles (16). 4-[4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)phenyl]butyronitrile (16b) A mixture of (*E*)-3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-propen-1-ol (**15b**, 3.0 g, 9.3 mmol), 5% Pd–C (50% wet, 500 mg), and 1,4-dioxane (50 ml) was hydrogenated at 1 atm. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give 3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propan-1-ol (2.8 g, 93%). mp 72—73 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (1H, br s), 1.8—2.0 (2H, m), 2.43 (3H, s), 2.66 (2H, t, J=7.5 Hz), 3.67 (2H, br q, J=6 Hz), 4.98 (2H, s), 6.95 (2H, d, J=8.5 Hz), 7.13 (2H, d, J=8.5 Hz), 7.4—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 73.94; H, 6.79; N, 4.17.

Phosphorus tribromide (1.1 g, 4.1 mmol) was added dropwise to a stirred solution of 3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propan-1-ol (2.6 g, 8.0 mmol) in benzene (50 ml) at room temperature. The mixture was stirred at 60 °C for 30 min, poured into water, and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give 3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl bromide (1.7 g, 55%). mp 81—82 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.05—2.25 (2H, m), 2.44 (3H, s), 2.73 (2H, t, J=7.5 Hz), 3.39 (2H, t, J=6.5

Hz), 4.98 (2H, s), 6.96 (2H, d, J=8.5 Hz), 7.13 (2H, d, J=8.5 Hz), 7.4—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22; N, 3.63. Found: C, 62.11; H, 5.30; N, 3.47.

A mixture of 3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl bromide (1.5 g, 3.9 mmol), powdered potassium cyanide (1.52 g, 23.4 mmol), and DMF (30 ml) was stirred at 80 °C for 3 h, poured into water, and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**16b**, 1.2 g, 92%). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m), 2.31 (2H, t, J=7 Hz), 2.44 (3H, s), 2.73 (2H, t, J=7.5 Hz), 4.98 (2H, s), 6.97 (2H, d, J=9 Hz), 7.12 (2H, d, J=9 Hz), 7.4—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.72; H, 6.28; N, 8.16. Compound **16a** was obtained similarly. The yield, recrystallization solvent, and melting point were listed in Table 2. **16a**; ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m), 2.29 (2H, t, J=7 Hz), 2.38 (3H, s), 2.71 (2H, t, J=7 Hz), 2.97 (2H, t, J=6.5 Hz), 4.23 (2H, t, J=6.5 Hz), 6.84 (2H, d, J=8.5 Hz), 7.07 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.9—8.0 (2H, m). *Anal.* Calcd for $C_{22}H_{22}N_2O_2 \cdot 1/2H_2O$: C, 74.34; H, 6.52; N, 7.88. Found: C, 74.68; H, 6.35; N, 7.83.

4-[4-(5-Methyl-2-phenyl-4-thiazolylmethoxy)phenyl]butyronitrile (16f) A mixture of 4-(4-hydroxyphenyl)butyronitrile (1.00 g, 6.20 mmol), 4-chloromethyl-5-methyl-2-phenylthiazole (1.53 g, 6.84 mmol), potassium carbonate (945 mg, 6.84 mmol), and DMF (30 ml) was stirred at 85—90 °C for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound. Recrystallization from acetone–isoPr$_2$O gave colorless prisms (**16f**, 1.73 g, 80%). mp 91—92 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m), 2.31 (2H, t, J=7 Hz), 2.53 (3H, s), 2.73 (2H, t, J=7.5 Hz), 5.16 (2H, s), 7.00 (2H, d, J=9 Hz), 7.12 (2H, d, J=9 Hz), 7.35—7.5 (3H, m), 7.85—7.95 (2H, m). *Anal.* Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.78; N, 8.04. Found: C, 72.37; H, 5.90; N, 7.90. Compounds **16c**—**e** and **16g** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 2. **16c**; ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.1 (2H, m), 2.32 (2H, t, J=7 Hz), 2.49 (3H, s), 2.74 (2H, t, J=7.5 Hz), 5.02 (2H, s), 6.99 (2H, d, J=9 Hz), 7.13 (2H, d, J=9 Hz), 7.45—7.6 (2H, m), 7.8—8.0 (3H, m), 8.13 (1H, dd, J=8.5, 1.5 Hz), 8.53 (1H, s). *Anal.* Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.06; H, 5.60; N, 7.07. **16d**; ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m), 2.31 (2H, t, J=7 Hz), 2.42 (3H, s), 2.72 (2H, t, J=7.5 Hz), 4.97 (2H, s), 6.52 (2H, dd, J=3.5, 2 Hz), 6.9—7.0 (3H, m), 7.10 (2H, d, J=9 Hz), 7.53 (1H, dd, J=2, 1 Hz). **16e**; ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m), 2.31 (2H, t, J=7 Hz), 2.48 (3H, s), 2.73 (2H, t, J=7.5 Hz), 5.02 (2H, s), 6.96 (2H, d, J=8.5 Hz), 7.12 (2H, d, J=9 Hz), 7.2—7.45 (3H, m), 7.55—7.7 (2H, m). *Anal.* Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73,87; H, 5,43; N, 7.23. **16g**; ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m), 2.30 (2H, t, J=7 Hz), 2.73 (2H, t, J=7.5 Hz), 4.00 (3H, s), 5.27 (2H, s), 6.98 (2H, d, J=9 Hz), 7.12 (2H, d, J=9 Hz), 7.3—7.5 (3H, m), 8.0—8.1 (2H, m). *Anal.* Calcd for $C_{20}H_{20}N_4O$: C, 72.27; H, 6.06; N, 16.86. Found: C, 72.17; H, 5.96; N, 16.71.

General Procedure for 5-(Azolylalkoxyphenyl)-2,4-pentadienonitriles (17). 5-[4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2,4-pentadienonitrile (17a) A mixture of (*E*)-3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-propen-1-ol (**15b**, 3.7 g, 12 mmol), manganese dioxide (activated, 9.0 g), and CH_2Cl_2 (80 ml) was stirred at room temperature for 1 h. The insoluble solid was filtered, and the filtrate was concentrated *in vacuo* to give (*E*)-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamaldehyde (2.6 g, 70%). mp 114—115 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 5.05 (2H, s), 6.63 (1H, dd, J=16, 8 Hz), 7.08 (2H, d, J=9 Hz), 7.4—7.5 (4H, m), 7.55 (2H, d, J=9 Hz), 7.95—8.1 (2H, m), 9.67 (1H, d, J=8 Hz). *Anal.* Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.15; H, 5.40; N, 4.36.

An ice-cooled solution of diethyl cyanomethylphosphonate (1.3 g, 7.5 mmol) in THF (50 ml) was treated with sodium hydride (60% in oil, 320 mg, 8.0 mmol) for 15 min. (*E*)-4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)-cinnamaldehyde (2.0 g, 6.3 mmol) was added to the mixture, and the stirring was continued for 30 min. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**17a**, 1.5 g, 68%). mp 120—121 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 5.03 (2H, s), 5.18 (d, J=10 Hz) and 5.38 (d, J=16 Hz) total 1H, 6.7—7.2 (5H, m), 7.35—7.55 (5H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.03; H, 5.24; N, 8.04. Compounds **17b** and **17c** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 2. **17b**; ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.90 (3H, s), 5.08 (2H, s), 5.39 (1H, d, J=16 Hz), 6.6—7.25 (6H, m), 7.35—7.55 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.12; H, 5.48; N, 7.41. **17c**; ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 5.05 (2H, s), 5.33 (1H, d, J=15.5 Hz), 6.8—7.4 (7H, m), 7.4—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.00; H, 5.42; N, 8.22.

General Procedure for 5-[4-(Azolylalkoxy)phenyl]valeronitriles (18). 5-[3-Fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]valeronitrile (18b) A mixture of (*E*)-3-[3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-propen-1-ol (**15c**, 6.63 g, 19.5 mmol), manganese dioxide (activated, 12.0 g), and CH_2Cl_2 (100 ml) was stirred at room temperature for 16 h. The insoluble solid was filtered, and the filtrate was concentrated *in vacuo* to give (*E*)-[3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)]cinnamaldehyde (5.91 g, 90%). mp 133—134 °C (CH_2Cl_2–MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 5.03 (2H, s), 6.59 (1H, dd, J=16, 7.5 Hz), 7.15—7.5 (7H, m), 7.95—8.05 (2H, m), 9.66 (1H, d, J=7.5 Hz). *Anal.* Calcd for $C_{20}H_{16}FNO_3$: C, 71.21; H, 4.78; N, 4.15. Found: C, 71.19; H, 4.68; N, 4.20.

An ice-cooled solution of (*E*)-[3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)]cinnamaldehyde (1.21 g, 3.59 mmol), diethyl cyanomethylphosphonate (700 mg, 3.95 mmol), and DMF (30 ml) was treated with sodium hydride (60% in oil, 160 mg, 4.0 mmol) for 30 min with stirring. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo.* The residue was dissolved in THF (30 ml)–EtOH (30 ml) and then hydrogenated at 1 atm. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo.* The residue was purified by column chromatography on SiO_2 (50 g) with AcOEt–hexane (1 : 4, v/v) to give the title compound (**18b**, 1.29 g, 99%). mp 68—69 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.85 (4H, m), 2.35 (2H, t, J=6.5 Hz), 2.43 (3H, s), 2.60 (2H, t, J=7 Hz), 5.05 (2H, s), 6.8—6.95 (2H, m), 7.05 (1H, t, J=8.5 Hz), 7.4—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{22}H_{21}FN_2O_2$: C, 72.51; H, 5.81; N, 7.69. Found: C, 72.36; H, 5.63; N, 7.74. Compounds **18a** and **18c** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 2. **18a**; ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.85 (4H, m), 2.33 (2H, t, J=7 Hz), 2.38 (3H, s), 2.59 (2H, t, J=7 Hz), 2.98 (2H, t, J=7 Hz), 4.22 (2H, t, J=7 Hz), 6.83 (2H, d, J=8.5 Hz), 7.06 (2H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.95—8.05 (2H, m). *Anal.* Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.70; H, 6.46; N, 7.69. **18c**; ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.9 (4H, m), 2.34 (2H, t, J=6.5 Hz), 2.5—2.7 (5H, m), 5.11 (2H, s), 6.97 (2H, d, J=8.5 Hz), 7.10 (2H, d, J=8.5 Hz), 7.2—7.5 (3H, m), 7.6—8.0 (2H, m). *Anal.* Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.98; H, 6.23; N, 7.89.

6-[4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)phenyl]hexanenitrile (20a) A stirred suspension of (4-cyanobutyl)triphenylphosphonium bromide (3.26 g, 7.68 mmol) in DMF (30 ml) was treated with sodium hydride (60% in oil, 310 mg, 7.75 mmol) for 1 h. 4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)benzaldehyde (1.50 g, 5.11 mmol) was added to the mixture, and the resultant was stirred at 70—80 °C for 5 h. The reaction mixture was poured into water, neutralized with 2 N HCl, and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo.* The residue was purified by column chromatography on SiO_2 (30 g) with AcOEt–hexane (1 : 4, v/v) to give an oil. The oil was dissolved in THF (40 ml) and hydrogenated on 5% Pd–C (50% wet, 300 mg) at 1 atm. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 (40 g) with AcOEt–hexane (1 : 4, v/v) to give the title compoumd (**20a**, 1.25 g, 68%). mp 76—77 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.8 (6H, m), 2.33 (2H, t, J=7 Hz), 2.44 (3H, s), 2.58 (2H, t, J=7.5 Hz), 4.98 (2H, s), 6.95 (2H, d, J=8.5 Hz), 7.10 (2H, d, J=8.5 Hz), 7.4—7.5 (3H, m), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.61; H, 6.70; N, 7.70.

General Procedure for 5-Amino-2-(oxazolylalkoxy)pyridines (21). 5-Amino-2-(5-methyl-2-phenyl-4-oxazolylmetoxy)pyridine (21a) An ice-cooled solution of 5-methyl-2-phenyl-4-oxazolemethanol (8.00 g, 42.3 mmol) and 2-chloro-5-nitropyridine (7.04 g, 44.4 mmol) in DMF (150 ml) was treated with sodium hydride (60% in oil, 1.78 g, 44.5 mmol) for 3 h, poured into ice-water, neutralized with 2 N HCl to give 2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-nitropyridine (11.0 g, 84%). mp 142—143 °C (CH_2Cl_2–isoPr$_2$O). *Anal.* Calcd for $C_{16}H_{13}N_3O_4$: C, 68.31; H, 5.37; N, 14.94. Found: C, 67.98; H, 5.35; N, 15.10.

A mixture of 2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-nitropyridine (6.00 g, 19.3 mmol), 5% Pd–C (50% wet, 4.00 g), THF (80 ml), and EtOH (80 ml) was hydrogenated at 1 atm. After removal of the catalyst by filtration and the filtrate was concentrated *in vacuo* to give the title compound (**21a**, 4.83 g, 81%). mp 106—107 °C (MeOH–isoPr$_2$O). ^{1}H-NMR ($CDCl_3$) δ: 2.46

(3H, s), 3.39 (2H, br s), 5.21 (2H, s), 6.68 (1H, d, J=9 Hz), 7.04 (1H, dd, J=9, 3 Hz), 7.35—7.5 (3H, m), 7.67 (1H, d, J=3 Hz), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{16}H_{15}N_3O_2$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.39; H, 4.18; N, 13.57.

5-Amino-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (**21b**) was obtained similarly. yield 65% (from 2-(5-methyl-2-phenyl-4-oxazolyl)-ethanol). mp 107—108 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.96 (2H, t, J=7 Hz), 4.47 (2H, t, J=7 Hz), 6.57 (1H, d, J=8.5 Hz), 7.02 (1H, dd, J=8.5, 3 Hz), 7.3—7.5 (3H, m), 7.65 (1H, d, J=3 Hz), 7.9—8.05 (2H, m). *Anal.* Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.01; H, 5.94; N, 13.99.

2-Bromo-3-[6-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-3-pyridyl]propionitrile (22) A solution of sodium nitrite (2.33 g, 33.8 mmol) in water (10 ml) was added dropwise to a stirred and ice-cooled mixture of 5-amino-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (**21b**, 9.00 g, 30.5 mmol), hydrobromic acid (47%, 21.2 g, 123 mmol), and acetone (150 ml) below 5 °C. After stirring for 20 min, acrylonitrile (9.75 g, 184 mmol) was added and the temperature was raised to 27 °C. Powdered copper(I) oxide (200 mg) was added gradually to the vigorously stirred mixture. After a nitrogen gas evolution had ceased, the reaction mixture was concentrated *in vacuo.* The residue was diluted with water, made alkaline with concentrated ammonium hydroxide, and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated to leave an oil which was purified by column chromatography on SiO_2 (250 g) with AcOEt–hexane (1 : 1, v/v) to give the title compound (**22**, 7.38 g, 59%). mp 93—94 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 2.99 (2H, t, J=7 Hz), 3.30 (2H, d, J=7 Hz), 4.36 (1H, t, J=7 Hz), 4.58 (2H, t, J=7 Hz), 6.73 (1H, d, J=9 Hz), 7.35—7.6 (4H, m), 7.9—8.1 (3H, m). *Anal.* Calcd for $C_{20}H_{18}BrN_3O_2$: C, 58.27; H, 4.40; N, 10.19. Found: C, 58.32; H, 4.40; N, 10.13.

3-[6-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]-3-pyridyl]propionitrile (23) A mixture of 2-bromo-3-[6-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-3-pyridyl]propionitrile (**22**, 2.00 g, 4.9 mmol), 5% Pd–C (50% wet, 200 mg), EtOH (50 ml), and 1,4-dioxane (30 ml) was hydrogenated at 1 atm. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 (40 g) with AcOEt–hexane (2 : 3, v/v) to give the title compound (**23**, 1.26 g, 78%). mp 105—106 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.59 (2H, t, J=7 Hz), 2.89 (2H, t, J=7 Hz), 2.99 (2H, t, J=7 Hz), 4.56 (2H, t, J=7 Hz), 6.71 (1H, d, J=8.5 Hz), 7.35—7.5 (4H, m), 7.9—8.05 (3H, m). *Anal.* Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.85; H, 5.78; N, 12.23.

Methyl 2-Bromo-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propionate (24) A solution of sodium nitrite (1.08 g, 15.7 mmol) in water (2 ml) was added dropwise to a stirrred and ice-cooled mixture of 5-amino-2-(5-methyl-2-phenyl-4-oxazolylmethoxy)pyridine (**21a**, 4.00 g, 14.2 mmol), hydrobromic acid (47%, 12.2 g, 70.9 mmol), and acetone (80 ml) below 5 °C. After stirring for 30 min, methyl acrylate (6.12 g, 71.1 mmol) was added and the temperature was raised to 20 °C. Powdered copper(I) oxide (200 mg) was added gradually to the vigorously stirred mixture. After a nitrogen gas evolution had ceased, the reaction mixture was concentrated *in vacuo.* The residue was diluted with water, made alkaline with concentrated ammonium hydroxide, and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated to leave an oil which was purified by column chromatography on SiO_2 (80 g) with AcOEt–hexane (1 : 5, v/v) to give the title compound as a colorless oil (**24**, 2.27 g, 37%). ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s), 3.18 (1H, dd, J=14.5, 7 Hz), 3.39 (1H, dd, J=14.5, 8 Hz), 3.76 (3H, s), 4.34 (1H, dd, J=8, 7 Hz), 5.28 (2H, s), 6.78 (1H, d, J=8.5 Hz), 7.35—7.5 (4H, m), 7.95—8.1 (3H, m).

(*E*)-3-[6-(5-Methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]-2-propen-1-ol (25) A mixture of methyl 2-bromo-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propionate (**24**, 4.00 g, 9.27 mmol), DBU (1.41 g, 9.26 mmol), and toluene (60 ml) was stirred at 90—100 °C for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated to leave an oil which was purified by column chromatography on SiO_2 (60 g) with AcOEt–hexane (1 : 3, v/v) to give methyl (*E*)-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]acrylate (2.71 g, 83%). mp 116—117 °C (Et_2O–$isoPr_2O$). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.81 (3H, s), 5.33 (2H, s), 6.34 (1H, d, J=16 Hz), 6.84 (1H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.65 (1H, d, J=16 Hz), 7.78 (1H, dd, J=8.5, 2.5 Hz), 7.95—8.1 (2H, m), 8.29 (1H, d, J=2.5 Hz). *Anal.* Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.41; H, 5.09; N, 8.06.

DIBAL-H (1.03 M in hexane, 17.3 ml, 17.8 mmol) was added dropwise to a stirred and ice-cooled solution of methyl (*E*)-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]acrylate (2.50 g, 7.14 mmol) in CH_2Cl_2 (100 ml). After stirring for 2 h, the reaction mixture was quenched with methnol (1 ml)–water (2 ml) at 0 °C. The insoluble material was removed by filtration, and then the filtrate was concentrated to leave an oil which was purified by column chromatography on SiO_2 (60 g) with AcOEt–hexane (1 : 1, v/v) to give the title compound (**25**, 1.75 g, 76%). mp 116—117 °C (CH_2Cl_2–$isoPr_2O$). ^{1}H-NMR ($CDCl_3$) δ: 1.65 (1H, br s), 2.48 (3H, s), 4.32 (2H, br t, J=5 Hz), 5.29 (2H, s), 6.26 (1H, dt, J=16, 5.5 Hz), 6.56 (1H, d, J=16 Hz), 6.78 (1H, d, J=8.5 Hz), 7.35—7.5 (3H, m), 7.66 (1H, dd, J=8.5, 2.5 Hz), 7.95—8.1 (2H, m), 8.12 (1H, d, J=2.5 Hz). *Anal.* Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.47; H, 5.59; N, 8.62.

4-[6-(5-Methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]butyronitrile (26) A mixture of (*E*)-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]-2-propen-1-ol (**25**, 2.0 g, 6.20 mmol), 5% Pd–C (50% wet, 500 mg), and EtOH (150 ml) was hydrogenated at 1 atm. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give 3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propan-1-ol (1.65 g, 82%). mp 89—90 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (1H, t, J=5 Hz), 1.75—1.95 (2H, m), 2.47 (3H, s), 2.65 (2H, t, J=7.5 Hz), 3.6—3.75 (2H, m), 5.27 (2H, s), 6.76 (1H, d, J=8.5 Hz), 7.35—7.5 (4H, m), 7.95—8.1 (3H, m). *Anal.* Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.30; H, 6.00; N, 8.43.

Methanesulfonyl chloride (MsCl) (630 mg, 5.50 mmol) was added dropwise to a stirred and ice-cooled solution of 3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propan-1-ol (1.62 g, 4.99 mmol) and triethylamine (560 mg, 5.53 mmol) in CH_2Cl_2 (30 ml). After stirring at room temperature for 16 h, the reaction mixture was washed with water, dried ($MgSO_4$), and concentrated to leave an oil which was purified by column chromatography on SiO_2 (60 g) with AcOEt–$CHCl_3$ (1 : 5, v/v) to give 3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propyl methanesulfonate as a colorless oil (1.78 g, 89%). ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.15 (2H, m), 2.48 (3H, s), 2.70 (2H, t, J=7.5 Hz), 3.01 (3H, s), 4.24 (2H, t, J=6.5 Hz), 5.28 (2H, s), 6.78 (1H, d, J=8.5 Hz), 7.35—7.5 (4H, m), 7.95—8.1 (3H, m).

A mixture of 3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]-propyl methanesulfonate (1.77 g, 4.40 mmol), powdered potassium cyanide (430 mg, 6.60 mmol), and DMF (50 ml) was stirred at 80—85 °C for 3 h, poured into water, and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**26**, 1.40 g, 95%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m), 2.35 (2H, t, J=7 Hz), 2.48 (3H, s), 2.73 (2H, t, J=7.5 Hz), 5.28 (2H, s), 6.80 (1H, d, J=8.5 Hz), 7.35—7.5 (4H, m), 7.95—8.1 (3H, m).

(*E*)-3-[6-(5-Methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]cinnamaldehyde (27) A mixture of (*E*)-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]-2-propen-1-ol (**25**, 2.31 g, 7.17 mmol), manganese dioxide (activated, 4.62 g), and CH_2Cl_2 (100 ml) was stirred at room temperature for 2 h. The insoluble solid was filtered, and the filtrate was concentrated *in vacuo* to give the title compound (**27**, 2.11 g, 92%). mp 147—148 °C (CH_2Cl_2–$isoPr_2O$). ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 5.36 (2H, s), 6.64 (1H, dd, J=16, 7.5 Hz), 6.89 (1H, d, J=9 Hz), 7.35—7.5 (4H, m), 7.82 (1H, dd, J=9, 2.5 Hz), 7.95—8.1 (2H, m), 8.35 (1H, d, J=2.5 Hz), 9.68 (1H, d, J=7.5 Hz). *Anal.* Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.22; H, 5.00; N, 8.73.

5-[6-(5-Methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]valeronitrile (28) An ice-cooled solution of (*E*)-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]cinnamaldehyde (**27**, 2.00 g, 6.24 mmol) and diethyl cyanomethylphosphonate (1.22 g, 6.89 mmol) in DMF (30 ml) was treated with sodium hydride (60% in oil, 275 mg, 6.88 mmol) for 30 min. The reaction mixture was poured onto ice-water and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated to leave an oil which was dissolved in EtOH (50 ml)–THF (50 ml). The solution was hydrogenated on 5% Pd–C (50% wet, 500 mg) at 1 atm. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give the title compound as a colorless oil (**28**, 2.08 g, 96%). ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.85 (4H, m), 2.37 (2H, t, J=6.5 Hz), 2.48 (3H, s), 2.59 (2H, t, J=7 Hz), 5.27 (2H, s), 6.77 (1H, d, J=8.5 Hz), 7.35—7.5 (4H, m), 7.95—8.1 (3H, m).

Acknowledgments We thank S. Imai for the syntheses, and J. Sakamoto and Y. Suwa for the biological assays.

References and Notes

1) *a*) DeFronzo R. A., Bonadonna R. C., Ferrannini E., *Diabetes Care*, **15**, 318—368 (1992); *b*) Martin B. C., Warram J. H., Krolewski A. S., Bergman R. N., Soeldner J. S., Kahn C. R., *Lancet*, **340**, 925—929

(1992); *c*) Wolffenbuttel B. H. R., Van Haeften T. W., *Eur. J. Clin. Invest*., **23**, 69—79 (1993).
2) Ruderman N. B., Schneider S. H., *Diabetes Care*, **15**, 1787—1793 (1992).
3) Gerich J. E., *N. Engl. J. Med*., **321**, 1231—1245 (1989).
4) Reaven G. M., *Am. J. Med*., **74**, 109—112 (1983).
5) Sohda T., Mizuno K., Imamiya E., Sugiyama Y., Fujita T., Kawamatsu Y., *Chem. Pharm. Bull*., **30**, 3580—3600 (1982).
6) Iwatsuka H., Shino A., Suzuoki Z., *Endocrinol. Jpn*., **17**, 23—35 (1970).
7) Ikeda H., Shino A., Matsuo T., Iwatsuka H., Suzuoki Z., *Diabetes*, **30**, 1045—1050 (1981).
8) *a*) Fujita T., Sugiyama Y., Taketomi S., Sohda T., Kawamatsu Y., Iwatsuka H., Suzuoki Z., *Diabetes*, **32**, 804—810 (1983); *b*) Chang A. Y., Wyse B. M. T., Diani A. R., *ibid*., **32**, 830—838 (1983).
9) *a*) Sohda T., Mizuno K., Kawamatsu Y., *Chem. Pharm. Bull*., **32**, 4460—4465 (1984); *b*) Sohda T., Momose Y., Meguro K., Kawamatsu Y., Sugiyama Y., Ikeda H., *Arzneim.-Forsch./Drug Res*., **40**, 37—42 (1990); *c*) Ikeda H., Taketomi S., Sugiyama Y., Shimura Y., Sohda T., Meguro K., Fujita T., *ibid*., **40**, 156—162 (1990); *d*) Sugiyama Y., Taketomi S., Shimura Y., Ikeda H., Fujita T., *ibid*., **40**, 263—267 (1990); *e*) Sugiyama Y., Shimura Y., Ikeda H., *ibid*., **40**, 436—440 (1990); *f*) Momose Y., Meguro K., Ikeda H., Hatanaka C., Oi S., Sohda T., *Chem. Pharm. Bull*., **39**, 1440—1445 (1991).
10) Sohda T., Mizuno K., Momose Y., Ikeda H., Fujita T., Meguro K., *J. Med. Chem*., **35**, 2617—2626 (1992).
11) *a*) Yoshioka T., Fujita T., Kanai T., Aizawa Y., Kurumada T., Hasegawa K., Horikoshi H., *J. Med. Chem*., **32**, 421—428 (1989); *b*) Zask A., Jirkovsky I., Nowicki J. W., McCaleb M. L., *ibid*., **33**, 1418—1423 (1990); *c*) Clark D. A., Goldstein S. W., Volkmann R. A., Eggler J. F., Holland G. F., Hulin B., Stevenson R. W., Kreutter D. K., Gibbs E. M., Krupp M. N., Merrigan P., Kelbaugh P. L., Andrews E. G., Tickner D. L., Suleske R. T., Lamphere C. H., Rajeckas F. J., Kappeler W. H., McDermott R. E., Hutson N. J., Johnson M. R., *ibid*., **34**, 319—325 (1991); *d*) Hulin B., Clark D. A., Goldstein S. W., McDermott R. E., Dambek P. J., Kappeler W. H., Lamphere C. H., Lewis D. M., Rizzi J. P., *ibid*., **35**, 1853—1863 (1992); *e*) Cantello B. C., Cawthorne M. A., Cottam G. P., Duff P. T., Haigh D., Hindley R. M., Lister C. A., Smith S. A., Thurlby P. L., *ibid*., **37**, 3977—3985 (1994); *f*) Iizima I., Ozeki M., Okamura K., Inamasu M., European Patent, 283035 (1988); *g*) Kees K. L., Cheeseman R. S., U. S. Patent, 4728739 (1988).
12) *a*) Kees K. L., Cheeseman R. S., Prozialeck D. H., Steiner K. E., *J. Med. Chem*., **32**, 11—13 (1989); *b*) Dow R. L., Bechle B. M., Chou T. T., Clark D. A., Hulin B., Stevenson R. W., *ibid*., **34**, 1538—1544 (1991); *c*) Ellingboe J. W., Alessi T. R., Dolak T. M., Nguyen T. T., Tomer J. D., Guzzo F., Bagli J. F., McCaleb M. L., *ibid*., **35**, 1176—1183 (1992); *d*) Willson T. M., Brown P. J., Sternbach D. D., Henke B. R., *ibid*., **43**, 527—550 (2000).
13) Kees K. L., Smith T. M., McCaleb M. L., Prozialeck D. H., Cheeseman R. S., Christos T. E., Patt W. C., Steiner K. E., *J. Med. Chem*., **35**, 944—953 (1992).
14) Meguro K., Tawada H., Sugiyama Y., Fujita T., Kawamatsu Y., *Chem. Pharm. Bull*., **34**, 2840—2851 (1986).
15) Willson T. M., Cobb J. E., Cowan D. J., Wiethe R. W., Correa I. D., Prakash S. R., Beck K. D., Moore L. B., Kleiwer S. A., Lehmann J. M., *J. Med. Chem*., **39**, 665—668 (1996).
16) Sakamoto J., Kimura H., Moriyama S., Odaka H., Momose Y., Sugiyama Y., Sawada H., *Biochem. Biophys. Res. Commun*., **278**, 704—711 (2000).