# Discovery of the orally effective thyrotropin-releasing hormone (TRH) mimetic:1-{*N*-[(4*S*,5*S*)-(5-methyl-2-oxooxazolidine-4-yl)carbonyl]-3-(thiazol-4-yl)-L-alanyl}-(2*R*)-2-methylpyrrolidine trihydrate (Rovatirelin Hydrate)

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**Supporting Information**

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**Compound synthesis and characterization.**

(1) *N*-Terminus fragments

**(4*S*)-2-Oxooxazolidine-4-carboxylic acid (3a).**

To a solution of *N*-benzyloxycarbonyl-L-serine (18.9 g, 79.0 mmol) in methanol (160 mL), 1 M aqueous sodium hydroxide solution (160 mL, 160 mmol) was added and the mixture was stirred for 4 h at room temperature. The mixture was concentrated under reduced pressure. To the residue, ethyl acetate (300 mL) was added and washing was conducted twice. The aqueous layer was acidified with 1 M aqueous hydrochloric acid solution (160 mL), and concentrated *in vacuo*. Ethanol (300 mL) was added to the residue, and the precipitate was filtered off. The filtrate was concentrated *in vacuo*. A small amount of diethyl ether was added to the residue, the precipitate was filtered and washed with ethanol and diethyl ether to give the title compound **3a** (5.09 g, 49%) as a colorless solid. An analytical sample was prepared by recrystallization from acetone-diethyl ether.
mp 114-116 °C.
IR (KBr) 3368, 2725, 2629, 2521, 1742, 1407, 1200 $cm^{-1}$
$^1H$ NMR (200 MHz, DMSO-$d_6$) δ 8.14 (br s, 1 H), 4.49 (m, 1 H), 4.32 (m, 2 H).
$[\alpha]_D^{25}$ -19.5° (c 1.0, $H_2O$).
Anal. Calcd for $C_4H_5NO_4 \cdot 0.1H_2O$: C, 36.15; H, 3.94; N, 10.54. Found: C, 36.17; H, 3.91; N, 10.53.
lit.[28] mp 114-117 °C., $[\alpha]_D^{20}$ -18.2° (c 2.23, $H_2O$).

**(4*S*,5*R*)-5-Methyl-2-oxooxazolidine-4-carboxylic acid (3b).**

To a solution of *N*-benzyloxycarbonyl-L-threonine (20.0 g, 79 mmol) in methanol (160 mL), 1 M aqueous sodium hydroxide solution (160 mL, 160 mmol) was added and the mixture was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure. To the residue, ethyl acetate (300 mL) was added and washing was conducted twice. The aqueous layer was acidified with 1 M aqueous hydrochloric acid solution (160 mL) and concentrated *in vacuo*. Ethanol (300 mL) was added to the residue, and the precipitate was filtered off. The filtrate was concentrated *in vacuo*. A small amount of diethyl ether was added to the residue, the precipitate was filtered and washed with ethanol and diethyl ether to give the title compound **3b** (6.27 g, 55%) as a colorless solid.
mp 137-138 °C.
IR (KBr) 3303, 3245, 2714, 2600, 2507, 1744, 1727, 1673, 1227, 1207 $cm^{-1}$
$^1H$ NMR (200 MHz, DMSO-$d_6$) δ 8.07 (br s, 1 H), 4.58 (m, 1 H), 3.95 (d, $J$ = 5.2 Hz, 1 H), 1.38 (d, $J$ = 6.2 Hz, 3 H).
$[\alpha]_D^{25}$ +40.9° (c 1.0, $H_2O$).
Anal. Calcd for $C_5H_7NO_4 \cdot 0.1H_2O$: C, 40.88; H, 4.94; N, 9.53. Found: C, 40.84; H, 4.90; N, 9.68.
lit.[32] mp 139.8-140.2 °C., $[\alpha]_D^{29.8}$ +41.8° (c 2.7, $H_2O$).

**(4*S*,5*S*)-5-Methyl-2-oxooxazolidine-4-carboxylic acid (3c).**

To a solution of *N*-benzyloxycarbonyl-*allo*-L-threonine (4.73 g, 18.0 mmol) in methanol

(36.0 mL), 1 M aqueous sodium hydroxide solution (36.0 mL, 36.0 mmol) was added and the mixture was stirred for 4.5 h at room temperature. The mixture was concentrated under reduced pressure. To the residue, ethyl acetate (200 mL) was added and washing was conducted twice. The aqueous layer was acidified with 1 M aqueous hydrochloric acid solution (36.0 mL), and concentrated *in vacuo*. Ethanol (250 mL) was added to the residue and precipitate was filtered off. The filtrate was concentrated *in vacuo*. A small amount of diethyl ether was added to the residue, the precipitate was filtered and washed with ethanol and diethyl ether to give the title compound **3c** (1.92 g, 73%) as colorless crystals.
mp 165-168 °C.
IR (KBr) 3363, 2632, 2550, 1746, 1685, 1412, 1224, 1156, 1060 $cm^{-1}$
$^1H$ NMR (200 MHz, DMSO-$d_6$) δ 7.89 (br s, 1 H), 4.85 (m, 1 H), 4.27 (d, $J$ = 8.4 Hz, 1 H), 1.24 (d, $J$ = 6.4 Hz, 3 H).
$[\alpha]_D^{25}$ -20.7° (c 1.0, $H_2O$).
Anal. Calcd for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65. Found: C, 41.23; H, 4.75; N, 9.63.
lit.[32] mp 169.5-170.5 °C., $[\alpha]_D$ -19.2° ($H_2O$).

**(4*S*,5*R*)-5-Methyl-2-oxooxazolidine-4-carboxylic acid benzyl ester (3d).**
To an ice cooled solution of (4*S*,5*R*)-5-methyl-2-oxooxazolidine-4-carboxylic acid (**3b**) (2.02 g, 13.9 mmol), benzyl alcohol (2.26 mL, 21.8 mmol) and DMAP (0.068 g, 0.555 mmol) in THF (150 mL), DCC (3.44 g, 16.7 mmol) was added and stirred for 30 min at same temperature. After the ice bath was removed, the reaction mixture was stirred for 5 h. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. To the mixture, water (30.0 mL) was added and extracted with ethyl acetate (100 mL). The organic layer was washed with 5% aqueous sodium hydrogen carbonate solution (30.0 mL) and water (30.0 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: toluene-acetone) to afford the title compound **3d** (2.98 g, 91%) as a colorless viscous oil.
$^1H$ NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 5 H), 5.71 (br s, 1 H), 5.26 (d, $J$ = 12.6 Hz, 1 H), 5.19 (d, $J$ = 12.6 Hz, 1 H), 4.74 (m, 1 H), 4.01 (d, $J$ = 5.1 Hz, 1 H), 1.56 (d, $J$ = 6.4 Hz, 3 H).
Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.24; H, 5.66; N, 5.97.

**(4*S*,5*R*)-3,5-Dimethyl-2-oxooxazolidine-4-carboxylic acid benzyl ester (3e).**
To an ice cooled solution of (4*S*,5*R*)-5-methyl-2-oxooxazolidine-4-carboxylic acid benzyl ester (**3d**) (0.488 g, 2.08 mmol) and iodomethane (0.17 mL, 2.73 mmol) in DMF (6.00 mL), sodium hydride (0.083 g, 2.08 mmol) was added portionwise and stirred for 3 h at same temperature. To the mixture, water (10.0 mL) was added slowly and extracted with ethyl acetate (20.0 mL). The organic layer was washed with water (10.0 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: toluene-acetone) to afford the title compound **3e** (0.444 g, 86%) as a colorless oil.
$^1H$ NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 5 H), 5.27 (d, $J$ = 12.3 Hz, 1 H), 5.20 (d, $J$ = 12.3 Hz, 1 H), 4.51 (m, 1 H), 3.86 (d, $J$ = 5.4 Hz, 1 H), 2.92 (s, 3H), 1.50 (d, $J$ = 6.3 Hz, 3

H).

**(4*S*,5*R*)-3-Benzyl-5-methyl-2-oxooxazolidine-4-carboxylic acid benzyl ester (3f).**
To an ice cooled solution of (4*S*,5*R*)-5-methyl-2-oxooxazolidine-4-carboxylic acid benzyl ester (**3d**) (0.706 g, 3.00 mmol) and benzyl bromide (0.39 mL, 3.28 mmol) in DMF (8.00 mL), sodium hydride (0.120 g, 3.00 mmol) was added portionwise and stirred for 3 h at same temperature. To the mixture, water (20.0 mL) was added slowly and extracted with ethyl acetate (40.0 mL). The organic layer was washed with water (20.0 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: toluene-acetone) to afford the title compound **3f** (0.859 g, 88%) as a colorless oil.
$^1$H NMR (200 MHz, $CDCl_3$) δ 7.50-7.10 (m, 5 H), 5.17 (s, 2 H), 4.92 (d, *J* = 14.6 Hz, 1 H), 4.56 (m, 1 H), 4.14 (d, *J* = 14.6 Hz, 1 H), 3.63 (d, *J* = 5.2 Hz, 1 H), 1.39 (d, *J* = 6.4 Hz, 3 H).

**(4*S*,5*R*)-3,5-Dimethyl-2-oxooxazolidine-4-carboxylic acid (3g).**
To a solution of (4*S*,5*R*)-3,5-dimethyl-2-oxooxazolidine-4-carboxylic acid benzyl ester (**3e**) (0.551 g, 2.21 mmol) in methanol (10.0 mL) and water (1.00 mL), 5% Pd-C (0.150 g) was added and hydrogenated for 1 h at room temperature. The catalyst was filtered through Celite and the filtrate was concentrated in vacuo to give the title compound **3g** (0.345 g, 98%) as colorless crystals.
mp 125-127 °C.
IR (KBr) 3433, 2585, 1743, 1697, 1483, 1443, 1408, 1227, 1034 cm$^{-1}$
$^1$H NMR (200 MHz, DMSO-$d_6$) δ 4.51 (m, 1 H), 3.99 (d, *J* = 5.4 Hz, 1 H), 2.79 (s, 3 H), 1.38 (d, *J* = 6.2 Hz, 3 H).
$[\alpha]_D^{24}$ -11.1° (c 1.0, MeOH).
Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.40; H, 5.63; N, 8.74.

**(4*S*,5*R*)-3-Benzyl-5-methyl-2-oxooxazolidine-4-carboxylic acid (3h).**
To a solution of (4*S*,5*R*)-3-benzyl-5-methyl-2-oxooxazolidine-4-carboxylic acid benzyl ester (**3f**) (0.850 g, 2.61 mmol) in THF (18.0 mL) and DME (2.70 mL), lithium hydroxide (0.548 g, 13.1 mmol) in water (10.0 mL) was added and stirred for 30 min. To the mixture, water (20.0 mL) was added and extracted with diethyl ether (40.0 mL x 3). To the aqueous layer, 5 M aqueous hydrochloric acid solution (3.00 mL) was added and extracted with ethyl acetate (40.0 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was recrystallized from hexane-acetone to give the title compound **3h** (0.493 g, 80%) as colorless crystals.
mp 127-128 °C.
IR (KBr) 2716, 2601, 1740, 1692, 1497, 1442, 1421, 1369, 1248, 1201, 1186, 1078 cm$^{-1}$
$^1$H NMR (200 MHz, DMSO-$d_6$) δ 7.50-7.20 (m, 5 H), 4.69 (d, *J* = 15.4 Hz, 1 H), 4.62 (m, 1 H), 4.15 (d, *J* = 15.4 Hz, 1 H), 3.71 (d, *J* = 4.4 Hz, 1 H), 1.32 (d, *J* = 6.2 Hz, 3 H).
$[\alpha]_D^{24}$ -7.8° (c 1.0, $CHCl_3$).
Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.30; H, 5.61; N, 5.91.

**(4*S*,5*S*)-5-Methyl-2-oxooxazolidine-4-carboxylic acid methyl ester (3i).**
To an ice cooled solution of (4*S*,5*S*)-5-methyl-2-oxooxazolidine-4-carboxylic acid (**3c**) (1.02 g, 7.00 mmol) in methanol (10.0 mL), thionyl chloride (0.510 mL, 7.00 mmol) was added dropwise and stirred for 10 min under nitrogen atmosphere. The ice bath was removed and stirred continuously for 4 h. The reaction mixture was concentrated *in vacuo* to afford the title compound **3i** (1.11 g, quant) as a colorless solid, which was used without further purification.
$^1$H NMR (200 MHz, $CD_3OD$) δ 4.96 (dq, *J* = 8.6, 6.4 Hz, 1 H), 4.46 (d, *J* = 8.6 Hz, 1 H), 3.79 (s, 3 H), 1.31 (d, *J* = 6.4 Hz, 3 H).

**(4*R*,5*S*)-5-Methyl-2-oxooxazolidine-4-methanol (3j).**
To an ice cooled solution of (4*S*,5*S*)-5-methyl-2-oxooxazolidine-4-carboxylic acid methyl ester (**3i**) (1.11 g, 7.00 mmol) in ethanol (20.0 mL), sodium borohydride (0.265 g, 7.00 mmol) was added portionwise and stirred for 20 min under nitrogen atmosphere. The ice bath was removed and stirred continuously for 1 h. To the mixture, 5 M aqueous hydrochloric acid solution (1.40 mL, 7.00 mmol) was added and stireed for 30 min at room temperature. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH) to afford the title compound **3j** (0.702 g, 76%) as colorless crystals. An analytical sample was prepared by recrystallization from acetone/diethyl ether.
mp 85-86 °C.
IR (KBr) 3275, 1697, 1447, 1416, 1392, 1334, 1259, 1234, 1128, 1099, 1062 $cm^{-1}$
$^1$H NMR (300 MHz, $CD_3OD$) δ 4.83 (m, 1 H), 3.80 (dd, *J* = 7.8, 5.4 Hz, 1 H), 3.65 (dd, *J* = 11.1, 5.4 Hz, 1 H), 3.58 (dd, *J* = 11.1, 5.4 Hz, 1 H), 1 40 (d, *J* = 6.6 Hz, 3 H).
$[\alpha]_D^{25}$ +30.5° (c 0.51, MeOH).
Anal. Calcd for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.93; H, 6.89; N, 10.86.

**(4*R*,5*S*)-5-Methyl-2-oxooxazolidin-4-ylmethyl trifluoromethanesulfonate (3k).**
To a suspension of (4*R*,5*S*)-5-methyl-2-oxooxazolidine-4-methanol (**3j**) (0.262 g, 2.00 mmol) in dichloromethane (13.0 mL) and pyridine (0.33 mL, 4.08 mmol) at -35 °C under nitrogen atmosphere, rifluoromethanesulfonic anhydride (0.40 mL, 2.40 mmol) was added dropwise and stirred for 1.5 h at the same temperature. To the mixture, ehyl acetate (20.0 mL) and water (10.0 mL) were added and extracted. The organic layer was washed with water (10.0 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title compound **3k** (0.235 g, 45%) as purple crystals, which was used without further purification.
mp 69-71 °C.
$^1$H NMR (200 MHz, $CDCl_3$) δ 6.03 (br s, 1 H), 4.92 (m, 1 H), 4.60 (dd, *J* = 10.6, 5.4 Hz, 1 H), 4.48 (dd, *J* = 10.6, 6.8 Hz, 1 H), 4.15 (m, 1 H), 1.47 (d, *J* = 6.6 Hz, 3 H).

(2) Middle-part fragments
**4-Chloromethylthiazole (7).**
To an ice cooled suspension of Lawesson's reagent (400 g, 0.989 mol) in THF (500 mL),

formamide (178 g, 3.95 mol) in THF (100 mL) solution was added dropwise for 30 min and the mixture was stirred for 10 min at 0 °C. The ice bath was removed and stirred continuously for 3 h. The mixture was cooled to 0 °C again, 1,3-dichloroacetone (251 g, 1.98 mol) in THF (150 mL) solution was added dropwise for 15 min at the same temperature and the mixture was stirred overnight. The precipitate was filtered and washed with acetone (500 mL x 3) to afford crude 4-chloromethylthiazole hydrochloride. Crude 4-chloromethylthiazole hydrochloride was dissolved in water (500 mL). To this solution, water (300 mL), 5% aqueous sodium hydrogen carbonate solution (500 mL) and toluene (800 mL) were added and extracted. The aqueous layer was extracted with toluene (600 mL x 2). The organic layers were combined and washed with water (1.00 L x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the title compound **7** (167 g, 63%) as a brown oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, $J$ = 2.1 Hz, 1 H), 7.37 (d, $J$ = 2.1 Hz, 1 H), 4.76 (s, 2 H).

**Ethyl α-acetamide-α-carboethoxy-β-(thiazol-4-yl)-propionate (8).**
Sodium (27.0 g, 1.17 mol) was added portionwise to ethanol (800 mL) and stirred for 1 h at 75 °C. To the mixture, diethyl acetamidemalonate (255 g, 1.18 mol) was added and refluxed for 2 h. To the mixture, potassium iodide (2.70 g, 16.3 mmol) in DMF (2.70 mL) and 4-chloromethylthiazole (**7**) (157 g, 1.18 mol) in ethanol (100 mL) were added and the mixture was stirred for 3 h at 60 °C. The mixture was cooled to room temperature and concentrated under reduced pressure. To the residue, water (1.00 L) was added and extracted with ethyl acetate (1.00 L x 2). The organic layers were combined and dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title compound **8** (329 g, 89%) as a pale yellow solid.
mp 103-104 °C.
IR ($CHCl_3$) 2980, 1741, 1683, 1493, 1371, 1290 cm$^{-1}$
$^1$H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, $J$ = 2.1 Hz, 1 H), 7.02 (d, $J$ = 2.1 Hz, 1 H), 6.69 (br s, 1 H), 4.29 (q, $J$ = 7.2 Hz, 4 H), 3.89 (s, 2 H), 1.97 (s, 3 H), 1.29 (t, $J$ = 7.2 Hz, 6 H).
Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91; S, 10.20. Found: C, 49.58; H, 5.75; N, 8.93; S, 10.33.
lit.[36] mp 104-105 °C.

**3-(Thiazol-4-yl)-DL-alanine dihydrochloride (9).**
Ethyl α-acetamide-α-carboethoxy-β-(thiazol-4-yl)-propionate (**8**) (329 g, 1.05 mol) in 6 M aqueous hydrogen chloride solution (1.75 L, 10.5 mol) was refluxed for 6 h. The mixture was cooled to room temperature and concentrated under reduced pressure until 718 g. The precipitate was filtered and washed with ice cooled ethanol (100 mL x 2) to give the title compound **9** (189 g, 74%) as a colorless solid.
mp 208-210 °C.
IR (KBr) 3459, 3122, 3054, 2805, 1976, 1848, 1735, 1583, 1512, 1492, 1421, 1408, 1364, 1316, 1264, 1234, 1198, 1187, 1160, 1094, 1071 cm$^{-1}$
$^1$H NMR (300 MHz, $D_2O$) δ 9.40 (d, $J$ = 2.1 Hz, 1 H), 7.75 (d, $J$ = 2.1 Hz, 1 H), 4.48 (t, $J$ = 6.9 Hz, 1 H), 3.59 (m, 2 H).

Anal. Calcd for $C_6H_{10}Cl_2N_2O_2S \cdot 0.1H_2O$: C, 29.19; H, 4.16; Cl, 28.72; N, 11.34; S, 12.99. Found: C, 29.10; H, 4.07; Cl, 11.35; N, 11.35; S, 12.93.

***N-tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanine (4a).**
To an ice cooled solution of 3-(thiazol-4-yl)-DL-alanine dihydrochloride (**9**) (150 g, 0.612 mol) in 3 M aqueous sodiun hydroxide solution (600 mL, 2.00 mol), acetic anhydride (63.6 mL, 0.673 mol) was added dropwise and the mixture was stirred for 1 h at the same temperature. The ice bath was removed and the mixture was stirred continuously for 2 h. This solution was adjusted to pH 7.2 with 3 M aqueous sodiun hydroxide solution (50.0 mL, 150 mmol) and acetic anhydride (2.00 mL, 21.2 mmol). To the solution, aminoacylase (17.0 g) was added and stirred for 2 d at 37 °C. The mixture was filtered through Celite, the filtrate was concentrated under reduced pressure. To the residue, triethylamine (42.7 mL, 0.306 mol) and di-*tert*-butyl dicarbonate (73.5 g, 0.337 mol) were added and the mixture was stirred overnight at room temperature. Ethyl acetate (1.00 L) was added to the mixture and separated. The aqueous layer was adjusted pH 3 with 20% aqueous citric acid solution at 0 °C. This solution was extracted with ethyl acetate (1.00 L x 3). The organic layers were combined and washed with brine (300 mL) and dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from hexane-ethyl acetate to give the title compound **4a** (47.4 g, 29%) as colorless crystals.
mp 119-121 °C.
IR (KBr) 3426, 1704, 1497, 1367, 1163, 1062 $cm^{-1}$
$^1H$ NMR (300 MHz, $CDCl_3$) δ 8.93 (d, $J$ = 2.1 Hz, 1 H), 7.15 (d, $J$ = 2.1 Hz, 1 H), 5.52 (d, $J$ = 5.4 Hz, 1 H), 4.58 (m, 1 H), 3.55 (dd, $J$ = 14.5, 5.4 Hz, 1 H), 3.40 (dd, $J$ = 14.5, 5.4 Hz, 1 H), 1.47 (s, 9 H).
$[\alpha]_D^{24}$ -4.7° (c 1.0, MeOH).
Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.77. Found: C, 48.52; H, 5.89; N, 10.28; S, 11.63.
lit.[33] mp 111-113 °C., $[\alpha]_D^{20}$ -4.5° (c 1.0, MeOH).

**2-Trimethylsilylthiazole (12).**
1.6 M *n*-buthyllithium solution in hexane (252 mL, 403 mmol) was added dropwise to diethyl ether (600 mL) at -78 °C under nitrogen atmosphere. To the solution, 2-bromothiazole (60.0 g, 366 mmol) was added dropwise for 15 min and the mixture was stirred for 1 h at the same temperature. Then trimethylsilyl chloride (46.5 mL, 366 mmol) was added dropwise for 1 h and the mixture was stirred for additional 1 h. Saturated aqueous sodium hydrogen carbonate solution (250 mL) was added slowly at 0 °C. The solution was separated and the aqueous layer was extracted with diethyl ether (200 mL). The organic layers were combined and dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was distilled under reduced pressure to afford the title compound **12** (51.0 g, 89%) as a colorless oil.
bp 67-72 °C (28 mmHg).
$^1H$ NMR (200 MHz, $CDCl_3$) δ 8.12 (d, $J$ = 3.0 Hz, 1 H), 7.53 (d, $J$ = 3.0 Hz, 1 H), 0.42 (s, 9 H).

**5-Formylthiazole (13).**
1.6 M *n*-buthyllithium solution in hexane (11.4 mL, 19.1 mmol) was added dropwise to diethyl ether (40.0 mL) at -78 °C under nitrogen atmosphere. To the solution, 2-trimethylsilylthiazole (**12**) (3.00 g, 19.1 mmol) in diethyl ether (10.0 mL) solution was added dropwise for 20 min and the mixture was stirred for 1 h at the same temperature. Then *N*-formylmorpholine (2.10 mL, 2.10 mmol) in diethyl ether (10.0 mL) solution was added dropwise for 15 min and the mixture was stirred for additional 2 h. Saturated aqueous sodium hydrogen carbonate solution (10.0 mL) was added slowly at 0 °C. The solution was separated and the aqueous layer was extracted with diethyl ether (100 mL x 2). The organic layers were combined and dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in THF (30.0 mL), 1 M aqueous hydrochloric acid solution (1.70 mL, 1.70 mmol) was added and stireed for 1 h at room temperature. The mixture was concentrated under reduced pressure. To the mixture, water (30.0 mL) was added and extracted with diethyl ether (100 mL x 2) and ethyl acetate (100 mL x 2). The organic layers were combined and dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate) to afford the title compound **13** (1.08 g, 50%) as a pale yellow oil.
$^1$H NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 9.13 (s, 1 H), 8.55 (s, 1 H).

**5-Hydroxymethylthiazole (14).**
To a suspension of sodium borohydride (0.860 g, 22.8 mmol) in THF (35.0 mL), 5-formylthiazole (**13**) (2.34 g, 20.7 mmol) in THF (10.0 mL) was added slowly and the mixture was stirred for 2 h at room temperature. The reaction was quenched with aqueous hydrochloric acid solution. To the mixture, saturated aqueous sodium hydrogen carbonate solution was added and extracted with ethyl acetate (100 mL x 10). The organic layers were combined and dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate) to afford the title compound **14** (1.45 g, 61%) as a pale yellow oil. An analytical sample was prepared as HCl salt.
mp 75-77 °C.
$^1$H NMR (200 MHz, DMSO-$d_6$) δ 9.34 (d, $J$ = 1.0 Hz, 1 H), 7.93 (d, $J$ = 1.0 Hz, 1 H), 4.72 (d, $J$ = 1.2 Hz, 2 H).
Anal. Calcd for $C_4H_6ClNOS \cdot 0.2H_2O$: C, 30.95; H, 4.16; Cl, 22.84; N, 9.02; S, 20.66.
Found: C, 30.99; H, 4.14; Cl, 23.08, N, 9.13; S, 20.71.
lit.[39] mp 73-76.5 °C.

**5-Chloromethylthiazole (15).**
To an ice cooled solution of 5-hydroxymethylthiazole (**14**) (1.52 g, 13.2 mmol), thionyl chloride (2.90 mL, 39.6 mmol) was added dropwise over 5 min and the mixture was stirred for 1 h. The mixture was concentrated and co-evapolated with toluene (10.0 mL x 3). To the residue, saturated aqueous sodium hydrogen carbonate solution (100 mL) was added and extracted with ethyl acetate (100 mL x 2). The organic layers were combined and dried

over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title compound **15** (1.75 g, quant) as a colorless oil.
$^1$H NMR (200 MHz, DMSO-$d_6$) δ 9.18 (s, 1 H), 7.99 (s, 1 H), 5.14 (s, 2 H).

**Ethyl α-acetamide-α-carboethoxy-β-(thiazol-5-yl)-propionate (16).**
Sodium ethoxide solution was prepared using sodium (0.760 g, 33.0 mmol) and ethanol (65.0 mL) under nitrogen atmosphere. To the solution, diethyl acetamidemalonate (7.17 g, 33.0 mmol) was added and the mixture was refluxed for 1 h. After cooling to 50 °C, 5-chloromethylthiazole (**15**) (4.00 g, 30.0 mmol) in ethanol (15.0 mL) was added and the mixture was stirred for 6 h. The precipitate was filtered on Celite and the filtrare was concentrated *in vacuo*. The residue was crystallized from water (50.0 mL) to give the title compound **16** (2.93 g, 71%) as colorless needles.
mp 116-118 °C.
IR ($CHCl_3$) 3410, 2987, 1740, 1682, 1493, 1371, 1291 cm$^{-1}$
$^1$H NMR (200 MHz, $CDCl_3$) δ 8.70 (s, 1 H), 7.56 (s, 1 H), 6.74 (br s, 1 H), 4.26 (q, $J$ = 7.2 Hz, 4 H), 3.96 (s, 2 H), 2.09 (s, 3 H), 1.29 (t, $J$ = 7.2 Hz, 6 H).
Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91; S, 10.20. Found: C, 49.58; H, 5.75; N, 8.93; S, 10.33.

***N*-Acetyl-3-(thiazol-5-yl)-DL-alanine ethyl ester (17).**
To a solution of ethyl α-acetamide-α-carboethoxy-β-(thiazol-5-yl)-propionate (**16**) (25.0 g, 79.5 mmol) in ethanol (300 mL), 1 M aqueous sodium hydroxide solution (87.5 mL, 87.5 mmol) was added and the mixture was stirred for 2 h at room temperature. 1 M aqueous hydrochloric acid solution (87.5 mL, 87.5 mmol) was added and refluxed for 2 h. After cooling to room temperature, the mixture was concentrated and extracted with ethyl acetate (200 mL x 4). The organic layers were combined and dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the title compound **17** (9.95 g, 52%) as a yellow oil.
IR ($CHCl_3$) 3426, 3014, 1737, 1677, 1504, 1377, 1344 cm$^{-1}$
$^1$H NMR (200 MHz, $CDCl_3$) δ 8.69 (s, 1 H), 7.58 (s, 1 H), 6.39 (d, $J$ = 7.0 Hz, 1 H), 4.87 (m, 1 H), 4.22 (q, $J$ = 7.0 Hz, 2 H), 3.50 and 3.40 (dd each, $J$ = 15.2, 5.0 Hz, 1 H each), 2.05 (s, 3 H), 1.30 (t, $J$ = 7.0 Hz, 3 H).
Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56; S, 13.23. Found: C, 49.40; H, 5.74; N, 11.52; S, 13.04.

***N*-*tert*-Butoxycarbonyl-3-(thiazol-5-yl)-L-alanine (4b).**
*N*-Acetyl-3-(thiazol-5-yl)-DL-alanine ethyl ester (**17**) (7.30 g, 30.1 mmol) was dissolved in 1 M aqueous sodium hydroxide solution (90.4 mL, 90.4 mmol) and the mixture was stirred for 1 h at room temperature. This solution was adjusted to pH 7.3 with 5 M aqueous hydrochloric acid solution and aminoacylase (0.730 g) was added to this solution. After stirring for 1 d at 37 °C, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (75.0 mL) and water (60.0 mL). To the solution, triethylamine (2.10 mL, 15.1 mmol) and di-*tert* butyl dicarbonate (3.62 g, 16.6 mmol) were added at 0 °C and the mixture was stirred for 16 h at

room temperature. Ethyl acetate (500 mL) was added to the mixture and separated. The aqueous layer was adjusted to pH 3 with 10% aqueous citric acid solution. This solution was extracted with ethyl acetate (500 mL x 3). The organic layers were combined and washed with water (100 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from hexane-ethyl acetate to give the title compound **4b** (3.57 g, 44%) as colorless crystals.
mp 121-123 °C.
IR ($CHCl_3$) 3426, 2981, 2480, 1707, 1496, 1368 $cm^{-1}$
$^1H$ NMR (200 MHz, $CDCl_3$) δ 8.77 (s, 1 H), 7.63 (s, 1 H), 5.39 (d, $J$ = 6.4 Hz, 1 H), 4.60 (m, 1 H), 3.48 (m, 2 H), 1.47 (s, 9 H).
$[\alpha]_D^{24}$ +43.0° (c 1.0, $CHCl_3$).
Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.77. Found: C, 48.45; H, 5.84; N, 10.25; S, 11.71.

The enantiomeric excess was determined to be > 99% by HPLC analysis after methyl esterified with diazomethane.
column: CHIRALCEL OC (Daicel) 0.46 x 25 cm; eluent: hexane/2-propanol (7/3); flow rate: 1.0 mL/min; UV detection: wavelengths of 240 nm.
Retention times ($t_R$) of *N-tert*-butoxycarbonyl-3-(thiazol-5-yl)-L-alanine methyl ester and *N-tert*-butoxycarbonyl-3-(thiazol-5-yl)-D-alanine methyl ester were 15.7 and 12.7 min, respectively.

(3) *C*-Terminus fragments

**_N_-Benzyloxycarbonyl-L-prolinamide (21).**

To a solution of *N*-benzyloxycarbonyl-L-proline (70.0 g, 281 mmol) in THF (470 mL) at -40 °C, triethylamine (43.1 mL, 309 mmol) was added once and ethyl chloroformate (29.5 mL, 309 mmol) was added dropwise for 15 min. The mixture was stirred for 2 h at the same temperature. 28% aqueous ammonia solution (34.1 mL, 562 mmol) was added dropwise for 5 min and the mixture was stirred for additional 2 h. Ethyl acetate (700 mL) and water (100 mL) were added to the mixture and extracted. The organic layer was washed with aqueous sodium hydrogen carbonate solution (100 mL) and brine (100 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title compound **21** (60.6 g, 87%) as colorless crystals.
mp 90-92 °C.
$^1H$ NMR (200 MHz, DMSO-$d_6$) δ 7.50-7.20 (m, 6 H), 6.97 (d, $J$ = 10.0 Hz, 1 H), 5.05 (m, 2 H), 4.12 (m, 1 H), 3.39 (m, 2 H), 2.30-1.90 (m, 1 H), 1.90-1.70 (m, 3 H).
$[\alpha]_D^{25}$ -33.8° (c 2.0, EtOH).
Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N,lit 11.28. Found: C, 62.94; H, 6.52; N, 11.28.
lit.[42] mp 90-91 °C., $[\alpha]_D^{27}$ -35.0° (c 2.0, EtOH).

**L-Prolinamide (22).**

To a solution of *N*-benzyloxycarbonyl-L-prolinamide (**21**) (25.0 g, 101 mmol) in methanol (235 mL), 5% Pd-C (2.50 g) was added and hydrogenated for 2 h at room temperature. The

catalyst was filtered through Celite and the filtrate was concentrated *in vacuo* to give the title compound **22** (12.1 g, quant) as a colorless solid.
mp 100-102 °C.
IR (KBr) 3384, 3286, 3149, 2742, 1702, 1683, 1654, 1599, 1532 $cm^{-1}$
$^1H$ NMR (300 MHz, DMSO-$d_6$) δ 9.10 (br s, 1 H), 8.06 (s, 1 H), 7.62 (s, 1 H), 4.11 (t, $J$ = 7.2 Hz, 1 H), 3.19 (m, 2 H), 2.31 (m, 1 H), 1.96-1.75 (m, 3 H).
$[\alpha]_D^{24}$ -89.4° (c 1.0, MeOH).
lit.[42] mp 101-102 °C., $[\alpha]_D^{27}$ -86.5° (c 1.0, MeOH).

**_N_-Benzyloxycarbonyl-L-prolylmorpholine (23).**
To a solution of *N*-benzyloxycarbonyl-L-proline (5.00 g, 20.1 mmol), morpholine (1.92 mL, 20.1 mmol) and HOSu (2.31 g, 20.1 mmol) in DMF (100 mL), DCC (4.14 g, 20.1 mmol) was added and stirred for 4 h at room temperature. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. To the residue, ethyl acetate (100 mL) and 10% aqueous hydrochlolic acid (50.0 mL) were added and extracted. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (50.0 mL) and water (100 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from hexane-ethyl acetate to give the title compound **23** (4.44 g, 70%) as a colorless solid.
mp 142-143 °C.
$^1H$ NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.12 (m, 2 H), 4.70 and 4.59 (dd, $J$ = 8.4, 3.6 Hz, total 1 H), 3.90-3.20 (m, 10 H), 2.30-1.80 (m, 4 H).
$[\alpha]_D^{23}$ -18.0° (c 1.0, $CHCl_3$).

**L-Prolylmorpholine *p*-toluenesulfonate (24).**
To a solution of *N*-benzyloxycarbonyl-L-prolylmorpholine (**23**) (3.60 g, 11.3 mmol) in methanol (50.0 mL) and water (10.0 mL), 5% Pd-C (1.60 g) and *p*-toluenesulfonic acid (2.15 g, 11.3 mmol) were added and hydrogenated for 3 h at room temperature. The catalyst was filtered through Celite and the filtrate was concentrated *in vacuo* to give the title compound **24** (4.31 g, quant) as a colorless solid.
mp 130-131 °C.
$^1H$ NMR (300 MHz, $CD_3OD$) δ 7.70 (m, 2 H), 7.24 (m, 2 H), 4.65 (dd, $J$ = 8.4, 6.2 Hz, 1 H), 3.80-3.20 (m, 10 H), 2.60-1.80 (m, 4 H), 2.37 (s, 3 H).
Anal. Calcd for $C_{16}H_{24}N_2O_5S$: C, 53.92; H, 6.79; N, 7.86; S, 9.00. Found: C, 53.91; H, 6.73; N, 7.97; S, 8.99.

**Methyl (4*R*)-4-thiazolidinecarboxylate hydrochloride (25).**
To an ice cooled solution of (4*R*)-4-thiazolidinecarboxylic acid (10.0 g, 75.0 mmol) in methanol (100 mL), thionyl chloride (20.0 mL, 274 mmol) was added dropwise for 10 min and the mixture was stirred for 1 h. The mixture was concentreted under reduced pressure. Toluene (10.0 mL) was added to the residue and the precipitate was filtered to give the title compound **25** (13.7 g, 99%) as a colorless solid.
mp 160-162 °C.

$^1$H NMR (300 MHz, $CD_3OD$) δ 4.85 (t, *J* = 6.6 Hz, 1 H), 4.49 (d, *J* = 9.9 Hz, 1 H), 4.42 (d, *J* = 9.9 Hz, 1 H), 3.90 (s, 3 H), 3.55 (dd, *J* = 12.0, 7.2 Hz, 1 H), 3.43 (dd, *J* = 12.0, 7.2 Hz, 1 H).
lit.[21b] mp 164-166.5 °C.

**(4*R*)-4-Thiazolidinecarboxamide (26).**
Methyl (4*R*)-4-thiazolidinecarboxylate hydrochloride (**25**) (72.0 g, 73.7 mmol) in liquid ammonia (41.0 mL) was reacted in sealed tube for 24 h. The mixture was concentrated under reduced pressure. Methanol (30.0 mL) and 2-propanol (30.0 mL) were added to the residue, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH/$H_2O$) to afford the title compound **26** (7.70 g, 78%) as a colorless solid.
mp 97-98 °C.
IR (KBr) 3420, 3294, 1625, 1440, 1256, 1219 $cm^{-1}$
$^1$H NMR (300 MHz, $CD_3OD$) δ 4.14 (s, 2 H), 3.93 (t, *J* = 6.6 Hz, 1 H), 3.08 and 3.07 (d each, *J* = 6.6 Hz, total 2 H).
$[\alpha]_D^{21}$ -129.0° (c 1.0, MeOH).
Anal. Calcd for $C_4H_8N_2OS$: C, 36.35; H, 6.10; N, 21.19; S, 24.26. Found: C, 36.26; H, 6.02; N, 20.97; S, 23.97.
lit.[21b] mp 96-98.5 °C.

***N-tert*-Butoxycarbonyl-L-prolinamide (27).**
To a solution of *N*-Boc-L-proline (13.0 g, 60.0 mmol) and triethylamine (9.20 mL, 66.0 mmol) in THF (200 mL) at -25 °C, ethyl chloroformate (6.31 mL, 66.0 mmol) was added dropwise for 10 min and the mixture was stirred for continuously for 1.5 h. To the mixture, 28% aqueous ammonia (7.30 mL, 120 mmol) was added and the mixture was stirred for 4 h at -20 °C. Ethyl acetate (300 mL) and water (100 mL) were added to the mixture and extracted. The organic layer was washed with water (100 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title compound **27** (11.0 g, 86%) as colorless crystals.
mp 102-104 °C.
$^1$H NMR (300 MHz, $CDCl_3$) δ 7.30 and 7.27 (s each, total 1 H), 6.90 and 6.86 (s each, total 1 H), 3.98 (m, 1 H), 3.27 (m, 2 H), 2.20-1.90 (m, 1 H), 1.90-1.60 (m, 3 H), 1.39 and 1.34 (s each, total 9 H).
$[\alpha]_D^{26}$ -44.8° (c 0.50, MeOH).

***N-tert*-Butoxycarbonyl-(2*S*)-2-cyanopyrrolidine (28).**
To an ice cooled soution of *tert*-butoxycarbonyl-L-prolinamide (**27**) (7.94 g, 37.1 mmol) and imidazole (5.04 g, 74.1 mmol) in pyridine (88.0 mL), phosphorous oxychloride (12.8 mL, 148 mmol) was added dropwise for 5 min and the mixture was stirred for 10 min. The ice bath was removed and the mixture was stirred for continuously for 1 h. The mixture was carefully poured into cold saturated aqueous sodium hydrogen carbonate solution (200 mL) and stirred for 30 min. Ethyl acetate (300 mL) was added to the mixture and extracted. The

organic layer was washed with 10% aqueous hydrochloric acid solution (200 mL), saturated aqueous sodium hydrogen carbonate solution (200 mL) and water (200 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. A small amount of methanol was added to the residue and filtered to give the title compound **28** (9.56 g, 90%) as a colorless solid.
mp 33-35 °C.
IR (Film) 2978, 2934, 2835, 2239, 1698, 1478, 1457 $cm^{-1}$
$^1H$ NMR (200 MHz, $CDCl_3$) δ 4.56 and 4.46 (m each, total 1 H), 3.51 (m, 1 H), 3.37 (m, 1 H), 2.40-1.90 (m, 4 H), 1.51 (s, 9 H).
$[\alpha]_D^{26}$ -106.1° (c 1.0, $CHCl_3$).
Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.21; N, 14.27. Found: C, 61.19; H, 8.16; N, 14.23.

**(2*S*)-2-Cyanopyrrolidine *p*-toluenesulfonate (29).**
To an ice cooled solution of *N*-*tert*-butoxycarbonyl-(2*S*)-2-cyanopyrrolidine (**28**) (2.00 g, 10.2 mmol) in anisole (13.0 mL), trifluoroacetic acid (13.0 mL) was added and the mixture was stirred for 2 h. Ethyl acetate (100 mL) and water (100 mL) were added to the mixture and extracted. *p*-Toluenesulfonic acid monohydrate (1.94 g, 10.2 mmol) was added to the aqueous layer and the aqueous layer was concentrated *in vacuo*. The residue was washed with a small amount of diethyl ether to give the title compound **29** (2.84 g, quant) as a white amorphous powder.
$^1H$ NMR (300 MHz, $CD_3OD$) δ 7.71 (d, $J$ = 8.1 Hz, 2 H), 7.24 (d, $J$ = 8.1 Hz, 2 H), 4.70 (t, $J$ = 6.9 Hz, 1 H), 3.50-3.30 (m, 2 H), 2.60-2.00 (m, 4 H), 2.37 (s, 3 H).
$[\alpha]_D^{25}$ -18.0° (c 1.0, MeOH).
Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44; S, 11.95. Found: C, 53.41; H, 6.25; N, 9.76; S, 11.91.

***N*-*tert*-Butoxycarbonyl-(2*S*)-2-pyrrolidinemethanol (30).**
To an ice cooled solution of *N*-*tert*-butoxycarbonyl-L-proline (172 g, 800 mmol) in THF (1.00 L), 1 M borane-THF complex in THF (1.60 L, 1.60 mol) was added dropwise for 2 h at 4-9 °C and the mixture was stirred continuously for 1 h. The mixture was poured into ice cooled 3 M aqueous hydrochloric acid solution (400 mL). Ethyl acetate (1.50 L) was added and extracted. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (400 mL) and water (400 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the title compound **30** (158 g, 98%) as a colorless solid.
mp 55-56 °C.
IR ($CHCl_3$) 3626, 3360, 1666, 1477, 1455, 1409, 1367, 1344, 1241, 1167 $cm^{-1}$
$^1H$ NMR (300 MHz, $CDCl_3$) δ 4.73 (br s, 1 H), 3.95 (m, 1 H), 3.60 (m, 2 H), 3.44 and 3.23 (m each, 1 H each), 2.50-1.70 (m, 4 H), 1.47 (s, 9 H).
$[\alpha]_D^{24}$ -49.2° (c 0.50, $CHCl_3$).
Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.42; H, 9.44; N, 7.26.

***N-tert*-Butoxycarbonyl-(2*S*)-2-[(methylsulfonyl)oxymethyl]pyrrolidine (31).**
To an ice cooled solution of *N-tert*-butoxycarbonyl-(2*S*)-2-pyrrolidinemethanol (**30**) (43.4 g, 198 mmol) and triethylamine (31.1 mL, 223 mmol) in THF, methanesulfonyl chloride (16.1 mL, 223 mmol) was added dropwise slowly. The mixture was stirred for 0.5 h at 0 °C and 5 h at room temperature. Ethyl acetate (1.50 L) and water (1.00 L) were added to the mixture and extracted. The organic layer was washed with water (1.00 L x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the title compound **31** (52.5 g, 95%) as a yellow viscous oil.
IR ($CHCl_3$) 1748, 1684, 1477, 1456, 1398, 1365, 1175 $cm^{-1}$
$^1H$ NMR (300 MHz, $CDCl_3$) δ 4.50-3.90 (m, 3 H), 3.35 (br s, 2 H), 3.01 (s, 3 H), 2.10-1.80 (m, 4 H), 1.47 (s, 9 H).
$[\alpha]_D^{22}$ -55.9° (c 1.0, $CHCl_3$).
Anal. Calcd for $C_{11}H_{21}NO_5S$: C, 47.29; H, 7.58; N, 5.01; S, 11.48. Found: C, 47.05; H, 7.63; N, 5.16; S, 11.68.

***N-tert*-Butoxycarbonyl-(2*R*)-2-methylpyrrolidine (32).**
Sodium borohydride (34.2 g, 904 mmol) was added to a solution of *N-tert*-butoxycarbonyl-(2*S*)-2-[(methylsulfonyl)oxymethyl]pyrrolidine (**31**) (127 g, 452 mmol) in dimethylsulfoxide (1.00 L). The mixture was stirred for 7 h at 80 ˚C. The mixture was poured into ice cooled water (1.00 L) and quenched carefully with 10% aqueous hydrochloric acid solution. The mixture was diluted with toluene (2.50 L) and the layers were separated. The organic layer was washed with water (1.00 L x 2) and dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was distilled under reduced pressure to afford the title compound **32** (37.5 g, 46%) as a colorless oil.
bp 56-58 °C (3 mmHg).
IR ($CHCl_3$) 1681, 1477, 1454, 1403, 1366, 1170 $cm^{-1}$
$^1H$ NMR (300 MHz, $CDCl_3$) δ 3.87 (br s, 1 H), 3.35 (br s, 2 H), 2.10-1.70 (m, 3 H), 1.60-1.40 (m, 1 H), 1.47 (s, 9 H), 1.16 (d, $J$ = 6.0 Hz, 3 H).
$[\alpha]_D^{25}$ -35.1° (c 1.0, $CHCl_3$).
Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.61; H, 10.34; N, 7.47.

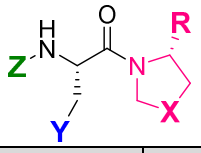
**(2*R*)-2-Methylpyrrolidine hydrochloride (33).**
To an ice cooled solution of *N-tert*-butoxycarbonyl-(2*R*)-2-methylpyrrolidine (**32**) (1.00 g, 5.40 mmol) in ethyl acetate (10.0 mL), 4 M hydrogen chloride in ethyl acetate solution (10.0 mL, 40.0 mmol) was added and the mixture was stirred for 5 h at the same temperature. The mixture was concentrated *in vacuo* to give 0.84 g of the title compound **33** as a hygroscopic colorless solid.
IR (KBr) 3436, 2976, 2780, 2506, 1624, 1587, 1455, 1405, 1388 $cm^{-1}$
$^1H$ NMR (300 MHz, $CD_3OD$) δ 3.64 (m, 1 H), 3.30 (m, 2 H), 2.30-1.95 (m, 3 H), 1.64 (m, 1 H), 1.40 (d, $J$ = 6.3 Hz, 3 H).
$[\alpha]_D^{22}$ -0.7° (c 1.0, MeOH)., $[\alpha]_D^{23}$ -1.0° (c 1.0, $H_2O$).
Anal. Calcd for $C_5H_{12}ClN \cdot 0.3H_2O$: C, 47.28; H, 10.00; Cl, 27.91; N, 11.03. Found: C,

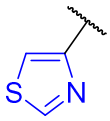
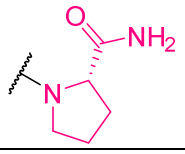
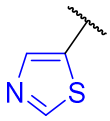
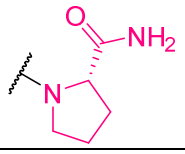
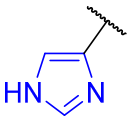
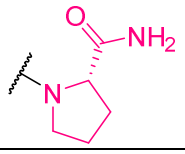
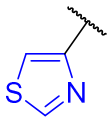
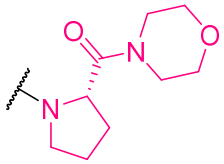
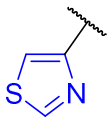
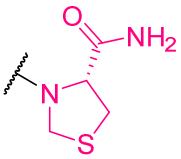
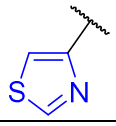
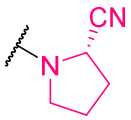
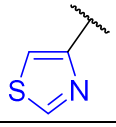
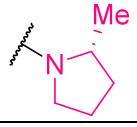
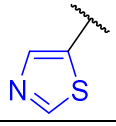
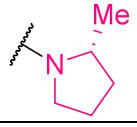
47.42; H, 9.89; Cl, 27.74; N, 11.01.

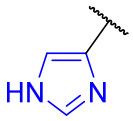
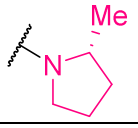
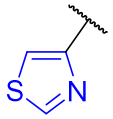
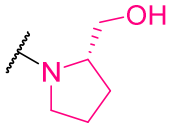
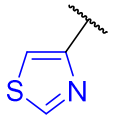
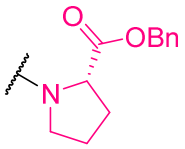
(4) *N*-Boc or *N*-Cbz dipeptide mimetics

The yields of *N*-Boc or *N*-Cbz dipeptide mimetics **34-44** are shown in Table S1.

**Table S1.** Yields of *N*-Boc or *N*-Cbz dipeptide mimetics **34-44**.




| Compound | **Z** | **Y** | **X** and **R** | Yield |
|---|---|---|---|---|
| **34** | Boc |  |  | 91% |
| **35** | Boc |  |  | 82% |
| **36** | Cbz |  |  | 48% |
| **37** | Boc |  |  | 67% |
| **38** | Boc |  |  | 89% |
| **39** | Boc |  |  | 32% |
| **40** | Boc |  |  | quant |
| **41** | Boc |  |  | 97% |

| | | | | |
|---|---|---|---|---|
| **42** | Cbz |  |  | 24% |
| **43** | Boc |  |  | 71% |
| **44** | Boc |  |  | 90% |

**General Procedure for the Synthesis of *N*-Protected Dipeptide Mimetics.**
**[*N*-*tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-L-prolinamide (34).**
To an ice cooled solution of *N*-*tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanine (**4a**) (8.17 g, 30.0 mmol), L-prolinamide (**16**) (3.42 g, 30.0 mmol) and HOBt (0.405 g, 3.00 mmol) in DMF (100 mL), DCC (6.81 g, 33.0 mmol) was added and the mixture was stirred for 0.5 h. The ice bath was removed and the mixture was stirred continuously for 8 h. The mixture was concentrated under reduced pressure. Ethyl acetate (200 mL) and water (100 mL) were added to the residue and extracted. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (100 mL) and water (100 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH) to afford the title compound **34** (10.0 g, 91%) as a white amorphous powder.
IR ($CHCl_3$) 3464, 2982, 1683, 1649, 1496, 1438, 1165 $cm^{-1}$
$^1H$ NMR (200 MHz, $CD_3OD$) δ 8.93 (d, $J$ = 2.0 Hz, 1 H), 7.39 (d, $J$ = 2.0 Hz, 1 H), 4.80-4.50 (m, 1 H), 4.43 (dd, $J$ = 8.2, 4.0 Hz, 1 H), 3.75 (m, 1 H), 3.47 (m, 1 H), 3.09 (dd, $J$ = 14.0, 5.8 Hz, 2 H), 2.30-1.80 (m, 4 H), 1.30 (s, 9 H).
$[\alpha]_D^{23.5}$ -57.1° (c 1.0, $CHCl_3$).
Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.77. Found: C, 48.45; H, 5.84; N, 10.25; S, 11.71.

In a similar manner, other *N*-Boc dipeptide mimetics (**35**, **37-41**, **43** and **44**) were prepared.
**[*N*-*tert*-Butoxycarbonyl-3-(thiazol-5-yl)-L-alanyl]-L-prolinamide (35).**
The condensation of *N*-*tert*-butoxycarbonyl-3-(thiazol-5-yl)-L-alanine (**4b**) (2.00 g, 7.34 mmol) and L-prolinamide (**22**) (0.840 g, 7.34 mmol) yielded the title compound **35** (2.20 g, 82%) as colorless crystals.
mp 216-218 °C.
IR (KBr) 3408, 3225, 3018, 2978, 1712, 1692, 1652, 1547, 1430, 1283, 1168 $cm^{-1}$
$^1H$ NMR (200 MHz, $CDCl_3$) δ 8.88 (s, 1 H), 7.73 and 7.70 (s each, total 1 H), 4.57 (dd, $J$ = 9.6, 4.2 Hz, 1 H), 4.43 (dd, $J$ = 8.2, 4.2 Hz, 1 H), 3.72 (m, 2 H), 3.40 (dd, $J$ = 15.2, 4.2 Hz, 1 H), 3.12 (dd, $J$ = 15.2, 9.8 Hz, 1 H), 2.40-1.80 (m, 4 H), 1.38 (s, 9 H).

$[\alpha]_D^{23.5}$ -53.9° (c 1.0, MeOH).
Anal. Calcd for $C_{16}H_{24}N_4O_4S$: C, 52.16; H, 6.57; N, 15.21; S, 8.72. Found: C,52.01; H, 6.56; N, 15.07; S, 8.79.

**($N^{\alpha}$-Benzyloxycarbonyl-L-histidyl)-L-prolinamide (36).**
To an ice cooled solution of $N^{\alpha}$-benzyloxycarbonyl-L-histidine hydrazide (3.51 g, 11.6 mmol) in 1 M aqueous hydrochloric acid solution (34.8 mL, 34.8 mmol) and ethyl acetate (46.0 mL), sodium nitrite (0.810 g, 11.7 mmol) in water (2.90 mL) was added and the mixture was stirred for 2 min. 50% aqueous potassium carbonate (13.9 mL) was added and the mixture was stirred for 5 min at 0 °C. The organic layer was separated and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered off. To the filtrate, L-prolinamide (**22**) (1.20 g, 10.5 mol) was added and the mixture was stirred for 7 h at 0 °C. The mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH/$H_2O$) to afford crude product, which was recrystallized from water to give the title compound **36** (1.93 g, 48%) as colorless crystals.
mp 106-108 °C.
IR (KBr) 3288, 1678, 1639, 1525, 1498, 1447 $cm^{-1}$
$^1H$ NMR (300 MHz, $CD_3OD$) δ 7.58 (s, 1 H), 7.31 (s, 1 H), 6.92 (s, 1 H), 5.04 (s, 2 H), 4.61 (t, *J* = 7.2 Hz, 1 H), 4.43 (dd, *J* = 8.4, 3.9 Hz, 1 H), 3.75 (m, 1 H), 3.39 (m, 1 H), 3.06 (dd, *J* = 14.4, 7.2 Hz, 1 H), 2.93 (dd, *J* = 14.4, 7.2 Hz, 1 H), 2.30-1.70 (m, 4 H).
$[\alpha]_D^{22.5}$ -40.9° (c 1.0, MeOH).
Anal. Calcd for $C_{19}H_{23}N_5O_4 \cdot 0.4H_2O$: C, 58.12; H, 6.11; N, 17.84. Found: C, 58.09; H, 6.17; N, 17.82.
lit.[47] mp 102-104 °C., $[\alpha]_D^{24}$ -40.7° (c 1.1, MeOH).

**[*N-tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-L-prolylmorpholine (37).**
The condensation of *N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanine (**4a**) (2.03 g, 7.57 mmol) and L-prolylmorpholine *p*-toluenesulfonate (**24**) (2.70 g, 7.57 mmol) yielded the title compound **37** (2.23 g, 67%) as a white amorphous powder.
IR ($CHCl_3$) 3433, 1707, 1644, 1501, 1441, 1232, 1167, 1115 $cm^{-1}$
$^1H$ NMR (300 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.1 Hz, 1 H), 7.21 (d, *J* = 2.1 Hz, 1 H), 5.46 (d, *J* = 9.0 Hz, 1 H), 4.83 (m, 2 H), 4.00-3.40 (m, 10 H), 3.35 (dd, *J* = 14.6, 5.1 Hz, 1 H), 3.08 (dd, *J* = 14.7, 7.8 Hz, 1 H), 2.30-1.70 (m, 4 H), 1.37 (s, 9 H).
$[\alpha]_D^{25}$ -23.1° (c 0.91, $CHCl_3$).
Anal. Calcd for $C_{20}H_{30}N_4O_5S \cdot 0.5H_2O$: C, 53.67; H, 6.98; N, 12.52; S, 7.16. Found: C, 53.71; H, 7.07; N, 12.34; S, 7.17.

**3-*N*-[*N-tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-(4*R*)-4-thiazolidinecarboxamide (38).**
The condensation of *N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanine (**4a**) (8.25 g, 30.3 mmol) and (4*R*)-4-thiazolidinecarboxamide (**26**) (4.00 g, 30.3 mmol) yielded the title compound **38** (10.4 g, 89%) as a white amorphous powder.
IR ($CHCl_3$) 3464, 3429, 3308, 3168, 1687, 1660, 1603, 1496, 1413, 1369, 1162 $cm^{-1}$

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, *J* = 2.1 Hz, 1 H), 8.32 (br s, 1 H), 7.20 (d, *J* = 2.1 Hz, 1 H), 5.70-5.40 (m, 2 H), 5.21 (dd, *J* = 7.2, 2.4 Hz, 1 H), 4.90-4.70 (m, 1 H), 4.75 (d, *J* = 8.7 Hz, 1 H), 4.18 (d, *J* = 8.7 Hz, 1 H), 3.53 (dd, *J* = 11.4, 2.1 Hz, 1 H), 3.42 (dd, *J* = 14.4, 7.8 Hz, 1 H), 3.27 (dd, *J* = 14.4, 3.3 Hz, 1 H), 3.13 (dd, *J* = 11.4, 7.2 Hz, 1 H), 1.45 (s, 9 H).
$[\alpha]_D^{23}$ -81.8° (c 0.50, MeOH).

**1-*N*-[*N-tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-(2*S*)-2-cyanopyrrolidine (39).**
The condensation of *N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanine (**4a**) (0.44 g, 1.62 mmol) and (2*S*)-2-cyanopyrrolidine *p*-toluenesulfonate (**29**) (0.44 g, 1.64 mmol) yielded the title compound **39** (0.18 g, 32%) as a white amorphous powder.
IR (Nujol) 3369, 3112, 3075, 2925, 2854, 2246, 1697, 1645, 1520, 1508, 1443, 1368, 1246, 1162 $cm^{-1}$
$^1$H NMR (200 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.0 Hz, 1 H), 7.15 (d, *J* = 2.0 Hz, 1 H), 5.41 (d, *J* = 8.2 Hz, 1 H), 4.79 (dt, *J* = 8.2, 7.0 Hz, 1 H), 4.72 (dd, *J* = 7.0, 3.6 Hz, 1 H), 3.62 (m, 1 H), 3.35 (m, 1 H), 3.22 (d, *J* = 7.0 Hz, 2 H), 2.30-1.90 (m, 4 H), 1.40 (s, 9 H).
$[\alpha]_D^{26}$ -37.2° (c 0.50, $CHCl_3$).
Anal. Calcd for $C_{16}H_{22}N_4O_3S$: C, 54.84; H, 6.33; N, 15.99; S, 9.15. Found: C, 54.66; H, 6.30; N, 15.80; S, 8.95.

**1-*N*-[*N-tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-(2*R*)-2-methylpyrrolidine (40).**
The condensation of *N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanine (**4a**) (13.6 g, 50.0 mmol) and (2*R*)-2-methylpyrrolidine hydrochloride (**33**) (6.08 g, 50.0 mmol) yielded the title compound **40** (16.5 g, quant) as a yellow viscous oil.
IR ($CHCl_3$) 3431, 1706, 1635, 1498, 1440, 1368 $cm^{-1}$
$^1$H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.1 Hz, 1 H), 7.08 (d, *J* = 2.1 Hz, 1 H), 5.43 (m, 1 H), 4.88 and 4.79 (m each, total 1 H), 4.17 and 3.81 (m each, total 1 H), 3.65-3.05 (m, 4 H), 2.00-1.40 (m, 4 H), 1.40 (s, 9 H), 1.21 and 1.06 (d each, *J* = 6.3 Hz, total 3 H).
$[\alpha]_D^{22}$ +5.2° (c 1.0, $CHCl_3$).
Anal. Calcd for $C_{16}H_{25}N_3O_3S \cdot 0.3H_2O$: C, 55.73; H, 7.48; N, 12.18; S, 9.30. Found: C, 55.89; H, 7.51; N, 11.91; S, 9.20.

**1-*N*-[*N-tert*-Butoxycarbonyl-3-(thiazol-5-yl)-L-alanyl]-(2*R*)-2-methylpyrrolidine (41).**
The condensation of *N-tert*-butoxycarbonyl-3-(thiazol-5-yl)-L-alanine (**4b**) (0.50 g, 1.84 mmol) and (2*R*)-2-methylpyrrolidine hydrochloride (**33**) (0.50 g, 1.84 mmol) yielded the title compound **41** (0.60 g, 97%) as a yellow oil.
IR (KBr) 3429, 2979, 2878, 1705, 1637, 1497, 1441, 1368, 1238, 1165 $cm^{-1}$
$^1$H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1 H), 7.65 (s, 1 H), 5.46 (m, 1 H), 4.69 and 4.61 (m each, total 1 H), 4.30-3.10 (m, 5 H), 2.10-1.50 (m, 4 H), 1.43 (s, 9 H), 1.17 and 1.13 (d each, *J* = 6.3 Hz, total 3 H).
$[\alpha]_D^{27}$ 0° (c 1.0, $CHCl_3$)., $[\alpha]_{365}^{27}$ -10.5° (c 1.0, $CHCl_3$).
Anal. Calcd for $C_{16}H_{25}N_3O_3S \cdot 0.4H_2O$: C, 55.44; H, 7.50; N, 12.12; S, 9.25. Found: C, 55.70; H, 7.41; N, 11.79; S, 9.08.

**1-*N*-($N^{\alpha}$-Benzyloxycarbonyl-L-histidyl)-(2*R*)-2-methylpyrrolidine (42).**
To a solution of $N^{\alpha}$-benzyloxycarbonyl-L-histidine hydrazide (3.00 g, 9.89 mmol) in DMF (25.0 mL) at -78 °C, 4 M hydrogen chloride in 1,4-dioxane solution (7.40 mL, 29.6 mmol) was added dropwise for 20 min. Isoamyl nitrite (1.46 mL, 10.9 mmol) was added and the mixture was stirred for 30 min at the same temperature. Triethylamine (5.50 mL, 39.6 mmol) and (2*R*)-2-methylpyrrolidine hydrochloride (**33**) (1.20 g, 9.89 mmol) were added and the mixture was stirred for 5 min. The mixture was warmed to 0 °C and stirred for 2 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. Ethyl acetate (100 mL) and saturated aqueous sodium hydrogen carbonate solution (100 mL) were added to the residue and extracted. The organic layer was washed with water (100 mL x 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$/MeOH) to afford the title compound **42** (0.83 g, 24%) as a white amorphous powder.
$^1$H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1 H), 7.32 (m, 5 H), 6.80 (s, 1 H), 6.01 and 5.92 (d each, $J$ = 8.1 Hz, total 1 H), 5.20-5.00 (m, 2 H), 4.80 and 4.70 (dd each, $J$ = 14.4, 6.9 Hz, total 1 H), 4.15 and 3.85 (m each, total 1 H), 3.70-3.40 (m, 1 H), 3.36 (m, 1 H), 3.10-2.80 (m, 2 H), 2.00-1.40 (m, 4 H), 1.22 and 1.09 (d each, $J$ = 6.6 Hz, total 3 H).

**[*N-tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-L-prolinol (43).**
The condensation of *N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanine (**4a**) (1.00 g, 3.67 mmol) and L-prolinol (0.409 g, 4.04 mmol) yielded the title compound **43** (0.920 g, 71%) as a white amorphous powder.
IR (KBr) 3353, 1706, 1636, 1498, 1440, 1368, 1268 $cm^{-1}$
$^1$H NMR (300MHz, $CDCl_3$) δ 8.72 (d, $J$ = 1.8 Hz, 1 H), 7.09 (d, $J$ = 1.8 Hz, 1 H), 5.58 (d, $J$ = 7.2 Hz, 1 H), 5.20 (br s, 1 H), 4.75 (dd, $J$ = 11.5, 4.8 Hz, 1 H), 4.20-4.00 (m, 2 H), 3.73 (m, 1 H), 3.44 (m, 1 H), 3.40-3.25 (m, 1 H), 3.31 (d, $J$ = 4.8 Hz, 2 H), 2.10-1.95 (m, 2 H), 1.90-1.70 (m, 2 H), 1.45 (s, 9 H).
$[\alpha]_D^{24}$ -6.2° (c 1.0, MeOH).
Anal. Calcd for $C_{16}H_{25}N_3O_4S \cdot 0.2H_2O$: C, 53.52; H, 7.13; N, 11.70; S, 8.93. Found: C, 53.60; H, 7.34; N, 11.72; S, 8.73.

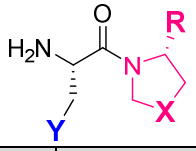
**[*N-tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-L-proline benzyl ester (44).**
The condensation of *N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanine (**4a**) (2.72 g, 10.0 mmol) and L-proline benzyl ester hydrochloride (2.42 g, 10.0 mmol) yielded the title compound **44** (4.16 g, 90%) as a colorless solid. The analytical sample was prepared by recrystallization from diethyl ether-MeOH.
mp 142-143 °C.
IR (KBr) 3352, 1728, 1712, 1653, 1433, 1281, 1269, 1159 $cm^{-1}$
$^1$H NMR (300 MHz, $CDCl_3$) δ 8.75 and 8.72 (d each, $J$ = 1.8 Hz, total 1 H), 7.35 (m, 5 H), 7.10 and 7.08 (d each, $J$ = 1.8 Hz, total 1 H), 5.39 (d, $J$ = 9.0 Hz, 1 H), 5.19 (d, $J$ = 12.3 Hz, 1 H), 5.27 (d, $J$ = 12.3 Hz, 1 H), 4.81 (m, 1 H), 4.58 (dd, $J$ = 8.4, 3.9 Hz, 1 H), 3.73 and 3.51 (m each, total 2 H), 3.26 (dd, $J$ = 14.1, 5.7 Hz, 1 H), 3.02 (dd, $J$ = 14.1, 7.5 Hz, 1 H),

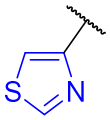
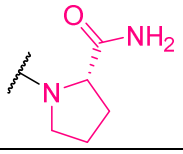
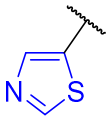
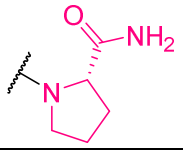
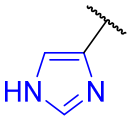
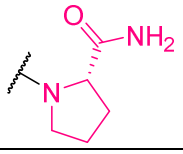
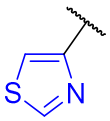
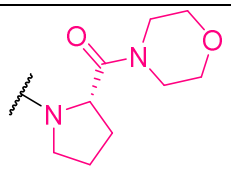
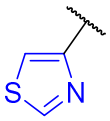
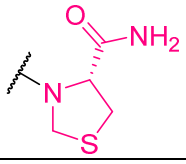
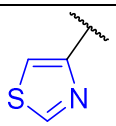
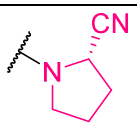
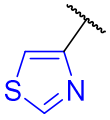
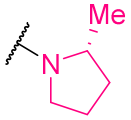
2.19 (m, 1 H), 1.97 (m, 3 H), 1.37 (s, 9 H).
$[\alpha]_D^{23}$ -55.6° (c 1.0, MeOH).
Anal. Calcd for $C_{23}H_{29}N_3O_5S$: C, 60.11; H, 6.36; N, 9.14; S, 6.98. Found: C, 60.06; H, 6.31; N, 9.05; S, 7.05.

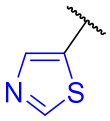
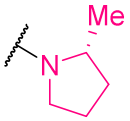
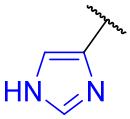
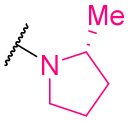
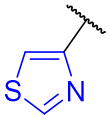
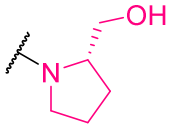
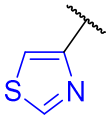
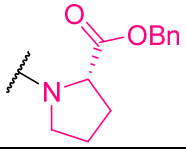
(5) Dipeptide mimetics

The yields of dipeptide mimetics **45-55** are shown in Table S2.

**Table S2.** Yields of dipeptide mimetics **45-55**.




| Compound | **Y** | **X** and **R** | Yield |
|---|---|---|---|
| **45** |  |  | -[a] HCl salt[b] |
| **46** |  |  | -[a] HCl salt[b] |
| **47** |  |  | -[a] HBr salt[b] |
| **48** |  |  | 94% HCl salt[b] |
| **49** |  |  | -[a] HCl salt[b] |
| **50** |  |  | -[a] TFA salt[b] |
| **51** |  |  | -[a] HCl salt[b] |

| | | | |
|---|---|---|---|
| **52** |  |  | -[a] HCl salt[b] |
| **53** |  |  | -[a] Free base[b] |
| **54** |  |  | -[a] HCl salt[b] |
| **55** |  |  | 98% HCl salt[b] |

[a]not isolated.
[b]Compounds were obtained as HCl salt, HBr salt, TFA salt or free base and were not purified.

**General Procedure for the Synthesis of Dipeptide Mimetics.**
**[3-(Thiazol-4-yl)-L-alanyl]-L-prolinamide dihydrochloride (45).**
To an ice cooled solution of [*N*-*tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-L-prolinamide (**34**) (5.53 g, 15.0 mmol) in ethyl acetate (30.0 mL), 4 M hydrogen chloride in ethyl acetate solution (75.0 mL, 300 mmol) was added slowly and the mixture was stirred for 2.5 h. Diethyl ether (400 mL) was added to the mixture and the precipitate was filtered off and washed with a small amount of diethyl ether to give 6.67 g of the title compound **45** as a colorless solid, which was used without further purification.
$^1$H NMR (300 MHz, $D_2O$) δ 9.53 (d, $J$ = 2.1 Hz, 1 H), 7.89 (d, $J$ = 2.1 Hz, 1 H), 4.66 (t, $J$ = 5.7 Hz, 1 H), 4.53 (dd, $J$ = 8.4, 5.4 Hz, 1 H), 3.70-3.50 (m, 4 H), 2.50-1.80 (m, 4 H).

In a similar manner, other dipeptide mimetics (**46**, **48**, **49**, **51**, **52**, **54** and **55**) were prepared.
**[3-(Thiazol-5-yl)-L-alanyl]-L-prolinamide dihydrochloride (46).**
The deprotection of [*N*-*tert*-butoxycarbonyl-3-(thiazol-5-yl)-L-alanyl]-L-prolinamide (**35**) (1.66 g, 4.51 mmol) yielded 2.52 g of the title compound **46** as a colorless solid, which was used without further purification.
$^1$H NMR (300 MHz, $CD_3OD$) δ 9.98 (s, 1 H), 8.40 and 8.23 (s each, total 1 H), 4.72 (t, $J$ = 5.4 Hz, 1 H), 4.51 (dd, $J$ = 8.7, 5.4 Hz, 1 H), 4.20-3.40 (m, 4 H), 2.40-1.80 (m, 4 H).

**L-Histidyl-L-prolinamide dihydrobromide (47).**
25% hydrogen bromide in acetic acid (63.0 mL) was added to the ($N^{\alpha}$-benzyloxycarbonyl-L-histidyl)-L-prolinamide (**36**) (6.30 g, 16.3 mmol), the mixture was stirred for 2 h at room temperature. Diethyl ether (300 mL) was added to the mixture,

and the precipitate was filtered and washed with a small amount of diethyl ether to give 7.53 g of the title compound **47** as a colorless solid, which was used without further purification.
$^1$H NMR (300 MHz, $D_2O$) δ 8.74 (d, *J* = 1.5 Hz, 1 H), 7.51 (d, *J* = 1.5 Hz, 1 H), 4.90-4.70 (m, 1 H), 4.56 (dd, *J* = 8.7, 6.6 Hz, 1 H), 3.82 (m, 1 H), 3.60-3.30 (m, 3 H), 2.39 (m, 1 H), 2.15-1.90 (m, 3 H).

**[3-(Thiazol-4-yl)-L-alanyl]-L-prolylmorpholine dihydrochloride (48).**
The deprotection of [*N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-L-prolylmorpholine (**37**) (1.50 g, 3.42 mmol) yielded the title compound **48** (1.33 g, 94%) as a colorless solid, which was used without further purification.
$^1$H NMR (300 MHz, $CD_3OD$) δ 9.86 (d, *J* = 2.1 Hz, 1 H), 8.06 (d, *J* = 2.1 Hz, 1 H), 4.98 (dd, *J* = 8.4, 6.0 Hz, 1 H), 4.76 (t, *J* = 5.4 Hz, 1 H), 4.00-3.40 (m, 12 H), 2.40-1.80 (m, 4 H).

**3-*N*-[3-(Thiazol-4-yl)-L-alanyl]-(4*R*)-4-thiazolidinecarboxamide dihydrochloride (49).**
The deprotection of
3-*N*-[*N-tert*-Butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-(4*R*)-4-thiazolidinecarboxamide (**38**) (10.3 g, 26.6 mmol) yielded 10.9 g of the title compound **49** as a colorless solid, which was used without further purification.
$^1$H NMR (300 MHz, $CD_3OD$) δ 9.50 and 9.26 (d each, *J* = 2.1 Hz, total 1 H), 7.88 and 7.63 (d each, *J* = 2.1 Hz, total 1 H), 4.94 (dd, *J* = 7.5, 6.0 Hz, 1 H), 4.94 (d, *J* = 9.0 Hz, 1 H), 4.83 (t, *J* = 6.0 Hz, 1 H), 4.47 (d, *J* = 9.0 Hz, 1 H), 3.58 (t, *J* = 5.4 Hz, 2 H), 3.50 (t, *J* = 6.9 Hz, 1 H), 3.48 (t, *J* = 6.9 Hz, 1 H), 3.43 (dd, *J* = 12.0, 7.2 Hz, 1 H), 3.22 (dd, *J* = 12.0, 6.0 Hz, 1 H).

**1-*N*-[3-(Thiazol-4-yl)-L-alanyl]-(2*S*)-2-cyanopyrrolidine di-trifluoroacetate (50).**
Trifluoroacetic acid (5.00 mL) was added to the
1-*N*-[*N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-(2*S*)-2-cyanopyrrolidine (**39**) (0.500 g, 1.43 mmol) under ice cooling and the mixture was stirred for 2 h. The mixture was co-evaporated with toluene to give 0.97 g of the title compound **50** as a white amorphous powder, which was used without further purification.
$^1$H NMR (200 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.0 Hz, 1 H), 7.31 (d, *J* = 2.0 Hz, 1 H), 4.78 (dd, *J* = 6.6, 4.8 Hz, 1 H), 4.62 (t, *J* = 6.6 Hz, 1 H), 3.70-3.10 (m, 4 H), 2.30-1.80 (m, 4 H).

**1-*N*-[3-(Thiazol-4-yl)-L-alanyl]-(2*R*)-2-methylpyrrolidine dihydrochloride (51).**
The deprotection of
1-*N*-[*N-tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-(2*R*)-2-methylpyrrolidine (**40**) (1.50 g, 4.42 mmol) yielded 1.41 g of the title compound **51** as a colorless solid, which was used without further purification.
$^1$H NMR (200 MHz, $CD_3OD$) δ 9.15 and 9.13 (d each, *J* = 2.2 Hz, total 1 H), 7.89 and 7.53 (d each, *J* = 2.2 Hz, total 1 H), 4.51 (t, *J* = 6.8 Hz, 1 H), 4.15 and 3.80 (m each, total 1 H), 3.65-3.20 (m, 4 H), 2.20-1.50 (m, 4 H), 1.22 and 1.08 (d each, *J* = 6.3 Hz, total 3 H).

**1-*N*-[3-(Thiazol-5-yl)-L-alanyl]-(2*R*)-2-methylpyrrolidine dihydrochloride (52).**
The deprotection of
1-*N*-[*N*-*tert*-butoxycarbonyl-3-(thiazol-5-yl)-L-alanyl]-(2*R*)-2-methylpyrrolidine (**41**) (0.40 g, 1.18 mmol) yielded 0.30 g of the title compound **52** as a colorless solid, which was used without further purification.
$^1$H NMR (300 MHz, $CD_3OD$) δ 9.95 and 9.92 (s each, total 1 H), 8.32 and 8.31 (s each, total 1 H), 4.61 (t, *J* = 6.3 Hz, 1 H), 4.19 and 3.98 (m each, total 1 H), 3.65-3.50 (m, 4 H), 2.20-1.60 (m, 4 H), 1.26 and 1.21 (d each, *J* = 6.3 Hz, total 3 H).

**1-*N*-(L-Histidyl)-(2*R*)-2-methylpyrrolidine (53).**
To a solution of 1-*N*-($N^{\alpha}$-benzyloxycarbonyl-L-histidyl)-(2*R*)-2-methylpyrrolidine (**42**) (1.50 g, 4.21 mmol) in methanol (10.0 mL), 10% Pd-C (0.15 g) was added and hydrogenated for 8 h at room temperature. The catalyst was filtered through Celite and the filtrate was concentrated *in vacuo* to afford 1.00 g of the title compound **53** as a colorless oil, which was used without further purification.
$^1$H NMR (300 MHz, $CD_3OD$) δ 7.68 (s, 1 H), 6.94 and 6.92 (s each, total 1 H), 4.14 and 3.72 (m each, total 1 H), 3.60-3.40 (m, 1 H), 3.40-3.20 (m, 1 H), 3.10-2.90 (m, 2 H), 2.10-1.50 (m, 4 H), 1.17 and 1.09 (d each, *J* = 6.6 Hz, total 3 H).

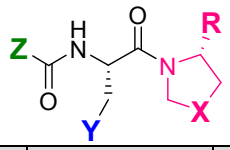
**[3-(Thiazol-4-yl)-L-alanyl]-L-prolinol dihydrochloride (54).**
The deprotection of [*N*-*tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-L-prolinol (**43**) (0.410 g, 1.15 mmol) yielded 0.460 g of the title compound **54** as a colorless solid, which was used without further purification.
$^1$H NMR (300 MHz, $CD_3OD$) δ 9.05 (d, *J* = 2.1 Hz, 1 H), 7.50 (d, *J* = 2.1 Hz, 1 H), 4.40 (dd, *J* = 8.1, 4.8 Hz, 1 H), 3.84 (dd, *J* = 11.5, 3.6 Hz, 1 H), 3.70 (m, 1 H), 3.62 (dd, *J* = 11.4, 7.2 Hz, 1 H), 3.52 (dd, *J* = 15.6, 4.8 Hz, 1 H), 3.41 (dd, *J* = 15.6, 8.1 Hz, 1 H), 3.29 (t, J = 6.9 Hz, 2 H), 2.20-1.90 (m, 3 H), 1.90-1.70 (m, 1 H).

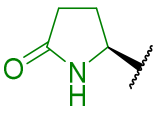
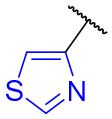
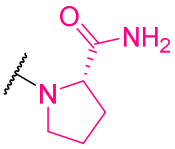
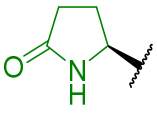
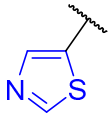
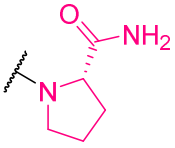
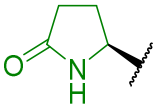
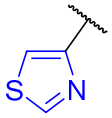
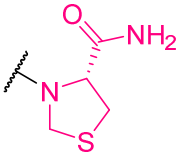
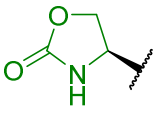
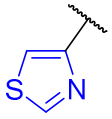
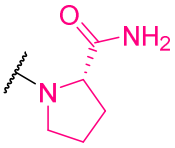
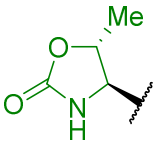
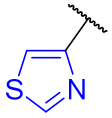
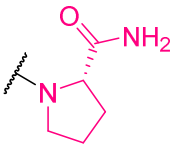
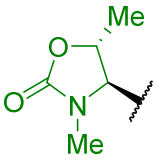
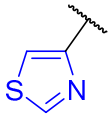
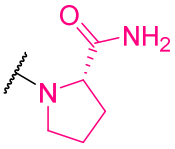
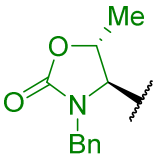
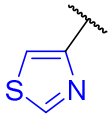
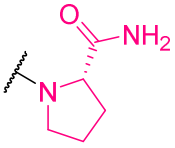
**[3-(Thiazol-4-yl)-L-alanyl]-L-proline benzyl ester dihydrochloride (55).**
The deprotection of [*N*-*tert*-butoxycarbonyl-3-(thiazol-4-yl)-L-alanyl]-L-proline benzyl ester (**44**) (3.00 g, 6.53 mmol) yielded the title compound **55** (2.77 g, 98%) as a colorless solid, which was used without further purification.
$^1$H NMR (300 MHz, $CD_3OD$) δ 9.41 and 9.24 (d each, *J* = 1.8 Hz, total 1 H), 7.68 (m, 5 H), 7.88 and 7.63 (d each, *J* = 1.8 Hz, total 1 H), 5.17 (s, 2 H), 4.60 (m, 2 H), 3.75 (m, 1 H), 3.45 (m, 2 H), 2.30 (m, 2 H), 2.00 (m, 2 H).

(6) TRH mimetics

The yields of TRH mimetics **1**, **56-74** are shown in Table S3.

**Table S3.** Yields of TRH mimetics shown in Scheme 6 and 7.




| Compound | **Z** | **Y** | **X** and **R** | Yield |
|---|---|---|---|---|
| **1** |  |  |  | 49% |
| **56** |  |  |  | 35% |
| **57** |  |  |  | 39% |
| **58** |  |  |  | 53% |
| **59** |  |  |  | 57% |
| **60** |  |  |  | 49% |
| **61** |  |  |  | 64% |

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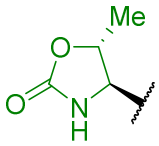
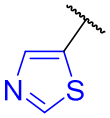
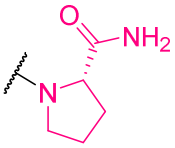
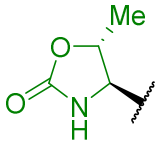
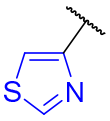
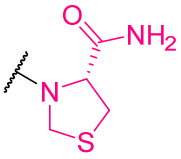
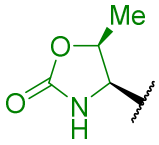
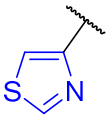
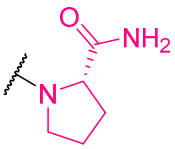
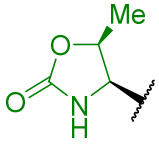
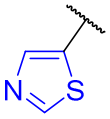
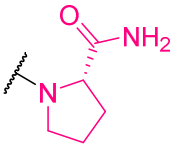
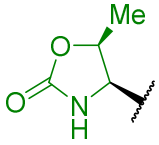
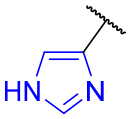
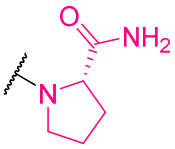
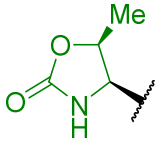
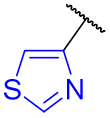
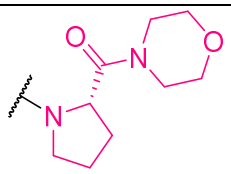
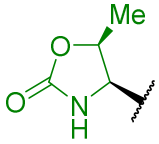
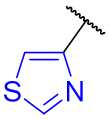
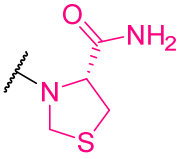
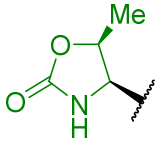
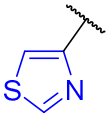
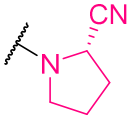
| **62** |  |  |  | 45% |
| **63** |  |  |  | 42% |
| **64** |  |  |  | 50% |
| **65** |  |  |  | 45% |
| **66** |  |  |  | 5.5% |
| **67** |  |  |  | 58% |
| **68** |  |  |  | 47% |
| **69** |  |  |  | 61% |

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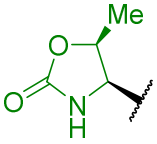
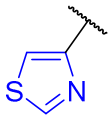
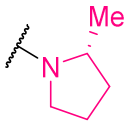
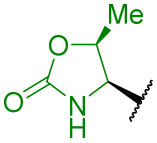
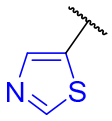
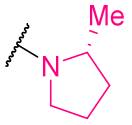
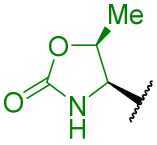
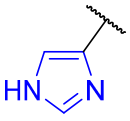
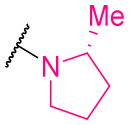
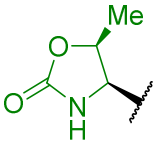
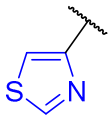
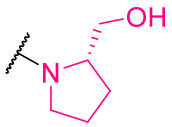
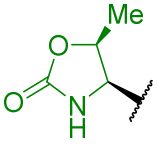
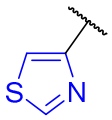
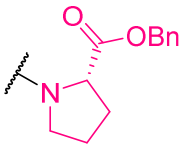
| **70** |  |  |  | 59% |
| **71** |  |  |  | 37% |
| **72** |  |  |  | 29% |
| **73** |  |  |  | 44% |
| **74** |  |  |  | 47% |

**X-ray Crystallographic data of Rovatirelin Hydrate.**

The measurements for single crystal of Rovatirelin Hydrate ($C_{16}H_{28}N_4O_7S$) were performed on a Rigaku XtaLAB P200 diffractometer using multi-layer mirror monochromated Cu-Kα (λ = 1.54187 Å) radiation. A total of 10329 reflections were measured, where 3575 were unique (Rint = 0.0191); equivalent reflections were merged. Data were collected and processed using CrystalClear.[63] Crystals belong to monoclinic space group $P2_1$ with cell parameters of a = 6.7950(4) Å, b = 10.3798(7)Å, c = 14.2270(9) Å, and β = 92.828(6)°. The structure was solved by direct methods implemented in SHELXS[64] and refined by a full-matrix least-squares procedure based on $F^2$ using SHELXL.[65] The final R1 was 0.0225 ($I > 2\sigma(I)$) and the weighted R value wR2 was 0.0569 (all data). All non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically, some were refined using the riding model, and the rest were included in fixed positions. The final Flack parameter[66] was 0.012(5). Summary of data collection and structure refinement parameters are provided in the Table S4-S9.

**REFERENCES**

(63) CrystalClear: Data Collection and Processing Software, Rigaku Corporation (1998-2015). Tokyo 196-8666, Japan.

(64) SHELXS Version 2013/1: Sheldrick, G. M. A short history of SHELX. *Acta Cryst*. *Section A* **2008**, *64*, 112-122.

(65) SHELXL Version 2014/7: Sheldrick, G. M. A short history of SHELX. *Acta Cryst*. *Section A* **2008**, *64*, 112-122.

(66) Flack, H. D.; Bernardinelli, G. Reporting and evaluating absolute-structure and absolute-configuration determinations. *J. Appl. Cryst*. **2000**, *33*, 1143-1148.

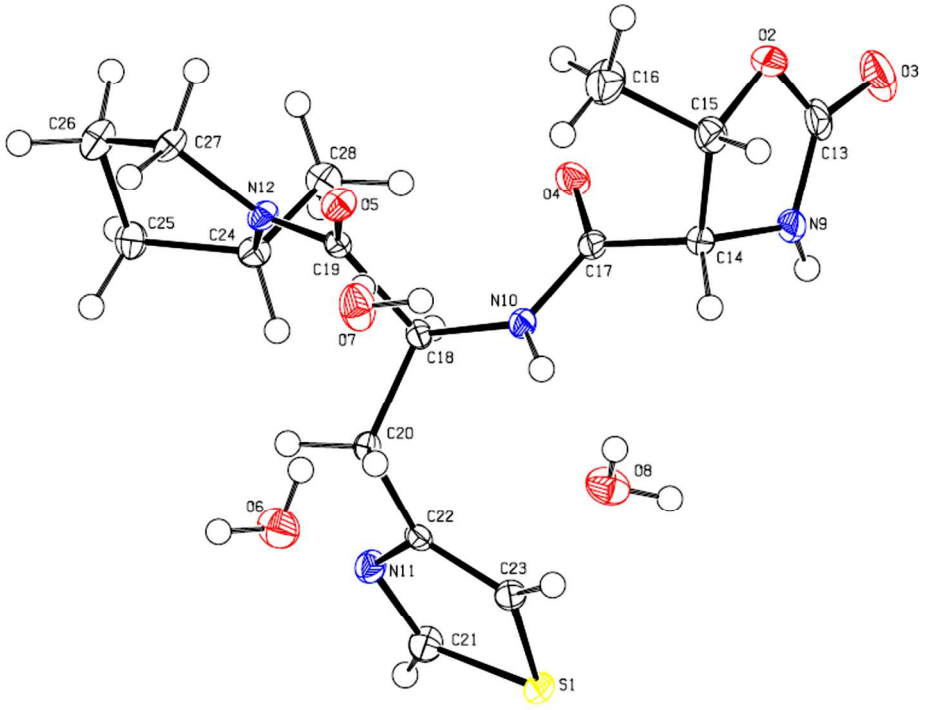



**Figure S1.** X-ray crystal structure of Rovatirelin Hydrate with the atom labeling scheme.

Non-hydrogen atoms were shown as thermal ellipsoids at the 50% probability. Three water molecules of Rovatirelin Hydrate were labeled O6, O7 and O8.

**Table S4.** Crystal data of Rovatirelin Hydrate.

| | |
|---|---|
| Empirical Formula | $C_{16}H_{28}N_4O_7S$ |
| Formula Weight | 420.48 |
| Crystal Color, Habit | colorless, platelet |
| Crystal Dimensions | 0.150 X 0.090 X 0.030 mm |
| Crystal System | monoclinic |
| Lattice Type | Primitive |
| Lattice Parameters | a = 6.7950(4) Å<br>b = 10.3798(7) Å<br>c = 14.2270(9) Å<br>β = 92.828(6) °<br>V = 1002.22(11) Å$^3$ |
| Space Group | $P2_1$ (#4) |
| Z value | 2 |
| $D_{calc}$ | 1.393 g/cm$^3$ |
| $F_{000}$ | 448.00 |
| μ(CuKα) | 18.468 cm$^{-1}$ |

**Table S5.** Intensity Measurements of Rovatirelin Hydrate.

| | |
|---|---|
| Diffractometer | XtaLAB P200 |
| Radiation | CuKα (λ = 1.54187 Å)<br>multi-layer mirror monochromated |
| Voltage, Current | 40kV, 30mA |
| Temperature | -173.0 °C |
| Detector Aperture | 83.8 x 70.0 mm |
| Data Images | 1800 exposure |
| ω oscillation Range (χ=55.0, φ=0.0) | -195.0 - -15.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -105.00° |
| ω oscillation Range (χ=55.0, φ=70.0) | -195.0 - -15.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -105.00° |
| ω oscillation Range (χ=55.0, φ=140.0) | -195.0 - -15.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -105.00° |
| ω oscillation Range (χ=55.0, φ=210.0) | -195.0 - -15.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -105.00° |
| ω oscillation Range (χ=55.0, φ=280.0) | -195.0 - -15.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -105.00° |
| ω oscillation Range (χ=55.0, φ=0.0) | -120.0 - 60.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -30.00° |
| ω oscillation Range (χ=55.0, φ=70.0) | -120.0 - 60.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -30.00° |
| ω oscillation Range (χ=55.0, φ=140.0) | -120.0 - 60.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -30.00° |
| ω oscillation Range (χ=55.0, φ=210.0) | -120.0 - 60.0° |
| Exposure Rate | 5.0 sec./° |
| Detector Swing Angle | -30.00° |
| ω oscillation Range (χ=55.0, φ=280.0) | -120.0 - 60.0° |

| | |
|---|---|
| Exposure Rate | 5.0 sec./$^{o}$ |
| Detector Swing Angle | -30.00$^{o}$ |
| Detector Position | 35.00 mm |
| Pixel Size | 0.172 mm |
| $2\theta_{max}$ | 149.6$^{o}$ |
| No. of Reflections Measured | Total: 10329<br>Unique: 3575 ($R_{int}$ = 0.0191)<br>Parsons quotients (Flack x parameter):<br><br>1332 |
| Corrections | Lorentz-polarization<br>Absorption<br>(trans. factors: 0.835 - 0.946) |

**Table S6.** Structure Solution and Refinement for Rovatirelin Hydrate.

| | |
|---|---|
| Structure Solution | Direct Methods (SHELXS Version 2013/1) |
| Refinement | Full-matrix least-squares on $F^2$ |
| Function Minimized | $\Sigma\ w\ (Fo^2 - Fc^2)^2$ |
| Least Squares Weights | $w = 1/\ [\ \sigma^2(Fo^2) + (0.0396 \cdot P)^2 + 0.0000 \cdot P\ ]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$ |
| $2\theta_{max}$ cutoff | $149.6^o$ |
| Anomalous Dispersion | All non-hydrogen atoms |
| No. Observations (All reflections) | 3575 |
| No. Variables | 279 |
| Reflection/Parameter Ratio | 12.81 |
| Residuals: R1 (I>2.00σ(I)) | 0.0225 |
| Residuals: R (All reflections) | 0.0234 |
| Residuals: wR2 (All reflections) | 0.0569 |
| Goodness of Fit Indicator | 1.005 |
| Flack parameter (Parsons' quotients = 1332) | 0.012(5) |
| Max Shift/Error in Final Cycle | 0.000 |
| Maximum peak in Final Diff. Map | $0.28\ e^-/Å^3$ |
| Minimum peak in Final Diff. Map | $-0.16\ e^-/Å^3$ |

**Table S7.** Atomic coordinates and $B_{iso}/B_{eq}$

| atom | x | y | z | $B_{eq}$ |
|---|---|---|---|---|
| S1 | -0.23484(6) | 0.43238(5) | 0.49133(3) | 1.259(9) |
| O2 | -0.0127(2) | 0.46550(15) | -0.09216(9) | 1.86(3) |
| O3 | -0.2868(3) | 0.58393(17) | -0.10101(12) | 2.64(3) |
| O4 | 0.1133(2) | 0.59591(13) | 0.10803(9) | 1.44(2) |
| O5 | 0.56699(19) | 0.45942(13) | 0.19678(9) | 1.31(2) |
| O6 | 0.5416(2) | 0.15381(16) | 0.41532(11) | 2.05(3) |
| O7 | 0.6047(2) | 0.19460(15) | 0.21659(11) | 2.09(3) |
| O8 | 0.0214(3) | 0.17225(15) | 0.25036(10) | 1.89(3) |
| N9 | -0.2075(2) | 0.45342(18) | 0.02681(11) | 1.40(3) |
| N10 | 0.1593(2) | 0.43132(18) | 0.20959(10) | 1.04(2) |
| N11 | 0.0885(2) | 0.55691(16) | 0.48956(11) | 1.28(3) |
| N12 | 0.5616(2) | 0.64696(16) | 0.27486(11) | 1.07(3) |
| C13 | -0.1814(3) | 0.5079(2) | -0.05723(14) | 1.73(3) |
| C14 | -0.0299(3) | 0.39212(19) | 0.06320(13) | 1.20(3) |
| C15 | 0.0735(3) | 0.3680(2) | -0.02928(14) | 1.58(3) |
| C16 | 0.2954(3) | 0.3801(3) | -0.02562(17) | 2.40(4) |
| C17 | 0.0874(3) | 0.48315(18) | 0.12928(13) | 1.08(3) |
| C18 | 0.2702(3) | 0.51084(19) | 0.27674(12) | 0.94(3) |
| C19 | 0.4780(3) | 0.53858(19) | 0.24446(13) | 1.00(3) |
| C20 | 0.2867(2) | 0.4443(2) | 0.37353(12) | 1.11(3) |
| C21 | -0.0814(3) | 0.5549(2) | 0.52816(14) | 1.40(3) |
| C22 | 0.1019(3) | 0.45632(18) | 0.42652(12) | 0.96(3) |
| C23 | -0.0593(3) | 0.37925(19) | 0.41870(13) | 1.15(3) |
| C24 | 0.4716(3) | 0.75223(19) | 0.32820(13) | 1.13(3) |
| C25 | 0.6513(3) | 0.8100(2) | 0.38139(14) | 1.45(3) |
| C26 | 0.8171(3) | 0.7972(2) | 0.31279(15) | 1.75(4) |
| C27 | 0.7727(3) | 0.6708(2) | 0.26158(14) | 1.39(3) |
| C28 | 0.3652(3) | 0.8464(2) | 0.26182(15) | 1.54(3) |

$B_{eq} = 8/3\ \Pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

**Table S8.** Atomic coordinates and $B_{iso}$ involving hydrogen atoms

| atom | x | y | z | $B_{iso}$ |
|---|---|---|---|---|
| H6A | 0.564(4) | 0.153(3) | 0.3597(11) | 3.0754 |
| H6B | 0.649(3) | 0.137(3) | 0.4395(16) | 3.0754 |
| H7A | 0.528(4) | 0.160(2) | 0.1786(17) | 3.1370 |
| H7B | 0.568(4) | 0.2682(16) | 0.214(2) | 3.1370 |
| H8A | -0.092(4) | 0.168(3) | 0.234(2) | 2.8338 |
| H8B | 0.074(4) | 0.129(3) | 0.210(2) | 2.8338 |
| H9 | -0.290(4) | 0.475(2) | 0.0583(18) | 1.6834 |
| H10 | 0.128(3) | 0.360(3) | 0.2231(17) | 1.2467 |
| H14 | -0.05949 | 0.30920 | 0.09537 | 1.438 |
| H15 | 0.03573 | 0.28073 | -0.05389 | 1.900 |
| H16A | 0.35282 | 0.32031 | 0.02146 | 3.599 |
| H16B | 0.33294 | 0.46854 | -0.00847 | 3.599 |
| H16C | 0.34443 | 0.35941 | -0.08747 | 3.599 |
| H18 | 0.19926 | 0.59453 | 0.28331 | 1.132 |
| H20A | 0.31656 | 0.35191 | 0.36463 | 1.327 |
| H20B | 0.39768 | 0.48289 | 0.41147 | 1.327 |
| H21 | -0.11744 | 0.61690 | 0.57336 | 1.675 |
| H23 | -0.07254 | 0.30624 | 0.37862 | 1.376 |
| H24 | 0.37821 | 0.71606 | 0.37353 | 1.356 |
| H25A | 0.68320 | 0.76172 | 0.44020 | 1.742 |
| H25B | 0.62819 | 0.90146 | 0.39713 | 1.742 |
| H26A | 0.81548 | 0.87029 | 0.26809 | 2.099 |
| H26B | 0.94742 | 0.79384 | 0.34707 | 2.099 |
| H27A | 0.79806 | 0.67860 | 0.19389 | 1.673 |
| H27B | 0.85451 | 0.60009 | 0.28908 | 1.673 |
| H28A | 0.30214 | 0.91334 | 0.29845 | 2.317 |
| H28B | 0.26465 | 0.80036 | 0.22314 | 2.317 |
| H28C | 0.46003 | 0.88619 | 0.22100 | 2.317 |

**Table S9.** Anisotropic displacement parameters

| atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|---|---|---|---|---|---|---|
| S1 | 0.0113(2) | 0.0207(2) | 0.0160(2) | -0.00134(19) | 0.00237(15) | 0.0001(2) |
| O2 | 0.0251(7) | 0.0325(9) | 0.0132(7) | -0.0085(6) | 0.0020(5) | 0.0008(6) |
| O3 | 0.0381(9) | 0.0289(9) | 0.0314(8) | -0.0021(8) | -0.0185(7) | 0.0067(7) |
| O4 | 0.0225(7) | 0.0153(7) | 0.0164(7) | -0.0017(6) | -0.0022(5) | 0.0022(6) |
| O5 | 0.0157(6) | 0.0163(7) | 0.0180(6) | 0.0006(5) | 0.0045(5) | -0.0033(5) |
| O6 | 0.0223(8) | 0.0307(9) | 0.0249(8) | 0.0077(7) | 0.0017(6) | 0.0034(7) |
| O7 | 0.0304(9) | 0.0182(8) | 0.0297(8) | -0.0026(7) | -0.0095(7) | -0.0005(7) |
| O8 | 0.0337(9) | 0.0198(8) | 0.0184(7) | -0.0004(7) | 0.0035(7) | -0.0029(6) |
| N9 | 0.0118(7) | 0.0270(11) | 0.0145(8) | -0.0004(7) | 0.0002(6) | -0.0009(7) |
| N10 | 0.0133(7) | 0.0122(7) | 0.0138(7) | -0.0025(7) | -0.0010(5) | 0.0004(7) |
| N11 | 0.0150(8) | 0.0181(9) | 0.0157(8) | -0.0023(7) | 0.0015(6) | -0.0030(7) |
| N12 | 0.0110(7) | 0.0151(8) | 0.0150(7) | -0.0004(6) | 0.0037(6) | -0.0016(7) |
| C13 | 0.0254(10) | 0.0203(11) | 0.0190(10) | -0.0086(9) | -0.0103(8) | -0.0000(8) |
| C14 | 0.0144(9) | 0.0182(10) | 0.0128(9) | -0.0033(8) | 0.0003(7) | 0.0003(7) |
| C15 | 0.0196(10) | 0.0247(12) | 0.0158(10) | -0.0039(8) | 0.0008(8) | -0.0056(8) |
| C16 | 0.0207(11) | 0.0428(14) | 0.0281(12) | -0.0019(10) | 0.0056(9) | -0.0111(10) |
| C17 | 0.0107(8) | 0.0180(10) | 0.0124(9) | -0.0002(7) | 0.0021(7) | -0.0015(7) |
| C18 | 0.0110(8) | 0.0140(9) | 0.0108(8) | 0.0010(7) | -0.0004(7) | -0.0013(7) |
| C19 | 0.0116(8) | 0.0154(10) | 0.0109(8) | 0.0008(7) | -0.0002(7) | 0.0014(7) |
| C20 | 0.0096(8) | 0.0185(10) | 0.0138(8) | 0.0006(8) | -0.0001(6) | 0.0018(8) |

| | | | | | |
|---|---|---|---|---|---|
| C21 | 0.0167(9) | 0.0188(10) | 0.0177(9) | 0.0003(8) | 0.0025(7) |
| | -0.0041(8) | | | | |
| C22 | 0.0125(8) | 0.0146(10) | 0.0095(8) | 0.0012(7) | -0.0005(6) |
| | 0.0020(7) | | | | |
| C23 | 0.0137(9) | 0.0161(9) | 0.0139(9) | 0.0007(7) | 0.0021(7) |
| | -0.0011(8) | | | | |
| C24 | 0.0155(9) | 0.0135(9) | 0.0142(9) | 0.0003(8) | 0.0035(7) |
| | -0.0030(7) | | | | |
| C25 | 0.0187(10) | 0.0171(10) | 0.0191(10) | -0.0026(8) | -0.0011(8) |
| | -0.0029(8) | | | | |
| C26 | 0.0158(10) | 0.0224(11) | 0.0285(11) | -0.0035(8) | 0.0028(8) |
| | -0.0025(9) | | | | |
| C27 | 0.0113(9) | 0.0196(11) | 0.0225(10) | -0.0024(8) | 0.0047(8) |
| | -0.0003(8) | | | | |
| C28 | 0.0196(10) | 0.0198(10) | 0.0194(10) | 0.0035(8) | 0.0016(8) |
| | -0.0001(8) | | | | |

The general temperature factor expression: $\exp(-2\Pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$