New Potent Prolyl Endopeptidase Inhibitors: Synthesis and Structure-Activity Relationships of Indan and Tetralin Derivatives and Their Analogues

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New compounds were synthesized by structural modification of 1-[1-(4-phenylbutanoyl)-L-prolyl]-pyrrolidine (SUAM-1221, 1) or 1-[1-(benzyloxycarbonyl)-L-prolyl]prolinal (Z-Pro-prolinal, 2) and were tested for *in vitro* inhibitory activities against purified prolyl endopeptidase (PEP) from canine brain. In a series of compounds which lack a formyl or a cyano group, 3-[3-[(*S*)-2-(1,2,3,4-tetrahydronaphthyl)acetyl]-L-thioprolyl]thiazolidine (13) exhibited an approximately 20-fold (IC_{50} = 2.3 nM) increase in potency compared with 1. Compounds having a formyl or a cyano group showed much more potent inhibitory activities than those which lack such a functional group. Among all compounds tested *in vitro*, 1-[1-(2-indanylacetyl)-L-prolyl]prolinal (27), 1-[1-[(*S*)-2-(1,2,3,4-tetrahydronaphthyl)acetyl]-L-prolyl]prolinal (29), 1-[3-[(*S*)-2-(1,2,3,4-tetrahydronaphthyl)-acetyl]-L-thioprolyl]prolinal (30), (*S*)-2-cyano-1-[2-[(*S*)-2-(1,2,3,4-tetrahydronaphthyl)acetyl]-L-prolyl]pyrrolidine (34), and (*S*)-2-cyano-1-[3-[(*S*)-2-(1,2,3,4-tetrahydronaphthyl)acetyl]-L-thioprolyl]pyrrolidine (35) showed an approximately 2-fold ($IC_{50} \simeq 0.5$ nM) increase in potency compared with 2. The structure-activity relationships of these compounds are discussed.

Introduction

Prolyl endopeptidase (PEP) [EC 3.4.21.26] is a serine protease that specifically cleaves peptidyl proline bonds.[1] This enzyme hydrolyzes many biologically active peptides, including thyrotropin-releasing hormone, substance P, angiotensin II, oxytocin, and bradykinin.[2-6] The enzyme also degrades arginine vasopressin which may facilitate learning and memory.[7-9] Yoshimoto et al. reported that the PEP inhibitor 1-[1-(benzyloxycarbonyl)-L-prolyl]prolinal (Z-Pro-prolinal, 2) reversed scopolamine-induced amnesia in the passive avoidance learning test in rats.[10,11] They also found that the antiamnesic effects of such compounds were approximately parallel to their inhibition potencies toward PEP *in vitro*.[10,11] Furthermore, Saito et al. reported that PEP plays an important role in the regulation of learning and memory consolidation in the brain, since in the passive avoidance test using amnesic rats treated with scopolamine, the pyrrolidine derivatives, which had potent inhibitory activities toward PEP, also showed strong antiamnesic effects.[12] These studies suggest that inhibitors of the enzyme are possible candidates for antiamnesic drugs for preventing and/or curing amnesia. These lines of evidence have prompted us to search for novel PEP inhibitors.

It is known that the PEP inhibitors having either a formyl,[3,11-18] a chloroacetyl,[11,19] or a diazoacetyl[20] group exhibit very potent inhibitory activities. The chloroacetyl or diazoacetyl derivatives irreversibly inhibit PEP in response to chemical reactivity of the functional group. Recently the formyl derivative 2 was reported to be a tight-binding reversible inhibitor.[18] It has also been reported that PEP inhibitors without such a functional group have reversible and competitive inhibitory manners.[12,17,21-23] Furthermore, a non-peptide PEP inhibitor, 2-[[8-(dimethylamino)octyl]thio]-6-isopropyl-3-pyridyl-2-thienyl ketone citrate (Y-29794), was also reported by Nakajima et al.[24] Tsuru et al. reported that introduction of a sulfur atom into the proline ring and/or pyrrolidine ring of 1-[1-(4-phenylbutanoyl)-L-prolyl]pyrrolidine (SUAM-1221)[12] (1) resulted in increased inhibitory activity.[17,21] It is also known that the inhibitory activities of prolinal, thioprolinal, or 2-cyanopyrrolidine derivatives with a formyl or a cyano[25] group are greater than those of compounds without the functional group. We have recently reported the synthesis and structure-activity relationships of a series of 4-arylbutanoyl derivatives having potent inhibitory effects against the PEP from canine brain.[26]

In the present paper, the synthesis of a new series of PEP inhibitors with high inhibitory activities was attempted since it was desired to find a PEP inhibitor suitable for clinical use. The compounds, general formula [A], of which the phenylbutanoyl or benzyloxycarbonyl group of 1 or 2[3,11-18] was replaced by 2-indanoyl, 3-(2-indanyl)propanoyl, 4-(2-indanyl)butanoyl, 2-indanylacetyl, (*R*)- and (*S*)-2-tetralinylacetyl, 2-indenylacetyl, 2-benzosubenylacetyl, 2-benzo[*b*]furylacetyl, 2-benzo[*b*]thienylacetyl, or 5-(4,5,6,7-tetrahydrobenzo[*b*]thienyl)acetyl groupings, were synthesized, and their inhibitory activities against PEP were evaluated. We also examined the inhibitory activities of the compounds with a formyl or a cyano group at the 2-position of the pyrrolidine or thiazolidine ring of the indan or the tetralin derivative, and structure-activity relationships of these compounds are discussed. Novel compounds 3-26 and 27-35 were prepared as outlined in Charts 2 and 3, respectively. Their potencies of PEP inhibition are listed in Tables 1 and 2, respectively.

Chemistry

For the synthesis of benzo- or thienocycloalkanylacetic acid derivatives, compound 37 was prepared in moderate yield from the corresponding ketone 36 by heating with glyoxylic acid in the presence of a small amount of sulfuric acid. Catalytic hydrogenation of 37 in the presence of

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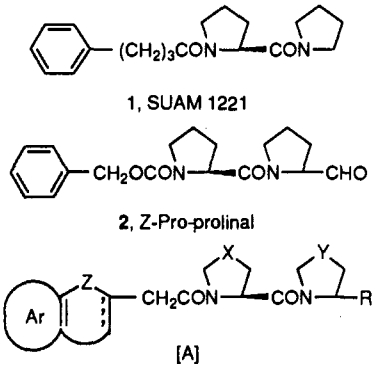
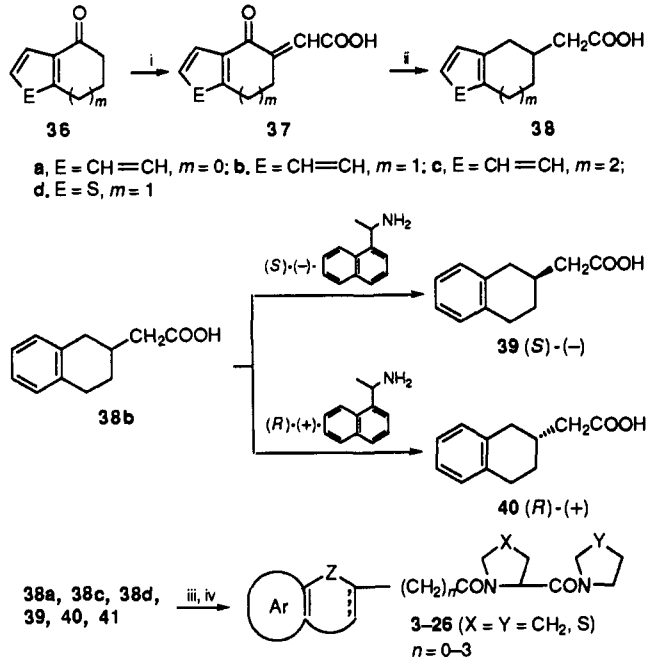
Chart 1



X = Y = CH_2, S; R = H, CHO, CN; Z = CH_2, O, S

Chart 2[a]



41: a, 2-indancarboxylic acid; b, 3-(2-indanyl)propionic acid; c, 4-(2-indanyl)butyric acid; d, 2-indenylacetic acid; e, 2-benzo[*b*]furylacetic acid; f, 2-benzo[*b*]thienylacetic acid

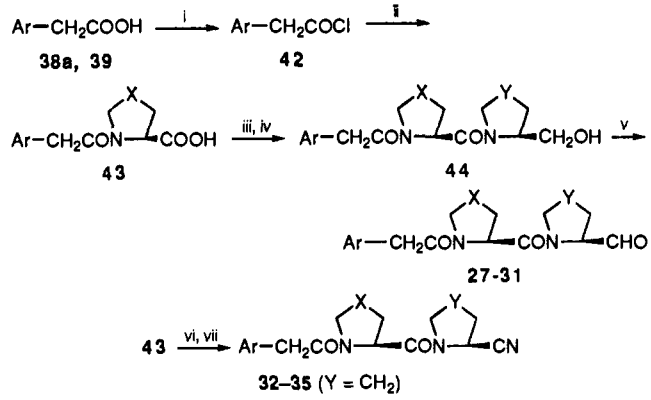
[a] (i) Glyoxylic acid, H_2SO_4, dioxane, 80 °C; (ii) 5% Pd–C, H_2SO_4, dioxane, 60 °C; (iii) pivaloyl chloride CH_2Cl_2, triethylamine; (iv) Pro-pyrrolidine, Pro-thiazolidine, thioPro-pyrrolidine, or thioPro-thiazolidine, triethylamine, CH_2Cl_2.

sulfuric acid under a hydrogen atmosphere gave the benzo- or thienocycloalkanylacetic acid **38** in moderate yield.

In the case of optically active tetralinylacetic acid, treatment of (*RS*)-2-(1,2,3,4-tetrahydronaphthyl)acetic acid **38b** with 0.5 mol of (*S*)-(−)- or (*R*)-(+)-1-(1-naphthyl)-ethylamine in AcOEt produced the corresponding salt. Each salt was then treated with base followed by acidification with HCl to afford optically active **39** or **40**, which was then purified by recrystallization from isopropyl ether. The absolute configuration of **39**, which was resolved with (*S*)-(−)-1-(1-naphthyl)ethylamine, was confirmed by comparing the rotation ($[\alpha]_D$ = −80°) of its methyl ester of 99% ee with the rotation ($[\alpha]_D$ = −32.2°) of the known *S*-configured (*S*)-2-(1,2,3,4-tetrahydronaphthyl)acetic acid methyl ester.[27] Optical rotation of **40** of 99% ee was +79.8°.

Compounds **3–26** were prepared from the corresponding carboxylic acids **38a,c,d** and **39–41** by treatment with pivaloyl chloride in the presence of triethylamine followed by condensation with L-proline or L-thioproline derivatives.[26] The yields and the physical and analytical data for **3–26** are summarized in Table 1.

Chart 3[a]



Ar: a, 2-indanyl; b, (*S*)-2-(1,2,3,4-tetrahydronaphthyl)
X, Y: (1) X = CH_2, (2) X = S, (3) X = Y = CH_2, (4) X = S, Y = CH_2, (5) X = Y = S

[a] (i) $SOCl_2$, CH_2Cl_2; (ii) L-proline or L-thioproline, Na_2CO_3; (iii) pivaloyl chloride or WSC·HCl; (iv) L-prolinol or L-thioprolinol; (v) pyridine–SO_3 complex, triethylamine, DMSO; (vi) pivaloyl chloride, triethylamine, CH_2Cl_2; (vii) (*S*)-2-cyanopyrrolidine.

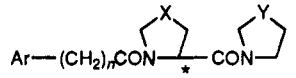
Novel formyl and cyano derivatives **27–31** and **32–35** were also synthesized as outlined in Chart 3. Acetyl chloride derivatives **42**, which were prepared from **38a** or **39** with thionyl chloride, were treated with L-proline or L-thioproline in the presence of sodium carbonate to afford **43**, which was condensed with L-prolinol or L-thioprolinol using pivaloyl chloride and triethylamine to give **44**. The formyl derivatives **27–31** were synthesized by oxidation of **44** with pyridine sulfur trioxide.[28-30] The cyano derivatives **32–35** were prepared from carboxylic acid **43** by treatment with pivaloyl chloride in the presence of triethylamine followed by condensation with (*S*)-2-cyanopyrrolidine.[31] The yields and the physical and analytical data for **27–31** and **32–35** are summarized in Table 2.

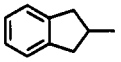
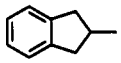
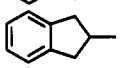
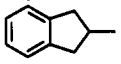
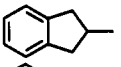
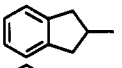
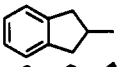
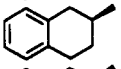
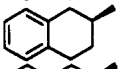
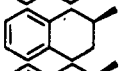
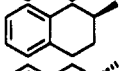
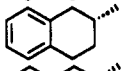
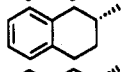
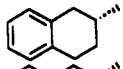
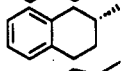
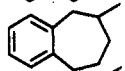
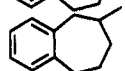
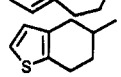
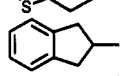
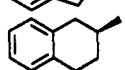
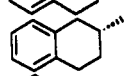
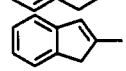
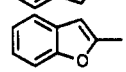
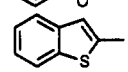
Results and Discussion

In our *in vitro* PEP inhibition assay, **1** showed inhibitory activity with an IC_{50} of 49 nM. Z-Pro-pyrrolidine, which lacks the formyl group of **2**, showed an IC_{50} of 86 nM. However, the potency of Y-29794, which is a non-peptide inhibitor, showed only an IC_{50} of 3.5 μM. To estimate the effect of the number of methylenes (*n*) for indan derivatives of general formula [A] on the inhibitory activity, we examined **3–6**, each having a different number of methylene groups. The 2-indanylacetyl derivative (*n* = 1) had the most potent inhibitory activity. The activity gradually decreased as *n* increased.[26] Compound **3**, which lacks a methylene group, had only about one-fiftieth of the inhibitory activity of **4**. Using this result, it was decided to set *n* = 1 for the synthesis of a series of arylcycloalkane derivatives. It has been reported that in the amino acid moiety, the L-form shows a much greater potency than the D-form, and the introduction of a sulfur atom into the proline and/or pyrrolidine ring increased the inhibitory activity.[21,26] On the basis of these results, the structure–activity relationship of arylcycloalkanyl series [A] was studied.

In a series of compounds containing a 2-indanylacetyl group, the activity increased with increasing number of sulfur atoms. Chiefly, the thioprolylthiazolidine derivative **8** gave the most potent inhibitory activity in this series. This is part of a general trend.[21,26] For example, **10–13**

Table 1. Structures, Physical Properties, and PEP Inhibitory Activities of the Synthesized Compounds 3–26

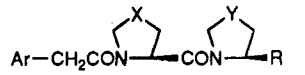


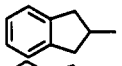
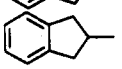
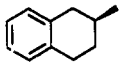
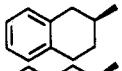
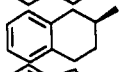
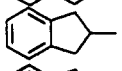
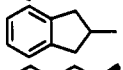
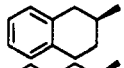
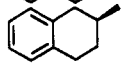
compd no.	Ar	n	X	Y	*	yield[a] (%)	mp (°C) recryst solv[b]	$[\alpha]_D$ (deg) (MeOH)	formula analysis[c]	activity IC_{50} (nM)[d]
3		0	S	CH_2	R	54	165–167 EA	−124.2 (c = 1.00)	$C_{18}H_{22}N_2O_2S$ C, H, N	520
4		1	S	CH_2	R	84	82–83 EA–IP	−108.1 (c = 1.02)	$C_{18}H_{24}N_2O_2S \cdot {}^1/_2H_2O$ C, H, N	10
5		2	S	CH_2	R	75	92–93 EA–IP	−97.0 (c = 1.12)	$C_{20}H_{26}N_2O_2S$ C, H, N	36
6		3	S	CH_2	R	59	99–100 EA–NH	−96.2 (c = 0.99)	$C_{21}H_{28}N_2O_2S$ C, H, N	60
7		1	CH_2	CH_2	S	62	oil[e] –	−30.3 (c = 1.05)	$C_{20}H_{26}N_2O_2$ ND[g]	17
8		1	CH_2	S	S	69	oil[e] –	−23.0 (c = 1.03)	$C_{18}H_{24}N_2O_2S$ ND[g]	8.7
9		1	S	S	R	55	oil[e] –	−78.9 (c = 1.00)	$C_{18}H_{22}N_2O_2S_2$ ND[g]	6.5
10		1	CH_2	CH_2	S	52	104–106 EA	−83.8 (c = 1.00)	$C_{21}H_{28}N_2O_2$ C, H, N	5.4
11		1	S	CH_2	R	59	121–123 EA–NH	−154.1 (c = 0.65)	$C_{20}H_{26}N_2O_2S$ C, H, N	4.0
12		1	CH_2	S	S	63	83–84 EA–NH	−76.8 (c = 1.04)	$C_{20}H_{26}N_2O_2S$ C, H, N	3.4
13		1	S	S	R	38	123–125 EA–IP	−136.6 (c = 0.68)	$C_{19}H_{24}N_2O_2S_2$ C, H, N	2.3
14		1	CH_2	CH_2	S	44	109–110 EA	+16.7 (c = 1.00)	$C_{21}H_{28}N_2O_2$ C, H, N	48
15		1	S	CH_2	R	31	154–156 EA–NH	−52.3 (c = 0.85)	$C_{20}H_{26}N_2O_2S$ C, H, N	38
16		1	CH_2	S	S	30	97–99 EA–IP	−19.5 (c = 0.86)	$C_{20}H_{26}N_2O_2S$ C, H, N	40
17		1	S	S	R	37	152–154 EA–IP	−35.7 (c = 0.23)	$C_{19}H_{24}N_2O_2S_2$ C, H, N	24
18		1	S	CH_2	R	21	130–131 EA	−102.1 (c = 0.76)	$C_{21}H_{28}N_2O_2S$ C, H, N	150
19		1	S	CH_2	R	trace	amorphous[e] –	−114.7 (c = 0.77)	$C_{21}H_{28}N_2O_2S$ ND[g]	250
20		1	S	CH_2	R	83	87.5–130 EA–NH	ND[f]	$C_{18}H_{24}N_2O_2S_2$ C, H, N	18
21		1	CH_2	CH_2	R	73	oil[e] –	+28.7 (c = 1.06)	$C_{20}H_{26}N_2O_2$ ND[g]	80000
22		1	CH_2	CH_2	R	51	109–110 EA	−16.8 (c = 1.04)	$C_{21}H_{28}N_2O_2$ C, H, N	94000
23		1	CH_2	CH_2	R	56	104–105 EA	+86.3 (c = 1.00)	$C_{21}H_{28}N_2O_2$ C, H, N	91000
24		1	CH_2	CH_2	S	62	amorphous[e] –	−30.2 (c = 1.03)	$C_{20}H_{24}N_2O_2$ ND[g]	69
25		1	CH_2	CH_2	S	50	oil[e] –	−45.3 (c = 1.12)	$C_{19}H_{22}N_2O_3$ ND[g]	510
26		1	S	CH_2	R	66	162–163 EA–IP	−114.7 (c = 1.11)	$C_{18}H_{20}N_2O_2S_2$ C, H, N	130
1 (SUAM-1221)[h]										49
Y-29794[i]										3500
Z-Pro-pyrrolidine[j]										86

[a] No attempt was made to optimize yield. [b] EA, ethyl acetate, IP, isopropyl ether; NH, *n*-hexane. [c] All new crystalline compounds had C, H, and N microanalysis within ±0.4% theoretical value. [d] The IC_{50} values are effective concentration of compounds required to achieve 50% inhibition against PEP from canine brain. [e] Purified by column chromatography on silica gel. [f] Diasteroemer mixture. [g] Not determined, but were obtained satisfactory results by high resolution MS and TLC (silica gel) analysis. [h] 1-[1-(4-Phenylbutanoyl)-L-prolyl]pyrrolidine, see refs 12 and 22. [i] 2-[[8-(Dimethylamino)octyl]thio]-6-isopropyl-3-pyridyl-2-thienyl ketone citrate, see ref 25. [j] See ref 11.

and 14–17 each showed the same activity pattern as 4 and 7–9. Interestingly, 10–13, having the *S*-configuration at the 2-position of the tetralin ring, gave an 8–11-fold increase in potency over 14–17 having the *R*-configuration. This is probably the result of favorable steric interactions with the enzyme. Compounds 18 and 19 each had a

Table 2. Structures, Physical Properties, and PEP Inhibitory Activities of the Synthesized Compounds 27–35



compd no.	Ar	X	Y	R	yield,[a] (%)	mp (°C) recryst solv[b]	[α]D (deg) ($CHCl_3$)	formula analysis[c]	activity IC_{50} (nM)[d]
27		CH_2	CH_2	CHO	38	amorphous[e] –	−93.6 (c = 1.03)	$C_{21}H_{26}N_2O_3$ ND[f]	0.42
28		S	CH_2	CHO	51	amorphous[e] –	−162.0 (c = 1.02)	$C_{20}H_{24}N_2O_3S$ ND[f]	1.0
29		CH_2	CH_2	CHO	48	amorphous[e] –	−106.3 (c = 1.00)	$C_{22}H_{28}N_2O_3$ ND[f]	0.45
30		S	CH_2	CHO	50	117–118 EA–IP	−202.4 (c = 1.00)	$C_{21}H_{26}N_2O_3S$ C, H, N	0.46
31		S	S	CHO	38	195–196.5 EA–NH	−149.5 (c = 1.02)	$C_{20}H_{24}N_2O_3S_2$ C, H, N	0.85
32		CH_2	CH_2	CN	53	oil[e] –	−101.1 (c = 1.05)	$C_{21}H_{25}N_3O_2$ ND[f]	1.2
33		S	CH_2	CN	30	89.7–99.5 EA–ether	−183.7 (c = 1.00)	$C_{20}H_{23}N_3O_2S$ C, H, N	1.1
34		CH_2	CH_2	CN	35	100.5–101.5 EA–IP	−153.6 (c = 1.00)	$C_{22}H_{27}N_3O_2$ C, H, N	0.52
35		S	CH_2	CN	44	128.5–129.5 EA–IP	−228.0 (c = 1.01)	$C_{21}H_{25}N_3O_2S$ C, H, N	0.55
2	(Z-Pro-prolinal)[g]								1.1

[a–e] Same as in Table 1. [f] Not determined, but were obtained satisfactory results by high resolution MS and TLC (silica gel) analysis. [g] See ref 16.

decrease in potency. The racemic thieno[*b*]cyclohexanylacetyl derivative **20**, which corresponds to **5** or **11**, showed moderate potency. On the other hand, all of **21–23** having D-proline in the amino acid moiety showed a remarkable decrease in potency.[21] Arylacetyl derivatives **24–26** also had decreased potency.

In a series of formyl derivatives, **27–31** gave an approximately 4–40-fold increase in potency over **7**, **4**, **10**, and **11**. The inhibitory potency of known compound **2**, Z-Pro-prolinal, gave an IC_{50} of 1.1 nM. In a series of cyano derivatives, **32–35** also showed an approximately 7–14-fold increase in potency over **7**, **4**, **10**, and **11**. The (*S*)-tetralin derivatives, **34** and **35**, showed approximately a 2-fold increase in potency over the indan derivatives **32** and **33**, and the potency showed almost the same level as the formyl derivatives **27**, **29**, and **30**.

In summary, a series of (*S*)-2-(1,2,3,4-tetrahydronaphthyl)acetyl derivatives **10–13** showed the most potent inhibitory activities among the compounds which lack a formyl or a cyano group. The formyl derivatives and cyano derivatives showed more powerful inhibitory activities than the former series. The five compounds, **27**, **29**, **30**, **34**, and **35**, were the most active among all compounds tested *in vitro*. Further investigations of the compounds having such potent inhibitory effects are currently in progress, and the results will be published in forthcoming papers.

Experimental Section

Melting points were determined on Yamato melting point apparatus or a Büchi 535 digital melting point apparatus and are uncorrected. IR spectra were measured with a JASCO A102 or a Shimadzu DR-8000 spectrophotometer. ^{1}H-NMR spectra were taken on a JEOL JNM RMX60 or a GSX270 spectrometer with tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL JMS DX300 or a DX302 instrument. Optical rotations were recorded with a JASCO DIP370 digital polarimeter in methanol or $CHCl_3$.

Synthesis of 37: General Procedure. A solution of 40% glyoxylic acid (38 g, ca. 0.21 mol), **36** (20 g, 0.137 mol), and 80% sulfuric acid (5 mL) in dioxane (200 mL) was refluxed for 1 h. After cooling, precipitated solid was filtered and washed with isopropyl ether (IPE). The resulting crystals were allowed to air-dry at room temperature.

1-Oxoindan-Δ$^{2,\alpha}$-acetic acid (37a): 23.2 g (90% yield); mp 205–206 °C dec (EtOH–H_2O); IR (KBr) 3300–2800, 1715, 1670, 1635, 1595, 1400 cm^{-1}; NMR (DMSO-d_6) δ 4.14 (2H, d, *J* = 2 Hz), 6.82 (1H, t, *J* = 2 Hz), 7.42 (1H, t, *J* = 8 Hz), 7.53 (1H, d, *J* = 7 Hz), 7.64 (1H, t, *J* = 8 Hz), 7.87 (1H, d, *J* = 7 Hz). Anal. ($C_{11}H_8O_3$) C, H.

1-Oxo-1,2,3,4-tetrahydronaphthalene-Δ$^{2,\alpha}$-acetic acid (37b): 21.3 g (77% yield); mp 186–188 °C (EtOH–H_2O); IR (KBr) 3100–2800, 1690, 1670, 1630, 1590 cm^{-1}; NMR (DMSO-d_6) δ 2.98–3.03 (2H, m) 3.29–3.34 (2H, m), 6.67 (1H, br s), 7.38–7.44 (2H, m), 7.58–7.64 (1H, m) 7.95 (1H, d, *J* = 8 Hz). Anal. ($C_{12}H_{10}O_3$) C, H.

5-Oxobenzocycloheptane-Δ$^{6,\alpha}$-acetic acid (37c): 13.0 g (44% yield); mp 225 °C dec (AcOEt); NMR ($CDCl_3$) δ 1.89–1.99 (2H, m), 2.68–2.80 (4H, m), 6.57 (1H, s), 7.32 (1H, d, *J* = 7.2 Hz), 7.41 (1H, dt, *J* = 1.1 and 7.3 Hz), 7.57 (1H, dt, *J* = 1.5 and 7.3 Hz), 7.68 (1H, dd, *J* = 1.5 and 7.3 Hz). Anal. ($C_{13}H_{12}O_3$) C, H.

4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-Δ$^{5,\alpha}$-acetic acid (37d): 17.1 g (60% yield); mp 162–164 °C (AcOEt); IR (KBr) 3100–2800, 1696, 1614, 1521 cm^{-1}; NMR ($CDCl_3$) δ 1.74 (2H, t, *J* = 6.2 Hz), 3.55 (2H, dd, *J* = 1.6 and 6.2 Hz), 6.90 (1H, t, *J* = 1.6 Hz), 7.14 (1H, d, *J* = 5.2 Hz), 7.48 (1H, d, *J* = 5.2 Hz). Anal. ($C_{10}H_8O_3S$) C, H.

Synthesis of 38: General Procedure. A stirred solution of **37** (15 g, 74.3 mmol) in dioxane (150 mL) was reduced in the presence of 98% of sulfuric acid (2.4 mL) and 10% Pd on carbon (1 g) over 3.5 kg/cm^3 of hydrogen atmosphere at 40–50 °C for 5 h. After the mixture was allowed to cool, the catalyst was filtered off, and the filtrate was evaporated *in vacuo*. CH_2Cl_2 (300 mL) was added to the resulting residue and extracted with 10% NaOH (100 mL × 2). The aqueous layer was acidified with concentrated HCl and extracted with CH_2Cl_2. The organic layer was then dried over $MgSO_4$ and evaporated *in vacuo*. The resulting residue was crystallized from the appropriate solvent.

2-Indanylacetic acic (38a):[31] 11.4 g (87% yield); mp 88–90 °C (EtOH–H_2O); bp 142–144 °C (0.8 mmHg); IR (KBr) 3200–2750, 1707, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (2H, d, *J* = 7 Hz), 2.67 (2H, dd, *J* = 7 and 15 Hz), 2.84 (1H, m), 3.17 (2H, dd, *J* = 7 and 15 Hz), 7.12–7.22 (4H, m). Anal. ($C_{11}H_{12}O_2$) C, H.

(RS)-2-(1,2,3,4-Tetrahydronaphthyl)acetic acid (38b): 10.1 g (72% yield); mp 85–87 °C (EtOH–H_2O); IR (KBr) 3200–2700, 1705, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.44–1.58 (1H, m), 1.96–2.06 (1H, m), 2.21–2.37 (1H, m), 2.52 (1H, dd, J = 9 and 16 Hz), 2.82–2.98 (3H, m). Anal. ($C_{12}H_{14}O_2$) C, H.

2-Subenylacetic acid (38c): 11.9 g (78% yield); mp 91–92.5 °C (AcOEt–IPE); IR (KBr) 3200–2700, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.45–1.72 (2H, m), 1.75–1.87 (1H, m), 1.93–2.05 (1H, m), 2.05–2.24 (1H, m), 2.27 (1H, dd, J = 15.2 and 25 Hz), 2.30 (1H, dd, J = 15.2 and 26 Hz), 2.75–2.85 (4H, m), 7.05–7.12 (4H, m). Anal. ($C_{13}H_{16}O_2$) C, H.

4,5,6,7-Tetrahydro-5-benzo[b]thienylacetic acid (38d): 7.9 g (33% yield); mp 77–83.5 °C (EtOH–H_2O); bp 170 °C (0.2 mmHg); IR (KBr) 3200–2710, 1715 cm^{-1}. Anal. ($C_{10}H_{12}O_2S$) C, H.

Optical Resolution of 38b. (S)-2-(1,2,3,4-Tetrahydronaphthyl)acetic Acid (39) and (R)-2-(1,2,3,4-Tetrahydronaphthyl)acetic Acid (40). (S)-(−)-1-(1-Naphthyl)ethylamine (8.6 g, 50 mmol) was added to a solution of (RS)-2-(1,2,3,4-tetrahydronaphthyl)acetic acid (**38b**; 19.0 g, 100 mmol) in AcOEt (200 mL). The solution was allowed to stand at room temperature overnight. Precipitated crystals were collected by filtration and recrystallized twice from AcOEt to give the salt (S)-(−)-1-(1-naphthyl)ethylamine (S)-2-(1,2,3,4-tetrahydronaphthyl)acetic acid: 12.5 g (34.6% yield); mp 153–155 °C; $[\alpha]^{28}_D$ = −50.7° (c = 1.00, MeOH). This salt (1.31 g, 3.63 mmol) was dissolved in a solution of 1 N NaOH (10 mL) and stirred at room temperature for 10 min. The solution was extracted with CH_2Cl_2 to recover (S)-(−)-1-(1-naphthyl)ethylamine (0.47 g; 76% yield). The aqueous layer was acidified with 1 N HCl, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residual solid was recrystallized twice from IPE to give **39**: 0.61 g (89% yield); mp 118–119 °C; $[\alpha]^{22}_D$ −80.1° (c = 1.00, MeOH); 98.9% ee (HPLC conditions: detection, 210 nm; column, ULTRON ES-OVM (4.6 × 150 mm); mobile phase, 20 mM KH_2PO_4/AcCN (8:1); flow rate, 0.5 mL/min; column temperature, 26 °C; retention time, 13.7 min); IR (KBr) 1771, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.44–1.59 (1H, m), 1.95–2.05 (1H, m), 2.20–2.38 (1H, m), 2.42 (2.2H, m), 2.44 (0.8H, m), 2.53 (1H, dd, J = 16.2 and 10.2 Hz), 2.85 (1H, dd, J = 4.7 and 8.0 Hz), 2.94 (1H, dd, J = 4.7 and 16.2 Hz), 7.04–7.12 (4H, m, J = 18.5–12.0 Hz). Anal. ($C_{12}H_{14}O_2$) C, H. Compound **40** was obtained from the filtrate of (S)-(−)-1-(1-naphthyl)ethylamine (S)-2-(1,2,3,4-tetrahydronaphthyl)acetic acid using (R)-(+)-1-(1-naphthyl)ethylamine (8.6 g, 50 mmol) through in the the same manner as described above. (R)-(+)-1-(1-Naphthyl)ethylamine (R)-2-(1,2,3,4-tetrahydronaphthyl)-acetic acid: 12.6 g (35% yield); mp 152–154 °C (AcOEt); $[\alpha]^{24}_D$ = +48.2° (c = 1.00, MeOH). The salt (1.5 g) obtained was treated with NaOH and HCl as described above to afford **40**: 0.67 g (85% yield); mp 118–119 °C (IPE); $[\alpha]^{28}_D$ = +79.8° (c = 0.96, MeOH); 99.1% ee. (The HPLC condition was the same as the case of **39**; retention time, 17.1 min.) The NMR spectra showed the same signal patterns as that of **39**. Anal. ($C_{12}H_{14}O_2$) C, H.

Synthesis of 41. 2-Indancarboxylic acid (**41a**),[32] 2-indenylacetic acid (**41d**),[32] 2-benzo[b]furanylacetic acid (**41e**),[33] and 2-benzo[b]thienylacetic acid (**41f**)[34] were synthesized according to the literature procedures.

3-(2-Indanyl)propionic Acid (41b). (1) Ethyl 2-Indanylacetate. HCl gas was introduced to a stirred solution of **38a** (17.6 g, 0.1 mol) in EtOH (100 mL) under ice-cooling. The solution was stirred at room temperature for 1 h and heated under reflux for 30 min. After cooling, the solvent was evaporated *in vacuo*. The resulting residue was dissolved in ether and successively washed with water and saturated aqueous $NaHCO_3$. The ether layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give ethyl 2-indanylacetate: oil; 17 g (83.3% yield); bp 114–116 °C (0.2 mmHg); IR (neat) 2940, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.72 (3H, t, J = 7.3 Hz), 2.48 (2H, d, J = 7 Hz), 2.63 (2H, dd, J = 6.5 and 15.2 Hz), 2.76–2.95 (1H, m), 3.10–3.12 (2H, m), 4.15 (2H, q, J = 7.3 and 15.2 Hz), 7.10–7.18 (4H, m).

(2) 2-(2-Indanyl)ethanol. A solution of ethyl 2-indanylacetate (1.2 g, 5.88 mmol) in dry Et_2O (5 mL) was added dropwise to stirred suspension of $LiAlH_4$ (0.38 g, 10 mmol) in dry Et_2O (20 mL). The mixture was stirred for 1 h at room temperature, and the excess $LiAlH_4$ was decomposed by addition of a small amount of ice. The ether layer was removed by decantation, and the resulting residue was extracted twice with ether. The extracts were combined, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The resulting oil was purified by column chromatography (silica gel) using $CHCl_3$–MeOH (9:1) as an eluent to give 2-(2-indanyl)ethanol: oil; 0.7 g (86.4% yield); IR (neat) 3330, 2920, 1480, 1055, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (1H, s), 1.76–1.84 (2H, m), 2.54–2.68 (3H, m), 3.30–3.11 (2H, m), 3.75 (2H, t, J = 6 Hz), 7.10–7.20 (4H, m).

(3) 1-Bromo-2-(2-indanyl)ethane. Concentrated H_2SO_4 (5.4 g) was added to a solution of 2-(2-indanyl)ethanol (8.1 g, 0.05 mol) in 48% HBr (50 mL). The solution was heated under reflux for 4 h over an argon atmosphere. After cooling, ice–water (30 mL) was added to the solution, and the precipitated solid was collected by filtration. The solid was crystallized from EtOH–H_2O to give 1-bromo-2-(2-indanyl)ethane: 8.5 g (74% yield); mp 35–37 °C; MS (EI) m/e 226 (M^+), 117 (base peak); IR (KBr) 3100–2800, 1490–1430, 1225, 1205, 745; NMR ($CDCl_3$) δ 2.02–2.10 (2H, m), 2.55–2.71 (3H, m), 3.05–3.16 (2H, m), 3.46 (2H, m, J = 7 Hz), 7.10–7.20 (4H, m).

(4) 41b. To magnesium (0.27 g, 1.1 mmol) in dry Et_2O (5 mL) was added a catalytic amount of iodine, and the mixture was stirred at room temperature until the color of iodine disappeared. A solution of 1-bromo-2-(2-indanyl)ethane (2.25 g, 10 mmol) in dry Et_2O (45 mL) was added dropwise to the magnesium solution over 20-min period. The Grignard was then stirred at room temperature for 30 min. Carbon dioxide gas was continuously introduced to the solution at −5 °C. After 20 min, the reaction mixture was allowed to warm to room temperature, 25% H_2SO_4 (40 mL) was added to the solution, and the Et_2O layer was separated. The aqueous layer was extracted with Et_2O. The extracts were combined and extracted again with 2 N NaOH. The aqueous layer was acidified with 1 N HCl, and precipitated crystals were collected by filtration to give **41b**: 1.0 g (53% yield); mp 120–121 °C (IPE); IR (KBr) 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.87 (2H, q, J = 7 Hz), 2.45 (2H, t, J = 7 Hz), 2.48–2.65 (3H, m), 3.07 (2H, dd, J = 7 and 14 Hz), 7.10–7.20 (4H, m). Anal. ($C_{12}H_{14}O_2$) C, H.

Synthesis of 4-(2-Indanyl)butyric Acid (41c). Diethyl malonate (3.20 g, 20 mmol) was added to a solution of sodium ethoxide (0.23 g, 10 mmol, as metallic Na). 1-Bromo-2-(2-indanyl)ethane (2.25 g, 10 mmol) was added to the solution, and the reaction mixture was refluxed for 1 h. After cooling, the solution was evaporated *in vacuo*. Water was added to the resulting residue and extracted with Et_2O. The ether was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oil, which was used to the next reaction step without purification. A solution of KOH (3.2 g) in water (3.5 mL) was added to a solution of the oil in MeOH (20 mL). The mixture was heated under reflux for 1 h, and the solvent was evaporated *in vacuo*. Water was added to the resulting residue, and this was extracted with ether. The aqueous layer was acidified with 10% HCl and extracted with AcOEt. The AcOEt solution was evaporated *in vacuo*. The resulting solid was heated at 180 °C for 1 h. After cooling, saturated $NaHCO_3$ (10 mL) was added to it. After the aqueous layer was extracted with Et_2O, it was acidified with 1 N HCl. Crystals were collected by filtration to give **41c**: 58% yield; mp 73.8–74.6 °C (*n*-hexane); MS m/z 204 (M^+), IR (KBr) 3200–2800, 1710, 1210, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.51–1.59 (2H, m), 1.66–1.79 (2H, m), 2.39 (2H, t, J = 7 Hz), 2.36–2.52 (1H, m), 2.58 (2H, dd, J = 8 and 15 Hz), 7.07–7.19 (4H, m), 10.98 (1H, br). Anal. ($C_{13}H_{16}O$) C, H.

Synthesis of 3–26: General Procedure. To a stirred solution of the corresponding carboxylic acid (20 mmol) and triethylamine (22 mmol) in chloroform (40 mL) was added dropwise pivaloyl chloride (20 mmol) during a 10-min period under ice-cooling. After the mixture was stirred for 1 h, a solution of prolyl- or thioprolylpyrrolidine or -thiazolidine[26] (iv in Chart 2) (20 mmol) and triethylamine (20 mmol) in chloroform (10 mL) was added dropwise. The mixture was stirred for 3 h at room temperature and was successively washed with 10% HCl, water, saturated aqueous Na_2CO_3, and brine. The chloroform layer was dried and evaporated *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (20:1) as an eluent to give **3–26**. The physical and analytical data of **3–26** are listed in Table 1.

1-[3-(2-Indanylcarbonyl)-L-thioprolyl]pyrrolidine (3): IR (KBr) 1642 cm^{-1}; NMR ($CDCl_3$) δ 1.78–2.04 (4H, m), 3.13–3.60

(10H, m), 3.79–3.88 (1H, m), 4.82 (2H, s), 5.10–5.16 (1H, t, J = 7 Hz), 7.09–7.21 (4H, m).

1-[3-(2-Indanylacethyl)-L-thioprolyl]pyrrolidine (4): IR (KBr) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.79–2.09 (4H, m), 2.54–2.70 (4H, m), 2.90–3.03 (1H, m), 3.09–3.30 (4H, m), 3.38–3.47 (1H, m), 3.80–3.89 (1H, m), 4.61 (1H, d, J = 9 Hz), 4.67 (2H, d, J = 9 Hz), 5.08 (1H, t, J = 7 Hz), 7.10–7.20 (4H, m).

1-[3-[3-(2-Indanyl)propanoyl]-L-thioprolyl]pyrrolidine (5): IR (neat) 1660, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.84–2.04 (6H, m), 2.44–2.65 (5H, m), 3.02–3.61 (7H, m), 3.82–3.91 (1H, m), 4.67–4.75 (2H, m), 5.06 (1H, t, J = 7 Hz), 7.09–7.19 (4H, m).

1-[3-[4-(2-Indanyl)butanoyl]-L-thioprolyl]pyrrolidine (6): IR (KBr) 1660, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.53–1.60 (2H, m), 1.67–2.05 (6H, m), 2.39–2.52 (3H, m), 2.53–2.54 (2H, m), 3.04 (2H, dd, J = 7.5 and 15.4 Hz), 3.16 (1H, dd, J = 6.6 and 11.4 Hz), 3.28 (1H, dd, J = 7.3 and 11.4 Hz), 3.35–3.63 (2H, m), 3.80–3.92 (1H, m), 4.66 (1H, d, J = 8.8 Hz), 4.71 (1H, d, J = 8.8 Hz), 5.07 (1H, t, J = 7.3 Hz), 7.09–7.19 (4H, m).

1-[1-(2-Indanylacetyl)-L-prolyl]pyrrolidine (7): IR (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.79–2.30 (8H, m), 2.38–2.72 (4H, m), 2.90–3.04 (1H, m), 3.02–3.13 (2H, m), 3.34–3.74 (5H, m), 3.80–3.87 (1H, m), 4.62–4.72 (1H, m), 7.11–7.20 (4H, m); HRMS 326.1996, calcd for $(C_{20}H_{26}N_2O_2)$ 326.1994; TLC R_f (silica gel, 1:9 MeOH/$CHCl_3$) 0.71.

3-[1-(2-Indanylacetyl)-L-prolyl]thiazolidine (8): IR (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.85–2.05 (2H, m), 2.05–2.34 (2H, m), 2.35–2.73 (4H, m), 2.88–3.26 (5H, m), 3.40–3.58 (1H, m), 3.60–4.00 (3.5H, m), 4.50–4.24 (0.5H, m), 4.50–4.90 (2H, m), 7.24–7.80 (4H, m); HRMS 344.1583, calcd for $(C_{19}H_{24}N_2O_2S)$ 344.1559; TLC R_f (silica gel, 1:19 MeOH/$CHCl_3$) 0.68.

3-[3-(2-Indanylacetyl)-L-thioprolyl]thiazolidine (9): IR (KBr) 1640 cm^{-1}; NMR ($CDCl_3$) δ 2.40–2.73 (4H, m), 2.80–3.38 (7H, m), 3.65–4.00 (1H, m), 4.20 (0.5H, br), 4.40–4.72 (4H, m), 4.90 (0.5H, br), 5.03–5.20 (1H, m), 7.10–7.28 (4H, m); HRMS 362.1106, calcd for $(C_{19}H_{22}N_2O_2S)$ 362.1123; TLC R_f (silica gel, 1:19 MeOH/$CHCl_3$) 0.52.

1-[1-[(*S*)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-prolyl]pyrrolidine (10): IR (KBr) 1645, 1632 cm^{-1}; NMR ($CDCl_3$) δ 1.38–1.52 (1H, m), 1.71–1.25 (13H, m), 2.77–2.87 (2H, m), 2.94 (1H, br, d, J = 13.5 Hz), 3.34–3.46 (2H, m), 3.49–3.63 (2H, m), 3.66–3.74 (1H, m), 3.84 (1H, dt, J = 6.9 and 10.2 Hz), 4.68 (1H, dd, J = 3.5 and 8.5 Hz), 7.07 (4H, s).

1-[3-[(*S*)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-thioprolyl]pyrrolidine (11): IR (KBr) 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.41–1.59 (1H, m), 1.80–2.10 (5H, m), 2.31–2.57 (4H, m), 2.80–2.88 (1H, m), 2.96 (1H, dd, J = 3 and 15.5 Hz), 3.15 (1H, dd, J = 6.5 and 11 Hz), 3.30 (1H, dd, J = 7.3 and 11 Hz), 3.37–3.49 (2H, m), 3.52–3.64 (1H, m), 3.32–3.91 (1H, m), 4.66 (1H, d, J = 8.5 Hz), 4.72 (1H, d, J = 8.5 Hz), 5.12 (1H, t, J = 6.6 Hz), 7.00–7.13 (4H, m).

3-[1-[(*S*)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-prolyl]thiazolidine (12): IR (KBr) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.38–1.55 (1H, m), 1.80–2.58 (9H, m), 2.68–2.75 (2H, m), 2.69–3.23 (3H, m), 3.47–3.60 (1H, m), 3.63–3.98 (2.5H, m), 4.21–4.24 (0.5H, m), 4.48–4.62 (1.5H, m), 4.65–4.77 (1H, br), 4.85 (0.5H, m), 7.04–7.07 (4H, m).

3-[3-[(*S*)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-thioprolyl]thiazolidine (13): IR (KBr) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.45–1.56 (1H, m), 1.99–2.04 (1H, m), 2.30–2.56 (4H, m), 2.81–3.20 (7H, m), 3.31 (1H, dd, J = 7.5 and 11.5 Hz), 3.67–3.98 (1.5H, m), 4.16–4.25 (0.5H, m), 4.50–4.92 (2H, m), 5.07–5.21 (1H, br), 7.00–7.14 (4H, m).

1-[3-((*R* or *S*)-2-Benzosubenylacetyl)-L-thioprolyl]pyrrolidine (18 and 19). The residue obtained was crystallized from Et_2O and recrystallized three times from AcOEt–Et_2O to give 18. From the first filtrate, 19 was obtained. Each compound showed a single isomer by HPLC analysis (HPLC conditions: detection, 230 nm; column, ODS (4.6 × 150 mm); mobile phase, MeOH/H_2O (15:7); flow rate, 0.8 mL/min; column temperature, 26 °C; retention time, 18 18.2 min, 19 20.0 min). **18**: optical purity 99.8% ee; IR (KBr) 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.10 (8H, m), 2.14–2.37 (3H, m), 2.70–2.88 (4H, m), 3.14 (1H, dd, J = 6.6 and 11.4 Hz), 3.26 (1H, dd, J = 7.3 and 11.4 Hz), 3.37–3.49 (2H, m), 3.52–3.65 (1H, m), 3.82–3.90 (1H, m), 4.55 (1H, d, J = 8.8 Hz), 4.60 (1H, d, J = 8.8 Hz), 4.06 (1H, t, J = 7.3 Hz), 7.01–7.06 (4H, m). **19**: optical purity >94% ee; IR (KBr) 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.57–2.08 (8H, m), 2.15–2.35 (3H, m), 2.70–2.85 (4H, m), 3.13 (1H, m, dd, J = 6.3 and 11.5 Hz), 3.28 (1H, dd, J = 6.3 and 11.5 Hz), 3.36–3.48 (2H, m), 3.50–3.62 (1H, m), 3.82–3.93 (1H, m), 4.43 (1H, d, J = 8.4 Hz), 4.60 (1H, d, J = 8.4 Hz), 5.10 (1H, t, J = 7 Hz), 7.08 (4H, s); HRMS 372.1821, calcd for $(C_{21}H_{26}N_2O_2S)$ 372.1872.

Synthesis of 27–31 and 32–35. (1) Synthesis of 42: General Procedure. A stirred solution of $SOCl_2$ (0.2 mol) in dry toluene (50 mL) was added dropwise to a solution of **38a** or **39** (0.1 mol) in dry toluene (150 mL) at room temperature. Catalytic pyridine (1 mL) was then added to the mixture. After the mixture was stirred at room temperature for 1 h, it was evaporated under reduced pressure to give an oily product which was purified by distillation.

2-Indanylacetyl chloride (42a): colorless oil; 82% yield; bp 115–116 °C (3 mmHg); MS m/z 196, 194, 116; IR (neat) 1800 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.61 (2H, ddd, J = 4, 7, and 15 Hz), 2.08–2.86 (3H, m), 3.16 (2H, ddd, J = 4, 7, and 15 Hz), 7.11–7.24 (4 H, m).

(*S*)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl chloride (42b): colorless oil; 93.7% yield; bp 98–100 °C (0.5 mmHg); MS m/z 210, 208, 130; NMR ($CDCl_3$) δ 1.45–1.67 (1H, m), 1.92–2.08 (1H, m), 2.34–2.60 (2H, m), 2.81–3.00 (5H, m), 7.00–7.15 (4H, m).

(2) Synthesis of 43: General Procedure. L-Proline or L-thioproline (50 mmol) was dissolved in a solution of K_2CO_3 (100 mmol) in water (100 mL). Toluene (100 mL) was then added to the solution. A solution of **42** (50 mmol) in toluene (50 mL) was added dropwise to the vigorously stirred solution, and stirring continued for 30 min under ice-cooling and then for over 30 min at room temperature. The reaction mixture was acidified with concentrated HCl, and water (100 mL) was added to it. The aqueous layer was extracted with AcOEt (150 mL) and successively washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting crystals were recrystallized from an appropriate solvent.

1-(1-Indanylacetyl)-L-proline (43a–1): 89% yield; mp 97–99 °C (AcOEt); IR (KBr) 3460–2500, 1730, 1600, 1440, 1315 cm^{-1}; NMR ($CDCl_3$) δ 1.51–3.80 (13H, m), 4.19–4.67 (1H, m), 7.04 (4H, s), 9.92 (1H, br s). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

3-(2-Indanylacetyl)-L-thioproline (43a–2): 72% yield; mp 114–115 °C (AcOEt–*n*-hexane); IR (KBr) 2900, 1720, 1600, 1430 cm^{-1}; NMR ($CDCl_3$) δ 2.45–2.71 (4H, m), 2.92–3.05 (1H, m), 3.14–3.41 (4H, m), 2.50 (1H, d, J = 8.4 Hz), 4.57 (1H, d, J = 8.4 Hz), 5.09–5.13 (1H, m), 6.00–6.30 (1H, br), 7.10–7.19 (4H, m). Anal. ($C_{15}H_{17}NO_3S$) C, H, N.

1-[(*S*)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-proline (43b–1): 85% yield; mp 134–136 °C (acetone–*n*-hexane); $[\alpha]^{28}_D$ = −144° (c = 1.00, MeOH); IR (KBr) 3200, 2450, 1745, 1710, 1605, 1450 cm^{-1}; NMR ($CDCl_3$) δ 1.45–1.56 (1H, m), 1.90–2.10 (4H, m), 2.60–2.58 (5H, m), 2.60–3.00 (3H, m), 3.40–3.65 (2H, m), 4.63–4.70 (1H, m), 7.03–7.12 (4H, m), 9.0–9.6 (1H, br). Anal. ($C_{17}H_{21}NO_3$) C, H, N.

3-[(*S*)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-thioproline (43b–2): 82% yield; mp 150–152.3 °C (IPE); $[\alpha]^{24}_D$ −146.1° (c = 1.00, MeOH); IR (KBr) 2925, 1725, 1580, 1450 cm^{-1}; NMR ($CDCl_3$) δ 1.36–1.60 (1H, m), 1.86–2.10 (1H, m), 2.16–3.46 (9H, m), 4.40–5.17 (3H, m), 7.03–7.34 (4H, m), 8.74–9.15 (1H, br). Anal. ($C_{16}H_{19}NO_3S$) C, H, N.

(3) Synthesis of 44: General Procedure. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSC·HCl) (20 mmol) was added to a solution of **43** (20 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred for 30 min at room temperature. A solution of L-prolinol (20 mmol) in CH_2Cl_2 (2 mL) was added to the stirring solution, and after the solution was stirred at room temperature for 5 h, the reaction mixture was successively washed with water, 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The resulting residue was purified by chromatography (silica gel) using AcOEt as an eluent to give **44**.

1-[1-(2-Indanylacetyl)-L-prolyl]-L-prolinol (44a–3): amorphous solid; 57% yield; $[\alpha]^{28}_D$ = 19.2° (c = 1.01, $CHCl_3$); MS m/z 356 (M^+), 70 (base peak); IR (neat) 3400, 2980, 1630, 1440 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.30 (9H, m), 2.38–2.85 (4H, m), 2.87–3.05 (1H, m), 3.10–3.23 (2H, m), 3.40–3.80 (4H, m), 3.90–4.25 (2.5H, m), 4.30–4.40 (0.5H, m), 4.65–4.80 (0.5H, m), 5.10–5.20 (0.5H,

m), 7.05–7.23 (4H, m); HRMS 356.2091, calcd for ($C_{21}H_{28}N_2O_3$) 356.2099; TLC R_f (silica gel, 1:9 MeOH/$CHCl_3$) 0.5.

1-[3-(2-Indanylacetyl)-L-thioprolyl]-L-prolinol (44a–4): amorphous solid; 58% yield; $[\alpha]^{26}_D = -107.3°$ (c = 1.03, $CHCl_3$); MS m/z 374 (M^+), 156 (base peak); IR (neat) 3600–3100, 3000–2800, 1630, 1410 cm^{-1}; NMR ($CDCl_3$) δ 13.60–2.12 (4H, m), 2.52–2.69 (4H, m), 2.90–3.37 (5H, m), 3.44–4.35 (5H, m), 4.40–4.85 (3H, m), 5.07–5.41 (1H, t, J = 7 Hz), 7.10–7.20 (4H, m); HRMS 374.1644, calcd for ($C_{20}H_{28}N_2O_3S$) 374.1664; TLC R_f (silica gel, 1:5 MeOH/AcOEt) 0.45.

1-[1-[(S)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-prolyl]-L-prolinol (44b–3): amorphous solid; 70% yield; NMR ($CDCl_3$) δ 1.40–1.55 (1H, m), 1.80–2.55 (13H, m), 2.75–2.87 (2H, m), 2.95 (1H, d, J = 14.8 Hz), 3.42–3.79 (5.5H, m), 3.92–4.01 (0.5H, m), 4.10–4.20 (0.5H, m), 4.28–4.38 (0.5H, m), 4.66–4.85 (1H, m), 5.12–5.30 (1H, m), 7.02–7.10 (4H, m); HRMS 370.2252, calcd for ($C_{22}H_{30}N_2O_3$) 370.2256; TLC R_f (silica gel, 1:10 MeOH/AcOEt) 0.48.

1-[3-[(S)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-thioprolyl]-L-prolinol (44b–4): amorphous solid; 65% yield; $[\alpha]^{26}_D = -130.2°$ (c = 1.04, MeOH); MS m/z 388 (M^+), 156 (base peak); IR (KBr) 3400, 2910, 1625, 1410 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.20 (6H, m), 2.30–2.60 (4H, m), 2.80–4.40 (10H, m), 4.40–4.90 (4H, m), 4.90–5.50 (1H, m), 7.00–7.20 (4H, m); HRMS 388.1820, calcd for ($C_{21}H_{28}N_2O_3S$) 388.1821; TLC R_f (silica gel, 1:5 MeOH/AcOEt) 0.62.

3-[3-[(S)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-thioprolyl]-L-thioprolinol (44b–5): amorphous solid; 77% yield; MS m/z 406 (M^+), 129 (base peak); IR (KBr) 3400, 2910, 1630, 1410 cm^{-1}; NMR ($CDCl_3$) δ 1.43–1.60 (1H, m), 1.95–2.10 (1H, m), 2.32–2.60 (4H, m), 2.79–3.42 (7H, m), 3.64–4.12 (2H, m), 4.40–4.58 (2H, m), 4.60–4.78 (2H, m), 5.10–5.48 (1H, m), 7.03–7.18 (4H, m); HRMS 406.1415, calcd for ($C_{20}H_{26}N_2O_3S_2$) 406.1385; TLC R_f (silica gel, AcOEt) 0.5.

Synthesis of 27–31: General Procedure. Triethylamine (12 mmol) was added to a solution of 44 (2 mmol) in DMSO (2 mL) at 60 °C. A solution of pyridinium sulfur trioxide (12 mmol) in DMSO (4 mL) was added in one portion to the mixture under stirring, and the reaction mixture was stirred at 60 °C for 5 min. After cooling, the mixture was poured into ice–water (40 mL) and then extracted with CH_2Cl_2 (40 mL × 3). The organic layer was washed successively with 10% citric acid and saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting oily material was purified by chromatography (silica gel, AcOEt) to give 27–31. The physical and analytical data of 27–31 are listed on Table 2.

1-[1-(2-Indanylacetyl)-L-prolyl]prolinal (27): MS m/z 354 (M^+); IR (KBr) 1725, 1635 cm^{-1}; NMR ($CDCl_3$) 1.85–2.30 (8H, m), 2.39–2.71 (4H, m), 2.90–3.05 (1H, m), 3.11–3.23 (2H, m), 3.44–3.70 (2H, m), 3.90–3.99 (1H, m), 4.60–4.65 (1H, m), 4.71 (1H, dd, J = 3.7 and 7.7 Hz), 7.09–7.26 (4H, m), 9.53 (1H, d, J = 1.4 Hz); HRMS 354.1921, calcd for ($C_{21}H_{26}N_2O_3$) 354.1943; TLC R_f (silica gel, 1:9 MeOH/AcOEt) 0.57.

1-[3-[(S)-2-(1,2,3,4-Tetrahydronaphthyl)acetyl]-L-thioprolyl]prolinal (30): MS m/z 386 (M^+); IR (KBr) 1725, 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.45–1.57 (1H, m), 1.94–2.40 (5H, m), 2.30–2.58 (4H, m), 2.77–2.86 (2H, m), 2.95 (1H, dd, J = 4 and 11.5 Hz), 3.21 (1H, dd, J = 7.5 and 11.5 Hz), 3.39 (1H, dd, J = 7.4 and 11.5 Hz), 3.45–3.75 (1H, m), 3.89–4.05 (1H, m), 4.58–4.72 (3H, m), 5.10 (1H, t, J = 7 Hz), 7.17 (4H, m), 9.52 (1H, s). Anal. ($C_{21}H_{26}N_2O_3S$) C, H, N.

Synthesis of 32–35: General Procedure. To a solution of 43 (3 mmol) in CH_2Cl_2 (10 mL) were added pivaloyl chloride (3.3 mmol) and triethylamine (3.3 mmol). The mixture was stirred for 30 min at room temperature. A solution of (*S*)-2-cyanopyrrolidine (3.3 mmol) in CH_2Cl_2 (5 mL) was added to the solution, and the mixture was stirred at the same temperature for 3 h. The mixture was washed successively with 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a brownish residue which was purified by silica gel column chromatography using AcOEt as an eluent to give 32–35. The physical and analytical data of 32–35 are listed on Table 2.

(S)-2-Cyano-1-[1-(2-indanylacetyl)-L-prolyl]pyrrolidine (32): MS m/z 351 (M^+); IR (neat) 2240, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.86–2.31 (8H, m), 2.38–2.70 (4H, m), 2.88–2.98 (1H, m), 3.10–3.22 (2H, m), 3.40–3.55 (1H, m), 3.56–3.70 (2H, m), 3.83–3.89 (1H, m), 4.57–4.61 (1H, m), 4.82–4.84 (1H, m), 7.09–7.18 (4H, m); HRMS 351.1941, calcd for ($C_{21}H_{25}N_3O_2$) 351.1947; TLC R_f (silica gel, 1:19 MeOH/$CHCl_3$) 0.24.

(S)-2-Cyano-1-[3-[(S)-2-(1,2,3,4-tetrahydronaphthyl)-acetyl]-L-thioprolyl]pyrrolidine (35): MS m/z 383 (M^+); IR (KBr) 2240, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.41–1.55 (1H, m), 1.95–2.04 (1H, m), 2.19–2.54 (8H, m), 2.80–2.97 (3H, m), 3.20 (1H, dd, J = 7 and 12 Hz), 3.33 (1H, dd, J = 7 and 12 Hz), 3.62–3.67 (1H, m), 3.86–3.95 (1H, m), 4.67 (2H, dd, J = 9 and 12 Hz), 4.80–4.84 (1H, m), 4.94 (1H, t, J = 7 Hz), 7.01–7.10 (4H, m). Anal. ($C_{21}H_{25}N_3O_2S$) C, H, N.

***In Vitro* Experiments: (1) Enzyme.** PEP was purified from canine brain by the method of Tanaka et al.[35] The purified enzyme was homogeneous as judged by polyacrylamide gel electrophoresis in the presence or absence of sodium dodecyl sulfate. The enzyme activity was measured using Z-Gly-Pro-*p*-nitroanilide (Z-Gly-Pro-pNA) as a substrate according to the method of Yoshimoto et al.[36] One unit of enzyme activity was defined as the amount of enzyme which released 1 μmol of *p*-nitroaniline per minute at 37 °C. The specific activity of the enzyme was over 62 units/mg of protein.

(2) Measurement of PEP Inhibitory Potency. A test compound was dissolved in dimethyl sulfoxide (DMSO) at various concentrations. The solution (10 μL) was incubated for 10 min at 37 °C with purified PEP (3×10^{-3} units) in 990 μL of 0.1 M Tris-HCl buffer (pH 7.6) containing 1 mM EDTA, 1 mM 2-mercaptoethanol, and 0.05 mg/mL gelatin. To the mixture of the compound and the enzyme was added 0.1 mL of 2.5 mM Z-Gly-Pro-pNA in 40% dioxane, and the mixture was incubated for 10 min at 37 °C. The enzyme reaction was stopped by adding 0.1 mL of 5% Triton X-100 in 50% acetic acid, and then the absorbance at 410 nm was measured. The potency of inhibitory activity was represented by the IC_{50} value, which was defined as the concentration of the test compound that resulted in 50% inhibition of the enzyme with respect to the DMSO control.

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