Structure–Activity Relationship (SAR) Studies on Oxazolidinone Antibacterial Agents. 2.[1] Relationship between Lipophilicity and Antibacterial Activity in 5-Thiocarbonyl Oxazolidinones

Ryukou TOKUYAMA,* Yoshiei TAKAHASHI, Yayoi TOMITA, Masatoshi TSUBOUCHI, Toshihiko YOSHIDA, Nobuhiko IWASAKI, Noriyuki KADO, Eiichi OKEZAKI, and Osamu NAGATA

Research and Development Division, Hokuriku Seiyaku Co., Ltd., 37–1–1, Inokuchi, Katsuyama, Fukui 911–8555, Japan.
Received July 21, 2000; accepted December 22, 2000

5-Thiourea and 5-dithiocarbamate oxazolidinones were synthesized as a continuation of research on 5-thiocarbonyl oxazolidinone antibacterial agents considering the hydrophobic parameters of the molecule. The structure–activity relationship (SAR) study revealed that the antibacterial activity on 5-thiocarbonyl oxazolidinones was significantly affected by the lipophilicity, especially the calculated log *P* value and the balance between 5-hydrophilic (or hydrophobic) substituent and hydrophobic (or hydrophilic) substituents on the benzene ring. Some of 5-thiocarbonyl oxazolidinones were found to have good *in vitro* antibacterial activity against gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).

Key words oxazolidinone; antibacterial activity; structure–activity relationship; 5-thiourea oxazolidinone; 5-dithiocarbamate oxazolidinone

The oxazolidinones, exemplified by Dup-721 (**1**),[2] are a new class of synthetic antibacterial agents with activity against gram-positive bacteria. Pharmacia group found linezolid (**2**)[3] which was known to be the first candidate of effective oxazolidinones against serious gram-positive human pathogens caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) without severe toxicity.

In our preceding paper,[1] we demonstrated from our SAR study that the antibacterial activity was greatly affected by the conversion of 5-substituent. (*S*)-*N*-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl] thiourea (**3**), which has a 5-thiourea group, was found to show more excellent *in vitro* antibacterial activity than linezolid against gram-positive bacteria including MRSA and VRE.

Concerning a substituent on the benzene ring, on the other hand, Gregory *et al*. proposed earlier that the co-planarity between 4′-substituent and benzene ring is related to the antibacterial activity in case of 5-acetamide derivatives.[4] They also reported that there might be a small pocket around 3′-position on the benzene ring in the binding mode of 5-acetamide oxazolidinones.[5] While considering their suggestions, we focused our attention on lipophilicity to further study 5-thiocarbonyl oxazolidinones. Partition coefficient (log *P*), which is well known as an index of lipophilicity, is an important physicochemical parameter in the development of antibacterial agent because it is known to be closely related to the permeation through a lipid coat of bacteria. Concerning the lipophilicity on oxazolidinones, it has been reported that the balance between 5-hydrophilic substituent and hydrophobic substituent on the aromatic ring is important for the antibacterial activity.[2,4]

In this paper, we describe our SAR study, especially the relationship between lipophilicity and antibacterial activity, on (4′-cycloalkylamino)phenyl oxazolidinones bearing 5-thiocarbonyl groups.

Chemistry 5-Thiourea oxazolidinones **4** and 5-dithiocarbamate oxazolidinones **5** were synthesized as shown in Chart 2. They were prepared from key intermediates **12**, which were easily derived from **6** by the usual method.[3b] The key intermediates **12** were treated with carbon disulfide followed by ethyl chloroformate to give isothiocyanates **13**. Thiourea derivatives **4** were synthesized from **13** by treatment with ammonia (method A), or prepared from **14** (method B). Dithiocarbamate derivatives **5** were synthesized from the corresponding key intermediates **12** by treatment with carbon disulfide and iodomethane. The physicochemical data of compounds **4** and **5** are shown in the experimental

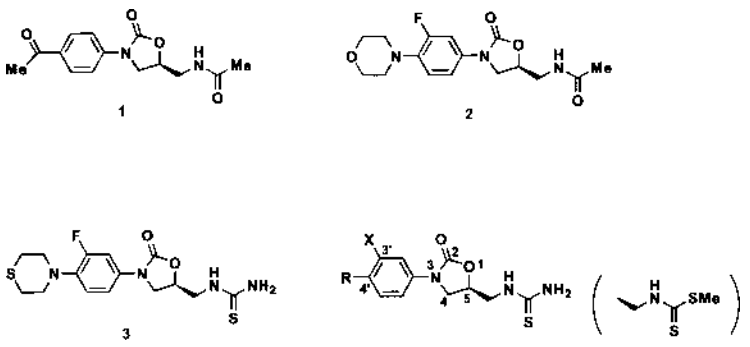


Chart 1

* To whom correspondence should be addressed. e-mail: organ-hs@mitene.or.jp

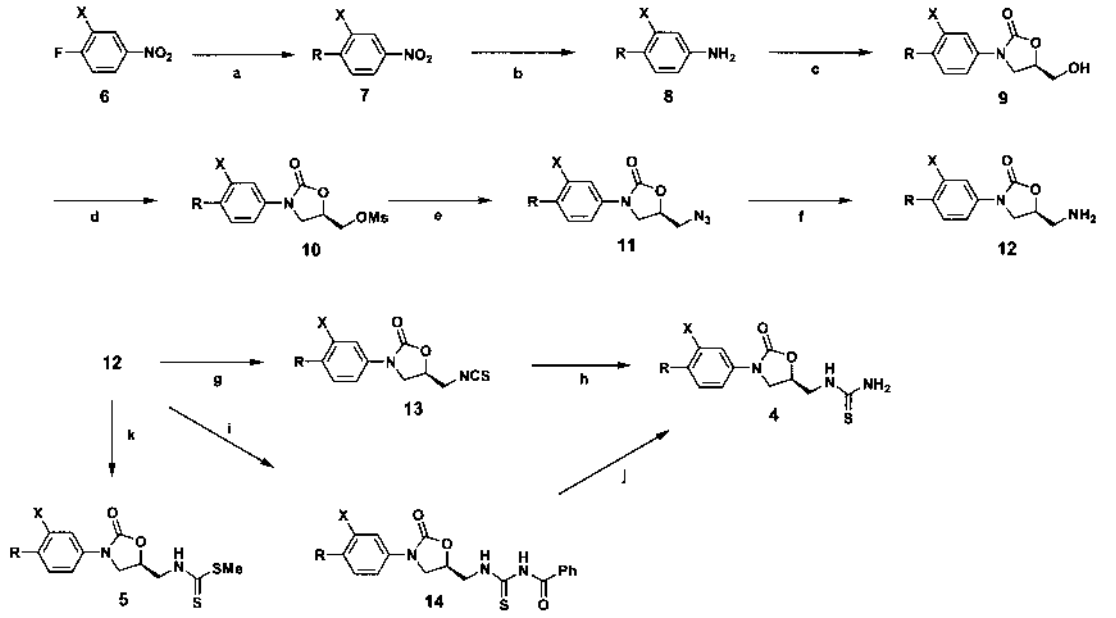


Chart 2

section.

Results and Discussion

All of the oxazolidinone derivatives were tested for antibacterial activity against both standard (*Staphylococcus aureus* Smith) and clinically isolated strains [*S. aureus* HPC1360 (MRSA), *S. aureus* HPC428 (MRSA), *Enterococcus faecium* HPC1322 and *E. casseliflavus* HPC1310 (VRE)]. Their minimum inhibitory concentrations (MICs μg/ml) are shown in Tables 1 and 2. Linezolid (**2**) and vancomycin were used as reference compounds.

The antibacterial activities and hydrophobic parameters (πa, πb and calculated log *P* values) of 5-thiourea oxazolidinones are shown in Table 1.

Some of the cycloalkylamino groups (**4a**—**l**) were quite suitable for antibacterial activity. The activities of compounds **4b** and **4c** were 4—16 times stronger than that of linezolid (**2**). Compound **4l**, which had a 3′-methyl group on benzene ring, showed weaker activity than compound **4k**. It clearly seemed that 3′-methyl group was not a desirable substituent in the case of 4′-cycloalkylamino groups.

On the other hand, we noticed that the oxidative derivatives **4i** and **4j** showed weaker activities than the parent compound **3**. We assumed that their physicochemical properties, such as lipophilicity, might be concerned with their activities.

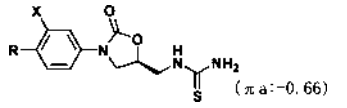
Since it has been reported that the balance between the 5-hydrophilic (πa) substituent and hydrophobic (πb) substituent on the aromatic ring is related to their antibacterial activity,[2,4] we investigated the balance in the 5-thiourea oxazolidinones. The hydrophobic parameters (πa and πb values) were calculated using the log *P* calculation program[6] as illustrated in Chart 3.

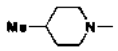
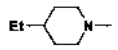
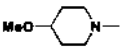
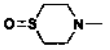
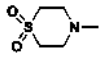
While a potent compound **3** had a good balance between 5-hydrophilic substituent (πa=−0.66) and hydrophobic substituents (πb=0.19) on the benzene ring, the weak activities of compounds **4i** (πb=−1.82) and **4j** (πb=−1.55) could be rationalized in terms of too hydrophilic combination between πa and πb. The activity of compound **4e**, which had a 4-ethylpiperidine group at 4′-substituent on the benzene ring, was weak in spite of its hydrophobic component (πb=2.28). Conversely, compound **4k** showed strong activity in spite of its hydrophilic substituents (πb=−0.36) on the benzene ring. These results suggested that not only the balance between the 5-hydrophilic substituent and hydrophobic substituents on the benzene ring but also another factor might be concerned with the antibacterial activity.

To determine the relationship between the lipophilicity and antibacterial activity in more detail, we must investigate another 5-thiocarbonyl oxazolidinone, which had, in contrast, a too hydrophobic substituent at 5-position. To enhance the lipophilicity of 5-substituent, we synthesized 5-dithiocarbamate derivatives and evaluated their antibacterial activity. The results of these activities and the hydrophobic parameters (πa, πb and calculated log *P* values) of 5-dithiocarbamate oxazolidinones are summarized in Table 2.

The antibacterial activities of compounds **5g**—**j** showed 2—4 times stronger than that of linezolid (**2**). Interestingly, compounds **5c**, **5d** and **5f** were remarkably lower in their antibacterial activities than the corresponding thiourea derivatives (**5c** *vs*. **4d**, **5d** *vs*. **4e**, **5f** *vs*. **4g**). On the contrary, compound **5i** had greater antibacterial activity than the corresponding thiourea derivative (**5i** *vs*. **4i**). The weak activities of compounds **5c** (πb=1.75), **5d** (πb=2.28) and **5f** (πb=1.82) can be rationalized in terms of the result of too hydrophobic combination between 5-substituent and substituents on the benzene ring. Conversely, the good activity of compound **5i** would reflect the good balance between 5-hydrophobic substituent (πa=0.88) and hydrophilic substituents (πb=−1.82) on the benzene ring. Thus, the difference of activity between 5-thiourea and 5-dithiocarbamate

Table 1. *In Vitro* Antibacterial Activities and Hydrophobic Parameters of 5-Thiourea Oxazolidinones



No.	R	X	Hydrophobic parameters		MICs (μg/ml)[a]				
					Standard strain	Clinical isolates			
			πb[b]	Calculated log P[b]	*S. aureus* Smith	*S. aureus* HPC1360[c]	*S. aureus* HPC428[c]	*E. faecium* HPC1322	*E. casseliflavus* HPC1310[d]
4a		F	0.13	−0.02	0.78	1.56	0.78	0.39	0.78
4b		F	0.69	0.54	0.39	0.39	0.39	0.39	0.39
4c		F	1.26	1.11	0.78	0.78	0.78	0.39	1.56
4d		F	1.75	1.60	1.56	1.56	1.56	0.78	1.56
4e		F	2.28	2.13	6.25	3.13	6.25	6.25	3.13
4f		F	0.23	0.08	1.56	3.13	1.56	1.56	1.56
4g		F	1.82	1.67	1.56	0.78	0.78	0.78	1.56
4h		H	−0.30	−0.45	1.56	1.56	1.56	0.78	1.56
4i		F	−1.82	−1.97	12.5	50	12.5	12.5	12.5
4j		F	−1.55	−1.70	1.56	6.25	1.56	1.56	0.78
4k[e]		F	−0.36	−0.51	0.78	3.13	0.78	0.39	0.39
4l		Me	−0.40	−0.55	3.13	3.13	3.13	1.56	1.56
3		F	0.19	0.04	0.78	1.56	0.78	0.78	0.78
2					6.25	6.25	3.13	3.13	6.25
Vancomycin					0.78	0.78	0.78	0.78	12.5

a) Inoculum size, one loopful of 10^6 CFU/ml. *b*) Ref. 6). *c*) MRSA. *d*) VRE. *e*) Ref. 7).

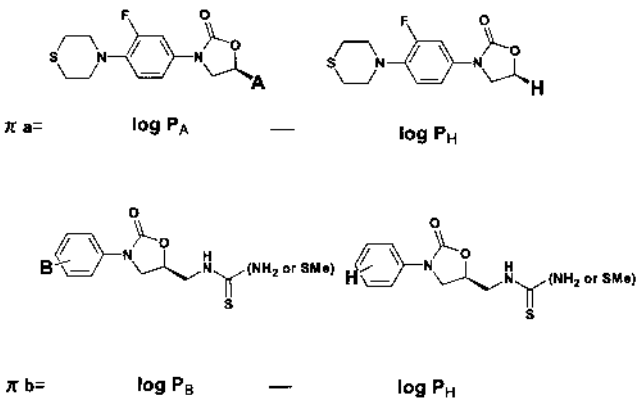


Chart 3

derivatives may result from the difference in 5-lipophilicity. Compounds **5g** (πb=0.19), **5i** (πb=−1.82) and **5j** (πb=−0.37), on the other hand, showed the same *in vitro* activity in spite of having different πb values. The similar tendency was observed in 5-thiourea derivatives. Since this exceptional result was obtained not only in 5-thiourea derivatives but also in 5-dithiocarbamate derivatives, another factor must be considered to elucidate the cause for this. We therefore gave attention to the calculated log P value. Regarding the lipophilicity, it was recently indicated that the antibacterial activity was increased with decreasing calculated log P value in 5-acetamide oxazolidinones.[8] To prove the existence of a correlation between the calculated log P value[6] and antibacterial activities in 5-thiocarbonyl oxazolidinones, the relationships were evaluated for *S. aureus* HPC1360 (MRSA), *S. aureus* HPC428 (MRSA) and *E. casseliflavus* HPC1310 (VRE), respectively. The relationships were evaluated in only 22 compounds, not in compound **4l**. The equations (Eqs. 1—3) are reported below, and the curve fittings are shown in Figs. 1—3.

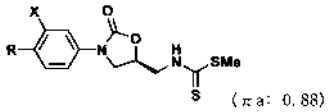
MRSA HPC1360

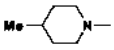
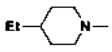
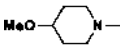
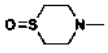
$$\log(1/\mathrm{MIC}) = -0.2075(\log P)^2 + 0.2536(\log P) + 0.1313 \quad (1)$$
$$(0.048) \quad (0.117) \quad (0.161)$$
$$n=22,\ r=0.912,\ s=0.270,\ F=47.206$$

MRSA HPC428

$$\log(1/\mathrm{MIC}) = -0.1866(\log P)^2 + 0.1159(\log P) + 0.1058 \quad (2)$$
$$(0.046) \quad (0.113) \quad (0.155)$$
$$n=22,\ r=0.922,\ s=0.261,\ F=53.587$$

Table 2. *In Vitro* Antibacterial Activities and Hydrophobic Parameters of 5-Dithiocarbamate Oxazolidinones



No.	R	X	Hydrophobic parameters		MICs (μg/ml)[a]				
					Standard strain	Clinical isolates			
			πb[b]	Calculated log P[b]	*S. aureus* Smith	*S. aureus* HPC1360[c]	*S. aureus* HPC428[c]	*E. faecium* HPC1322	*E. casseliflavus* HPC1310[d]
5a		F	0.69	2.09	1.56	3.13	1.56	3.13	6.25
5b		F	1.25	2.65	6.25	6.25	6.25	6.25	6.25
5c		F	1.75	3.15	>50	>50	>50	12.5	>50
5d		F	2.28	3.68	>50	>50	>50	>50	>50
5e		F	0.23	1.63	6.25	6.25	3.13	6.25	6.25
5f		F	1.82	3.22	>50	>50	>50	>50	>50
5g		F	0.19	1.59	1.56	1.56	0.78	0.78	1.56
5h		H	−0.30	1.10	3.13	1.56	1.56	1.56	3.13
5i		F	−1.82	−0.42	1.56	1.56	1.56	1.56	1.56
5j[e]		F	−0.37	1.03	1.56	1.56	0.78	1.56	1.56
2					6.25	6.25	3.13	3.13	6.25
Vancomycin					0.78	0.78	0.78	0.78	12.5

a) Inoculum size, one loopful of 10^6 CFU/ml. *b*) Ref. 6). *c*) MRSA. *d*) VRE. *e*) Ref. 7).

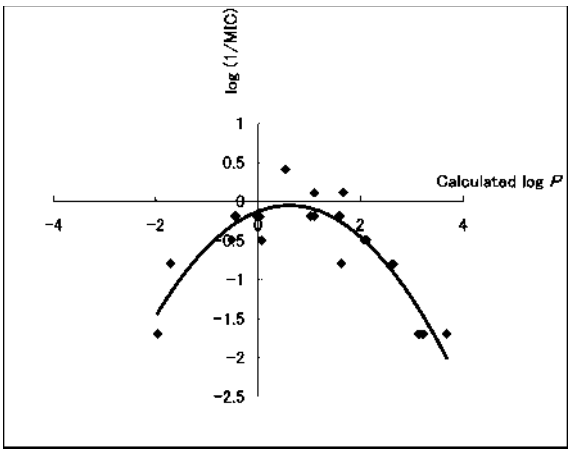


Fig. 1. Relationship between Calculated Log P Value and *in Vitro* Activity against MRSA HPC1360

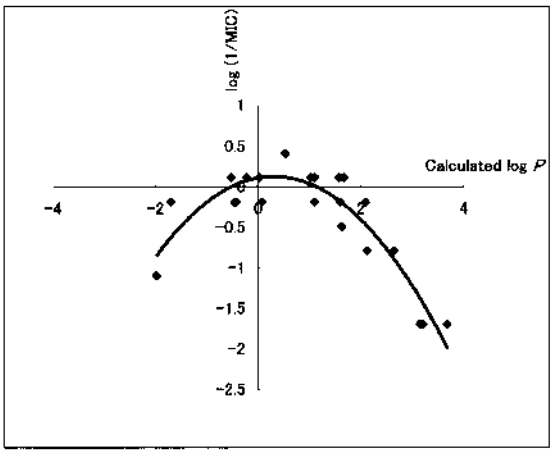


Fig. 2. Relationship between Calculated Log P Value and *in Vitro* Activity against MRSA HPC428

VRE HPC1310

$$\log(1/\mathrm{MIC}) = -0.151\,(\log P)^2 + 0.0074\,(\log P) + 0.0303 \quad (3)$$
$$(0.053) \qquad (0.202) \qquad (0.180)$$
$$n=22,\quad r=0.891,\quad s=0.301,\quad F=36.726$$

Here, log P indicates calculated log P value, n is the number of compounds, r is the correlation coefficient, s is the standard deviation from the regression, F is the observed F value, and the values in parentheses give the 95% confidence intervals. Equations 1—3 indicate that the calculated log P value is parabolically related to the inhibition of MRSA and VRE in this series. The curves in Fig. 1—3 show that the favorable calculated log P values for antibacterial activities against MRSA and VRE were −1 to +2. This indicated that not only the balance between 5-hydrophilic (or 5-hydrophobic) substituent and hydrophobic (or hydrophilic) substituents on benzene ring but also the calculated log P value affected the antibacterial activity in the case of 5-thiocar-

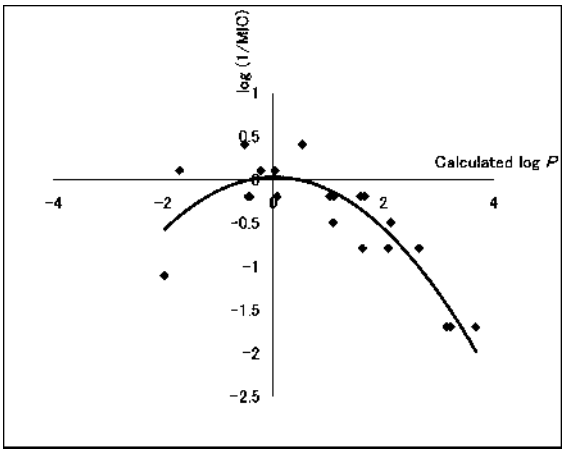


Fig. 3. Relationship between Calculated Log *P* Value and *in Vitro* Activity against VRE HPC 1310

bonyl oxazolidinones.

In conclusion, 5-thiourea and 5-dithiocarbamate oxazolidinones were synthesized and their antibacterial activities against gram-positive bacteria including MRSA and VRE were evaluated. Some of 5-thiocarbonyl oxazolidinones were found to show strong *in vitro* antibacterial activity. Moreover, this activity was significantly affected by the lipophilicity, especially the calculated log *P* value and the balance between 5-hydrophilic (or hydrophobic) substituent and hydrophobic (or hydrophilic) substituents on benzene ring.

Experimental

Melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. Elemental analyses were measured with a Yanagimoto MT-5 elemental analysis apparatus, and were within ±0.4% of calculated values. ^{1}H-NMR spectra were measured with a JEOL A-500 (500 MHz) or JEOL JNM-LA300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. Specific optical rotations were measured on a JASCO DIP-370 polarimeter. Column chromatography was carried out with silica gel [Kieselgel 60 (Merck)]. TLC was conducted on 0.25 mm pre-coated silica gel plates ($60F_{254}$, Merck). All extracted solvents were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*.

3-Fluoro-4-(4-methyl-1-piperidinyl)nitrobenzene (7d) A mixture of 3,4-difluoronitrobenzene (18.0 g, 0.113 mol), 4-methylpiperidine (14.7 ml, 0.124 mol) and *N*,*N*-diisopropylethylamine (30.0 ml, 0.170 mol) in CH_3CN (180 ml) was refluxed for 17 h. After the reaction mixture was concentrated, the residue was poured into water and extracted with AcOEt. The extract was washed with brine, dried and concentrated to afford **7d** (27.1 g, 100%) as yellow brown oil. ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, d, J=6 Hz), 1.20—1.35 (2H, m), 1.55—1.65 (1H, m), 1.65—1.80 (2H, m), 2.85—3.00 (2H, m), 3.60—3.75 (2H, m), 7.13 (1H, t, J=9 Hz), 7.93 (1H, dd, J=13.5, 2.5 Hz), 7.97 (1H, dd, J=9, 2.5 Hz).

Compounds **7** were respectively prepared in a similar manner.

3-Fluoro-4-(4-methyl-1-piperidinyl)aniline (8d) A suspension of **7d** (27.0 g, 0.113 mol) and platinum(IV) oxide (0.27 g) in MeOH (200 ml) was hydrogenated at ambient temperature under a hydrogen atmosphere (2 kg/cm^2) for 3 h. The catalyst was filtered off, and the filtrate was concentrated to afford **8d** (22.9 g, 97%) as black oil. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, d, J=6.5 Hz), 1.20—1.30 (2H, m), 1.35—1.50 (1H, m), 1.60—1.70 (2H, m), 2.45—2.60 (2H, m), 3.00—3.10 (2H, m), 4.81 (2H, br s), 6.28 (1H, dd, J=9, 2.5 Hz), 6.32 (1H, dd, J=14.5, 2.5 Hz), 6.74 (1H, t, J=9 Hz).

Compounds **8** were respectively prepared from the corresponding **7** in a similar manner.

(*R*)-3-[3-Fluoro-4-(4-methyl-1-piperidinyl)phenyl]-5-hydroxymethyloxazolidine-2-one (9d) To a solution of benzyloxycarbonyl chloride (17.2 ml, 0.120 mol) in tetrahydrofuran (THF) (100 ml), a mixture of **8d** (22.8 g, 0.109 mol) and THF (130 ml) was added under ice cooling, followed by stirring at the same temperature for 1 h. Then NEt_3 (16.7 ml, 0.120 mol) was added to the reaction mixture, and stirred at ambient temperature for 17 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with brine, dried and concentrated to afford brown crystals (19.0 g, 51%) as carbamate.

To a solution of the carbamate (18.7 g, 54.6 mmol) in THF (190 ml) under N_2 at −70 °C, *n*-BuLi (38.0 ml of 1.54 M solution in hexane, 57.3 mmol) was added. The mixture was stirred at the same temperature for 1 h, and then (*R*)-glycidyl butyrate (8.20 ml, 57.3 mmol) was added, and the mixture was further stirred at room temperature for 19 h. The reaction mixture was quenched with 10% aqueous NH_4Cl and extracted with AcOEt. The extract was washed with brine, dried and concentrated. Then, a mixture of the residue and 2 N aqueous NaOH (23 ml) in MeOH (100 ml) was stirred at room temperature for 1 h. The solution was concentrated and extracted with AcOEt. The extract was washed with brine, dried and concentrated. The residue was washed with isopropyl ether (iso-Pr_2O) to afford **9d** (13.7 g, 81%) as pale brown crystals. Recrystallization from AcOEt–iso-Pr_2O gave pale brown needles. mp: 141.5—143 °C. $[\alpha]_D^{20}$ −42.9° (c=0.1, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, d, J=6 Hz), 1.20—1.35 (2H, m), 1.45—1.55 (1H, m), 1.65—1.75 (2H, m), 2.55—2.70 (2H, m), 3.20—3.30 (2H, m), 3.50—3.60 (1H, m), 3.60—3.70 (1H, m), 3.78 (1H, dd, J=9, 6 Hz), 4.03 (1H, t, J=9 Hz), 4.60—4.70 (1H, m), 5.08 (1H, t, J=5.5 Hz), 7.03 (1H, t, J=9 Hz), 7.16 (1H, dd, J=9, 2.5 Hz), 7.45 (1H, dd, J=15.5, 2.5 Hz). *Anal*. Calcd for $C_{16}H_{21}FN_2O_3$: C, 62.32; H, 6.86; N, 9.09. Found: C, 62.21; H, 6.94; N, 9.01.

Compounds **9** were respectively prepared from the corresponding **8** in a similar manner.

(*R*)-[[3-[3-Fluoro-4-(4-methyl-1-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate (10d) To a mixture of **9d** (13.2 g, 42.8 mmol) and Et_3N (6.60 ml, 47.1 mmol) in THF (132 ml), methanesulfonyl chloride (3.50 ml, 44.9 mmol) was added under ice cooling, followed by stirring at room temperature for 2 h. The reaction mixture was washed with water and extracted with AcOEt. The extract was washed with brine, dried and concentrated to afford **10d** (15.9 g, 96%) as pale brown crystals. Recrystallization from AcOEt–iso-Pr_2O gave pale brown prisms. mp: 155—156.5 °C. $[\alpha]_D^{20}$ −52.9° (c=0.1, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, d, J=6.5 Hz), 1.20—1.35 (2H, m), 1.45—1.55 (1H, m), 1.65—1.75 (2H, m), 2.60—2.70 (2H, m), 3.20—3.30 (2H, m), 3.22 (3H, s), 3.79 (1H, dd, J=9, 6 Hz), 4.15 (1H, t, J=9 Hz), 4.44 (1H, dd, J=11.5, 5.5 Hz), 4.49 (1H, dd, J=11.5, 3 Hz), 4.90—5.00 (1H, m), 7.05 (1H, t, J=9 Hz), 7.16 (1H, dd, J=9, 2.5 Hz), 7.43 (1H, dd, J=15, 2.5 Hz). *Anal*. Calcd for $C_{17}H_{23}FN_2O_5S$: C, 52.84; H, 6.00; N, 7.25. Found: C, 52.65; H, 6.22; N, 7.07.

Compounds **10** were respectively prepared from the corresponding **9** in a similar manner.

(*R*)-5-Azidomethyl-3-[3-fluoro-4-(4-methyl-1-piperidinyl)phenyl]oxazolidine-2-one (11d) A suspension of **10d** (15.7 g, 40.6 mmol) and sodium azide (10.1 g, 154 mmol) in *N*,*N*-dimethylformamide (DMF) (150 ml) was heated at 65°C for 6 h. After cooling, the reaction mixture was poured into water and extracted with AcOEt. The extract was washed with brine, dried and concentrated to afford **11d** (12.7 g, 94%) as pale brown crystals. Recrystallization from AcOEt–iso-Pr_2O gave pale brown prisms. mp: 97.5—98.5 °C. $[\alpha]_D^{20}$ −122.4° (c=0.1, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, d, J=6.5 Hz), 1.25—1.35 (2H, m), 1.45—1.55 (1H, m), 1.65—1.75 (2H, m), 2.60—2.70 (2H, m), 3.20—3.30 (2H, m), 3.66 (1H, dd, J=13.5, 5.5 Hz), 3.70—3.80 (2H, m), 4.10 (1H, t, J=9 Hz), 4.80—4.90 (1H, m), 7.04 (1H, t, J=9 Hz), 7.17 (1H, dd, J=9, 2.5 Hz), 7.44 (1H, dd, J=15, 2.5 Hz). *Anal*. Calcd for $C_{16}H_{20}FN_5O_2$: C, 57.65; H, 6.05; N, 21.01. Found: C, 57.69; H, 6.21; N, 20.90.

Compounds **11a**—**h** and **11k**—**l** were respectively prepared from the corresponding **10** in a similar manner.

(*R*)-5-Azidomethyl-3-[3-fluoro-4-(1-oxo-4-thiomorpholinyl)phenyl]oxazolidine-2-one (11i) To a solution of sodium periodate (5.33 g, 24.9 mmol) in H_2O (56 ml), a mixture of (*R*)-5-azidomethyl-3-[3-fluoro-4-(4-thiomorpholinyl)phenyl]oxazoli–dine-2-one[9] (8.00 g, 23.7 mmol) in MeOH : CH_3CN=1 : 1 (160 ml) was added at room temperature. The reaction mixture was stirred at the same temperature for 17 h, then evaporated and extracted with 1,2-dichloroethane. The extract was dried and concentrated to afford **11i** (7.98 g, 95%) as pale brown crystals. Recrystallization from iso-PrOH gave colorless prisms. mp: 123.5—125 °C. $[\alpha]_D^{20}$ −114.1° (c=0.1, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 2.84 (2H, dt, J=13.5, 2.5 Hz), 3.02 (2H, td, J=13.5, 3 Hz), 3.15—3.25 (2H, m), 3.55 (2H, t, J=13.5 Hz), 3.67 (1H, dd, J=13.5, 5.5 Hz), 3.70—3.80 (2H, m), 4.12 (1H, t, J=9 Hz), 4.80—4.90 (1H, m), 7.15—7.25 (2H, m), 7.50 (1H, dd, J=15.5, 2 Hz). *Anal*. Calcd for $C_{14}H_{16}FN_5O_3S$: C, 47.58; H, 4.56; N, 19.82. Found: C, 47.58; H, 4.56; N, 19.69.

(*R*)-5-Azidomethyl-3-[4-(1,1-dioxo-4-thiomorpholinyl)-3-fluorophenyl]-oxazolidine-2-one (11j) To a suspension of (*R*)-5-azidomethyl-3-[3-flu-

oro-4-(4-thiomorpholinyl)phenyl]oxazolidine-2-one[9] (5.00 g, 14.8 mmol) in H_2O : acetone=1 : 4 (100 ml), 50% methyl morpholine *N*-oxide solution (10.0 ml, 440 mmol) and osmium tetroxide (3.77 g, 14.8 mmol) were added at room temperature. The reaction mixture was stirred at the same temperature for 10 min, then extracted with 1,2-dichloroethane, and the extract was washed with saturated sodium hydrosulfite solution, dried and concentrated to afford **11j** (4.71 g, 86%) as pale brown crystals. Recrystallization from acetone gave pale brown prisms. mp: 146—148 °C. $[\alpha]_D^{20}$ −108.8° (*c*=0.1, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 3.23 (4H, t, *J*=5.5 Hz), 3.48 (4H, t, *J*=5.5 Hz), 3.67 (1H, dd, *J*=13.5, 5.5 Hz), 3.70—3.80 (2H, m), 4.12 (1H, t, *J*=9 Hz), 4.80—4.90 (1H, m), 7.15—7.25 (2H, m), 7.50 (1H, dd, *J*=15, 2 Hz). *Anal*. Calcd for $C_{14}H_{16}FN_5O_4S$: C, 45.52; H, 4.37; N, 18.96. Found: C, 45.63; H, 4.32; N, 18.84.

(*S*)-5-Aminomethyl-3-[3-fluoro-4-(4-methyl-1-piperidinyl)phenyl]oxazolidine-2-one (12d) A mixture of **11d** (8.00 g, 24.0 mmol), triphenylphosphine (6.93 g, 26.4 mmol) and H_2O (4.40 ml, 240 mmol) in THF (80 ml) was heated at 40 °C for 11 h. After cooling, the reaction mixture was diluted with dilute hydrochloric acid and extracted with AcOEt. The aqueous layer was made alkaline with aqueous NaOH and extracted with 1,2-dichloroethane. The extract was washed with water, dried and concentrated to afford **12d** (6.59 g, 89%) as pale brown crystals. Recrystallization from AcOEt–iso-Pr_2O gave colorless needles. mp: 111.5—113 °C. $[\alpha]_D^{20}$ −35.9° (*c*=0.1, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, d, *J*=6 Hz), 1.25—1.35 (2H, m), 1.40—1.55 (1H, m), 1.51 (2H, br s), 1.65—1.75 (2H, m), 2.55—2.70 (2H, m), 2.79 (1H, dd, *J*=13.5, 5 Hz), 2.84 (1H, dd, *J*=13.5, 5 Hz), 3.20—3.30 (2H, m), 3.80 (1H, dd, *J*=9, 6.5 Hz), 4.01 (1H, t, *J*=9 Hz), 4.50—4.60 (1H, m), 7.03 (1H, t, *J*=9.5 Hz), 7.17 (1H, dd, *J*=9.5, 2.5 Hz), 7.45 (1H, dd, *J*=15.5, 2.5 Hz). *Anal*. Calcd for $C_{16}H_{22}FN_3O_2$: C, 62.52; H, 7.21; N, 13.67. Found: C, 62.43; H, 7.43; N, 13.59.

Compounds **12** were respectively prepared from the corresponding **11** in a similar manner.

(*R*)-[[3-[3-Fluoro-4-(4-methyl-1-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]isothiocyanate (13d) A mixture of **12d** (2.00 g, 6.51 mmol), carbon disulfide (0.80 ml, 13.0 mmol) and Et_3N (0.91 ml, 6.51 mmol) in THF (20 ml) was stirred at 0 °C for 4 h. Then ethyl chloroformate (0.63 ml, 6.51 mmol) was added dropwise to the reaction mixture under ice cooling, followed by stirring at the same temperature for 1 h. The reaction mixture was washed with water and extracted with AcOEt. The extract was washed with brine, dried and concentrated. The residue was purified by column chromatography [SiO_2, *n*-Heptane–AcOEt (3 : 1)] to give **13d** (1.54 g, 68%) as colorless crystals. Recrystallization from AcOEt–iso-Pr_2O gave colorless needles. mp: 133.5—134.5 °C. $[\alpha]_D^{20}$ −153.5° (*c*=0.1, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, d, *J*=6.5 Hz), 1.25—1.35 (2H, m), 1.45—1.55 (1H, m), 1.65—1.75 (2H, m), 2.60—2.70 (2H, m), 3.20—3.30 (2H, m), 3.77 (1H, dd, *J*=9, 6 Hz), 4.02 (1H, dd, *J*=15.5, 5 Hz), 4.10 (1H, dd, *J*=15.5, 3 Hz), 4.17 (1H, t, *J*=9 Hz), 4.90—5.00 (1H, m), 7.05 (1H, t, *J*=9 Hz), 7.17 (1H, dd, *J*=9, 2.5 Hz), 7.43 (1H, dd, *J*=14.5, 2.5 Hz). *Anal*. Calcd for $C_{17}H_{20}FN_3O_2S$: C, 58.43; H, 5.77; N, 12.03. Found: C, 58.39; H, 5.67; N, 11.95.

Compounds **13** were prepared from the corresponding **12** in a similar manner.

(*S*)-*N*′-Benzoyl-*N*-[[3-[3-fluoro-4-(1-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (14b) A mixture of **12b** (0.66 g, 2.35 mmol) and benzoylisothiocyanate (0.36 ml, 2.68 mmol) in acetone (13 ml) was stirred at room temperature for 5 h. The reaction mixture was concentrated to afford **14b** (0.86 g 83%) as pale brown crystals. Recrystallization from CH_3CN gave pale brown crystals. mp: 202.5—203.5 °C. $[\alpha]_D^{20}$ −36.0° (*c*=0.1, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 1.86—1.92 (4H, m), 3.24—3.30 (4H, m), 3.84 (1H, dd, *J*=9, 6 Hz), 4.01—4.11 (2H, m), 4.14 (1H, t, *J*=9 Hz), 5.07—5.14 (1H, m), 6.74 (1H, t, *J*=8.5 Hz), 7.10 (1H, dd, *J*=8.5, 2.5 Hz), 7.37 (1H, dd, *J*=16, 2.5 Hz), 7.51 (2H, t, *J*=8 Hz), 7.64 (1H, td, *J*=8, 1.0 Hz), 7.93 (2H, dd, *J*=8, 1 Hz), 11.1 (1H, t, *J*=5.5 Hz), 11.3 (1H, br s). *Anal*. Calcd for $C_{22}H_{23}FN_4O_3S$: C, 59.71; H, 5.24; N, 12.66. Found: C, 59.70; H, 5.27; N, 12.71.

Compound **14c** was prepared from the corresponding **13c** in a similar manner.

(*S*)-*N*-[[3-[3-Fluoro-4-(1-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]thiourea (4b) A mixture of **14b** (0.65 g, 1.47 mmol), MeOH (10 ml) and 2 N NaOH solution (0.47 ml) was stirred at 50 °C for 3 h. After cooling, the mixture was extracted with dichloromethane. The extract was dried and concentrated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2–MeOH (50 : 1)] to afford **4b** (0.25 g, 50%) as pale brown crystals. The physicochemical data are listed in Tables 3 and 4.

Compound **4c** was prepared from the corresponding **14c** in a similar manner. The physicochemical data are listed in Tables 3 and 4.

(*S*)-*N*-[[3-[3-Fluoro-4-(4-methyl-1-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (4d) A mixture of **13d** (0.70 g, 2.00 mmol) and 18% ammonia in MeOH solution (7 ml) in MeOH (7 ml) was stirred at 0 °C

Table 3. Physical and Analytical Data for Compounds **4**

No.	Yield (%)[a]	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found)			$[\alpha]_D^{20}$ DMSO (*c*=0.1)
				C	H	N	
4a	12	141—143 (AcOEt)	$C_{14}H_{17}FN_4O_2S \cdot 3/4H_2O$	49.77 (50.01	5.52 5.43	16.58 16.34)	−15.4
4b	50[b]	172—172.5 (CH_3CN)	$C_{15}H_{19}FN_4O_2S$	53.24 (53.38	5.66 5.75	16.56 16.37)	−11.0
4c	32[b]	165—166 (CH_3CN)	$C_{16}H_{21}FN_4O_2S$	54.53 (54.32	6.01 6.04	15.90 15.64)	−18.0
4d	45	188—189.5 (AcOEt)	$C_{17}H_{23}FN_4O_2S$	55.72 (55.71	6.33 6.26	15.29 15.23)	−14.9
4e	48	185—187 (MeOH)	$C_{18}H_{25}FN_4O_2S$	56.82 (56.74	6.62 6.79	14.73 14.53)	−11.1
4f	68	169—170.5 (EtOH)	$C_{17}H_{23}FN_4O_3S$	53.39 (53.33	6.06 6.20	14.65 14.62)	−16.9
4g	69	168.5—170.5 (EtOH)	$C_{17}H_{23}FN_4O_2S$	55.72 (55.56	6.33 6.47	15.29 15.09)	−11.0
4h	61	194.5—195 (DMF–H_2O)	$C_{15}H_{20}N_4O_2S_2$	51.11 (51.06	5.72 5.42	15.90 15.74)	−19.9
4i	80	199—199.5 (DMF–H_2O)	$C_{15}H_{19}FN_4O_3S_2$	46.62 (46.86	4.96 5.27	14.50 14.59)	−19.0
4j	50	201.5—203 (CH_3CN)	$C_{15}H_{19}FN_4O_4S_2$	44.76 (44.68	4.76 4.66	13.92 13.95)	−21.9
4k	40	204—205 (MeOH)	$C_{15}H_{19}FN_4O_3S$	50.84 (50.86	5.40 5.44	15.81 15.88)	−19.0
4l	85	223—224 (DMF–H_2O)	$C_{16}H_{22}N_4O_3S$	54.84 (54.74	6.33 6.29	15.99 15.88)	−17.0

a) Yields were calculated from the corresponding compounds **13** or **14**. *b*) Method B.

Table 4. Spectral Data for Compounds **4**

No.	^{1}H-NMR(in DMSO-d_6) δ (ppm)
4a	2.27 (2H, quint, J=7.5 Hz), 3.65—3.70 (3H, m), 3.86 (4H, td, J=7.5, 2 Hz), 4.04 (1H, t, J=9 Hz), 4.75—4.85 (1H, m), 6.54 (1H, dd, J=10.5, 8.5 Hz), 7.09 (1H, dd, J=10.5, 2.5 Hz), 7.15 (2H, br s), 7.34 (1H, dd, J=14.5, 2.5 Hz), 7.84 (1H, t, J=9 Hz)
4b	1.86—1.92 (4H, m), 3.25—3.30 (4H, m), 3.70—3.85 (3H, m), 4.05 (1H, t, J=9 Hz), 4.75—4.84 (1H, m), 6.75 (1H, t, 8.5 Hz), 7.08 (1H, dd, J=8.5, 2.5 Hz), 7.12 (2H, br s), 7.38 (1H, dd, J=16, 2.5 Hz), 7.84 (1H, t, J=5.5 Hz)
4c	1.48—1.56 (2H, m), 1.61—1.67 (4H, m), 2.93 (4H, t, J=5 Hz), 3.70—3.85 (3H, m), 4.08 (1H, t, J=9 Hz), 4.76—4.85 (1H, m), 7.04 (1H, t, J=9 Hz), 7.12 (2H, br s), 7.15 (1H, dd, J=9, 2.5 Hz), 7.44 (1H, dd, J=15, 2.5 Hz), 7.84 (1H, t, J=5.5 Hz)
4d	0.95 (3H, d, J=6 Hz), 1.20—1.35 (2H, m), 1.40—1.55 (1H, m), 1.65—1.75 (2H, m), 2.55—2.70 (2H, m), 3.20—3.30 (2H, m), 3.65—3.90 (3H, m), 4.08 (1H, t, J=9 Hz), 4.75—4.85 (1H, m), 7.04 (1H, t, J=9 Hz), 7.13 (2H, br s), 7.15 (1H, dd, J=9, 2.5 Hz), 7.43 (1H, dd, J=14.5, 2.5 Hz), 7.84 (1H, t, J=6 Hz)
4e	0.89 (3H, t, J=6.5 Hz), 1.20—1.30 (5H, m), 1.70—1.80 (2H, m), 2.55—2.65 (2H, m), 3.20—3.30 (2H, m), 3.60—3.90 (3H, m), 4.08 (1H, t, J=9 Hz), 4.75—4.85 (1H, m), 7.04 (1H, t, J=9 Hz), 7.06 (2H, br s), 7.15 (1H, dd, J=9, 2.5 Hz), 7.44 (1H, dd, J=14.5, 2.5 Hz), 7.84 (1H, t, J=5.5 Hz)
4f	1.55—1.65 (2H, m), 1.90—2.00 (2H, m), 2.74—2.81 (2H, m), 3.15—3.21 (2H, m), 3.27 (3H, s), 3.29—3.35 (1H, m), 3.70—3.85 (3H, m), 4.08 (1H, t, J=9 Hz), 4.77—4.85 (1H, m), 7.05 (1H, t, J=9 Hz), 7.14 (2H, br s), 7.15 (1H, dd, J=9, 2.5 Hz), 7.44 (1H, dd, J=14.5, 2.5 Hz), 7.84 (1H, t, J=6 Hz)
4g	1.50—1.60 (4H, m), 1.70—1.80 (4H, m), 3.25—3.35 (4H, m), 3.65—3.85 (3H, m), 4.05 (1H, t, J=9 Hz), 4.75—4.85 (1H, m), 6.92 (1H, t, J=9 Hz), 7.08 (1H, dd, J=9, 2.5 Hz), 7.12 (2H, br s), 7.36 (1H, dd, J=16, 2.5 Hz), 7.84 (1H, t, J=6 Hz)
4h	2.67 (4H, t, J=5 Hz), 3.46 (4H, t, J=5 Hz), 3.68—3.88 (3H, m), 4.06 (1H, t, J=9 Hz), 4.72—4.84 (1H, m), 6.94 (2H, dd, J=10, 3 Hz), 7.12 (2H, br s), 7.37 (2H, dd, J=10, 3 Hz), 7.85 (1H, t, J=5.5 Hz)
4i	2.80—2.90 (2H, m), 2.95—3.05 (2H, m), 3.15—3.25 (2H, m), 3.50—3.60 (2H, m), 3.75—3.85 (3H, m), 4.10 (1H, t, J=9 Hz), 4.75—4.85 (1H, m), 7.05—7.15 (4H, m), 7.50 (1H, dd, J=15, 2.5 Hz), 7.94 (1H, br s)
4j	3.23 (4H, t, J=5.5 Hz), 3.48 (4H, t, J=5.5 Hz), 3.70—3.85 (3H, m), 4.10 (1H, t, J=9 Hz), 4.80—4.85 (1H, m), 7.12 (2H, br s), 7.15—7.25 (2H, m), 7.51 (1H, dd, J=16, 2.5 Hz), 7.85 (1H, t, J=5.5 Hz)
4k	2.97 (4H, t, J=5 Hz), 3.73 (4H, t, J=5 Hz) 3.75—3.85 (3H, m), 4.08 (1H, t, J=9 Hz), 4.78—4.87 (1H, m), 7.06 (1H, t, J=9 Hz), 7.12 (2H, br s), 7.18 (1H, dd, J=9, 3 Hz), 7.48 (1H, dd, J=15, 3 Hz), 7.84 (1H, t, J=5.5 Hz)
4l	2.27 (3H, s), 2.80 (4H, t, J=5 Hz), 3.72 (4H, t, J=5 Hz), 3.75—3.85 (3H, m), 4.07 (1H, t, J=9 Hz), 4.75—4.85 (1H, m), 7.05 (1H, d, J=8.5 Hz), 7.12 (2H, br s), 7.31 (1H, dd, J=8.5, 2.5 Hz), 7.35 (1H, d, J=2.5 Hz), 7.84 (1H, br s)

Table 5. Physical and Analytical Data for Compounds **5**

No.	Yield (%)[a]	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found)			$[\alpha]_D^{20}$ DMSO (c=0.1)
				C	H	N	
5a	68	149.5—151 (MeOH)	$C_{16}H_{20}FN_3O_2S_2$	52.01 (52.03	5.46 5.41	11.37 11.32)	−23.0
5b	74	149—152 (MeOH)	$C_{17}H_{22}FN_3O_2S_2$	53.24 53.22	5.78 5.71	10.96 10.86)	−27.0
5c	68	150—151 (AcOEt)	$C_{18}H_{24}FN_3O_2S_2$	54.38 (54.23	6.09 6.02	10.57 10.50)	−28.9
5d	60	148—149 (MeOH)	$C_{19}H_{26}FN_3O_2S_2$	55.45 (55.39	6.37 6.48	10.21 10.09)	−27.9
5e	77	128—129 (AcOEt–iso-Pr_2O)	$C_{18}H_{24}FN_3O_3S_2$	52.28 (52.20	5.85 5.84	10.16 10.09)	−26.1
5f	71	137.5—138.5 (iso-PrOH)	$C_{18}H_{24}FN_3O_2S_2$	54.38 (54.25	6.09 6.34	10.57 10.46)	−24.1
5g	27	106—108 (MeOH)	$C_{16}H_{20}FN_3O_2S_3$	47.86 (48.00	5.02 4.92	10.46 10.25)	−27.9
5h	61	157.5—158.5 (AcOEt)	$C_{16}H_{21}N_3O_2S_3$	50.10 (50.16	5.52 5.55	10.96 10.77)	−27.8
5i	32	172—173 (CH_3CN)	$C_{16}H_{20}FN_3O_3S_3$	46.02 (46.38	4.83 4.94	10.06 10.41)	−34.0
5j	62	150.5—152 (EtOH)	$C_{16}H_{20}FN_3O_3S_2$	49.85 (49.75	5.23 5.19	10.90 10.86)	−25.9

a) Yields were calculated from the corresponding compounds **12**.

for 3 h. The precipitates were collected by filtration and washed with iso-Pr_2O to give **4d** (0.33 g, 45%) as colorless crystals. The physicochemical data are listed in Tables 3 and 4.

Compounds **4a** and **4e**—**l** were respectively prepared from the corresponding **13** in a similar manner. Their physicochemical data are listed in Tables 3 and 4.

***S*-Methyl (*S*)-*N*-[[3-[3-Fluoro-4-(1-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]dithiocarbamate (5a)** A mixture of **12b** (0.50 g, 1.97 mmol), carbon disulfide (0.24 ml, 3.95 mmol) and Et_3N (0.28 ml, 1.97 mmol) in THF (5 ml) was stirred at 0 °C for 7 h. Then methyl iodide (0.13 ml, 1.97 mmol) was added dropwise to the reaction mixture under ice cooling, followed by stirring at room temperature for 30 min, and the mixture was washed with water and extracted with AcOEt. The extract was washed with brine, dried and concentrated to afford **5a** (0.28 g, 68%) as pale yellow crystals. The physicochemical data are listed in Tables 5 and 6.

Compounds **5** were respectively prepared from the corresponding **12** in a similar manner. Their physicochemical data are listed in Tables 5 and 6.

***In Vitro* Studies** These studies were conducted according to the method

Table 6. Spectral Data for Compounds **5**

No.	^{1}H-NMR(in DMSO-d_6) δ (ppm)
5a	1.90—2.00 (4H, m), 2.54 (3H, s), 3.25—3.35 (4H, m), 3.77 (1H, dd, *J*=9, 6 Hz), 3.90—4.00 (2H, m), 4.09 (1H, t, *J*=9 Hz), 4.90—5.00 (1H, m), 6.75 (1H, t, *J*=9 Hz), 7.08 (1H, dd, *J*=9, 2.5 Hz), 7.35 (1H, dd, *J*=16, 2.5 Hz), 10.2 (1H, br s)
5b	1.50—1.60 (2H, m), 1.60—1.70 (4H, m), 2.55 (3H, s), 2.90—3.00 (4H, m), 3.80 (1H, dd, *J*=9, 6 Hz), 3.90—4.10 (2H, m), 4.12 (1H, t, *J*=9 Hz), 4.90—5.00 (1H, m), 7.04 (1H, t, *J*=9 Hz), 7.15 (1H, dd, *J*=9, 2.5 Hz), 7.43 (1H, dd, *J*=14.5, 2.5 Hz), 10.2 (1H, br s)
5c	0.95 (3H, d, *J*=6.5 Hz), 1.25—1.35 (2H, m), 1.40—1.55 (1H, m), 1.65—1.75 (2H, m), 2.54 (3H, s), 2.60—2.70 (2H, m), 3.20—3.30 (2H, m), 3.80 (1H, dd, *J*=9, 6.5 Hz), 3.97 (2H, t, *J*=5.5 Hz), 4.12 (1H, t, *J*=9 Hz), 4.90—5.00 (1H, m), 7.04 (1H, t, *J*=9 Hz), 7.15 (1H, dd, *J*=9, 2.5 Hz), 7.43 (1H, dd, *J*=15.5, 2.5 Hz), 10.2 (1H, t, *J*=5 Hz)
5d	0.89 (3H, t, *J*=7.5 Hz), 1.20—1.35 (5H, m), 1.74 (2H, d, *J*=10 Hz), 2.54 (3H, s), 2.61 (2H, t, *J*=11.5 Hz), 3.29 (2H, d, *J*=11.5 Hz), 3.80 (1H, dd, *J*=9, 5.5 Hz), 3.97 (2H, t, *J*=5.5 Hz), 4.11 (1H, t, *J*=9 Hz), 4.90—5.00 (1H, m), 7.04 (1H, t, *J*=9 Hz), 7.15 (1H, dd, *J*=9, 2.5 Hz), 7.42 (1H, dd, *J*=15, 2.5 Hz), 10.2 (1H, br s)
5e	1.55—1.65 (2H, m), 1.90—2.00 (2H, m), 2.54 (3H, s), 2.74—2.82 (2H, m), 3.15—3.23 (2H, m), 3.27 (3H, s), 3.29—3.36 (1H, m), 3.80 (1H, dd, *J*=9, 6 Hz), 3.97 (2H, t, *J*=6 Hz), 4.12 (1H, t, *J*=9 Hz), 4.90—4.98 (1H, m), 7.06 (1H, t, *J*=9 Hz), 7.15 (1H, dd, *J*=9, 2.5 Hz), 7.43 (1H, dd, *J*=15, 2.5 Hz), 10.2 (1H, br s)
5f	1.50—1.60 (4H, m), 1.70—1.80 (4H, m), 2.54 (3H, s), 3.25—3.35 (4H, m), 3.78 (1H, dd, *J*=9, 6.5 Hz), 3.97 (2H, t, *J*=5.5 Hz), 4.09 (1H, t, *J*=9 Hz), 4.85—4.95 (1H, m), 6.92 (1H, t, *J*=9 Hz), 7.09 (1H, dd, *J*=9, 2.5 Hz), 7.36 (1H, dd, *J*=16, 2.5 Hz), 10.2 (1H, br s)
5g	2.54 (3H, s), 2.70—2.80 (4H, m), 3.20—3.25 (4H, m), 3.81 (1H, dd, *J*=9, 6 Hz), 3.98 (2H, t, *J*=5.5 Hz), 4.12 (1H, t, *J*=9 Hz), 4.90—5.00 (1H, m), 7.09 (1H, t, *J*=9 Hz), 7.17 (1H, dd, *J*=9, 2 Hz), 7.45(1H, dd, *J*=14.5, 2 Hz), 10.2 (1H, br s)
5h	2.55 (3H, s), 2.67 (4H, t, *J*=5 Hz), 3.47 (4H, t, *J*=5 Hz), 3.79 (1H, dd, *J*=9, 6 Hz), 3.98 (2H, t, *J*=5 Hz), 4.10 (1H, t, *J*=9 Hz), 4.85—4.95 (1H, m), 6.95 (2H, d, *J*=9 Hz), 7.36 (2H, d, *J*=9 Hz), 10.2 (1H, br s)
5i	2.55 (3H, s), 2.80—2.90 (2H, m), 2.95—3.05 (2H, m), 3.15—3.25 (2H, m), 3.70—3.80 (2H, m), 3.82 (1H, dd, *J*=9, 6.5 Hz), 3.98 (2H, t, *J*=5.5 Hz), 4.13 (1H, t, *J*=9 Hz), 4.90—5.00 (1H, m), 7.15—7.25 (2H, m), 7.48 (1H, dd, *J*=14.5, 2.5 Hz), 10.2 (1H, br s)
5j	2.54 (3H, s), 2.97 (4H, t, *J*=5 Hz), 3.74 (4H, t, *J*=5 Hz), 3.81 (1H, dd, *J*=9, 6.5 Hz), 3.98 (2H, t, *J*=5.5 Hz), 4.13 (1H, t, *J*=9 Hz), 4.91—4.97 (1H, m), 7.06 (1H, t, *J*=9 Hz), 7.18 (1H, dd, *J*=9, 2.5 Hz), 7.46 (1H, dd, *J*=15, 2.5 Hz), 10.2 (1H, br s)

of the Japan Society of Chemotherapy.[10] The MICs (μg/ml) were determined by an agar dilution method with Muller–Hinton agar (MHA, Difco Laboratories, Detroit, Mich). Bacterial suspensions for inocula were prepared by diluting overnight cultures of organisms to give a final concentration of 10^6 CFU/ml, and one loopful (5 μl) of an inoculum, corresponding to about 5×10^3 CFU per spot was inoculated on drug-containing agar plates. The plates were incubated for 18—24 h at 37 °C. The MIC was defined as the lowest drug concentration that prevented visible growth of bacteria.

References and Notes

1) Part 1: Tokuyama R., Takahashi Y., Tomita Y., Suzuki T., Yoshida T., Iwasaki N., Kado N., Okezaki E., Nagata O., *Chem. Pharm. Bull.*, **49**, 347—352 (2001).
2) Gregory W. A., Brittelli D. R., Wang C.-L. J., Wuonola M. A., McRipley R. J., Eustice D. C., Eberly V. S., Bartholomew P. T., Slee A. M., Forbes M., *J. Med. Chem.*, **32**, 1673—1681 (1989).
3) *a*) Brickner S. J., Hutchinson D. K., Barbachyn M. R., Garmon S. A., Grega K. C., Hendges S. K., Manninen P. R., Toops D. S., Ulanowicz D. A., Kilburn J. O., Glickman S., Zurenko G. E., Ford C., 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September, 1995, F 208 p. 149; *b*) Brickner S. J., Hutchinson D. K., Barbachyn M. R., Manninen P. R., Ulanowicz D. A., Garmon S. A., Grega K. C., Hendges S. K., Toops D. S., Ford C. W., Zurenko G. E., *J. Med. Chem.*, **39**, 673—679 (1996).
4) Gregory W. A., Brittelli D. R., Wang C.-L. J., Kezar H. S. III, Carlson R. K., Park C-H., Corless P. F., Milller S. J., Rajagopalan P., Wuonola M. A., McRipley R. J., Eberly V. S., Slee A. M., Forbes M., *J. Med. Chem.*, **33**, 2569—2578 (1990).
5) Park C.-H., Brittelli D. R., Wang C.-L. J., Marsh F. D., Gregory W. A., Wuonola M. A., McRipley R. J., Eberly V. S., Slee A. M., Forbes M., *J. Med. Chem.*, **35**, 1156—1165 (1992); Brickner S. J., *Current Pharmaceutical Design*, **2**, 175—194, (1996).
6) Calculated log *P*, πa and πb values were measured by ACD/Labs log *P* calculated., ver. 3.0 (Advanced Chemistry Development, Inc.).
7) Some 5-thiocarbonyl oxazolidinones were revealed at the same time that we synthesized them: Hester J. B., Nidy E. G., Perricone S. C., Poel T. J., World Intellectual Property Organization 9854161 (1998) [*Chem. Abstr.*, **130**, 38373*q* (1999)].
8) Pae A. N., Kim S. Y., Kim H. Y., Joo H. J., Cho Y. S., Choi K. II, Choi J. H., Koh H. Y., *Bioorganic & Medicinal Chemistry Letters*, **9**, 2685—2690 (1999).
9) Barbachyn M. R., Brickner S. J., Hutchinson D. K., World Intellectual Property Organization 9507271 (1995) [*Chem. Abstr.*, **123**, 256742*f* (1995)]; Barbachyn M. R., Hutchinson D. K., Brickner S. J., Cynamon M. H., Kilburn J. O., Klemens S. P., Glickman S. E., Grega K. C., Hendges S. K., Toops D. S., Ford C. W., Zurenko G. E., *J. Med. Chem.*, **39**, 680—685 (1996).
10) Goto S., Jo K., Kawakita T., Kosakai N., Mitsuhashi S., Nishino T., Ohsawa N., Tanami H., *Chemotherapy*, **29**, 76—79 (1981).