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Original article

Synthesis and *in vitro*/*in vivo* antibacterial activity of oxazolidinones having thiocarbamate at C-5 on the A-ring and an amide- or urea-substituted [1,2,5]triazepane or [1,2,5]oxadiazepane as the C-ring

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ABSTRACT

Oxazolidinones bearing a seven-membered [1,2,5]triazepane or [1,2,5]oxadiazepane heterocycle substituted with an amide or urea functionality as the C-ring and having a [1,2,3]triazole, a thiocarbamate, an isoxazole-3-ylamino, or a thioacetamide C-5 side chain unit on the A-ring instead of the typical acetamide were synthesized and their *in vitro* antibacterial activities towards various pathogens were evaluated. Several derivatives exhibited potent *in vitro* antibacterial activity toward not only Gram-positive, but also Gram-negative and linezolid-resistant pathogens. The *in vivo* therapeutic effects of amide **11a** and ureas **16e**, **17a** were 2- to 3-fold greater than that of linezolid in a systemic mouse infection model treated by intravenous administration. Furthermore, compounds **11a** and **17a** showed lower monoamine oxidase (MAO)-inhibitory activity than our previously reported potent oxazolidinone antibacterials **3a** and **3b**.

1. Introduction

Linezolid (**1**) was the first oxazolidinone antibiotic to be approved by the US Food and Drug Administration (FDA) in 2000, and has been used for the treatment of serious infections caused by Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE) [1,2]. However, linezolid-resistant bacteria have already been reported [3–5], and although this problem is not yet serious, it may become serious in the near future. Although other oxazolidinone antibiotic candidates have been reported, none of them has yet been approved. However, tedizolid **2** (formerly called torezolid phosphate; Fig. 1) developed by Trius Therapeutics recently successfully completed a Phase III clinical trial [6,7]. Thus, there is great interest in new types of oxazolidinone antibiotics [8]. We have recently synthesized oxazolidinones in which the C-ring (see below) consists of a seven-membered heterocycle, [1,2,5]triazepane or [1,2,5]oxadiazepane, which can be considered analogous to the conventional pharmaceutical structural units piperazine and morpholine [9]. We have also investigated the effects of various side chain units at the 5-position of the oxazolidinone ring in eperezolid-type antibacterials, and found that the analogs **3a** and **3b** bearing a thiocarbamate-type side chain unit at the C-5 position in the A-ring showed potent *in vitro* and *in vivo* antibacterial efficacy (Fig. 2) [10]. However, derivatives other than the hydroxyacetamide were not explored, and analogs with other functional groups at the nitrogen atom of the seven-membered heterocyclic C-ring were not examined. Therefore, in the present work, we focused on the synthesis of a series of oxazolidinone analogs containing our seven-membered heterocycles substituted with an amide or urea functionality as the C-ring. Although **3a** and **3b** have a thiocarbamate side chain unit in the A-ring, we considered that a change of the C-ring functionality might alter the preferred C-5 side chain unit in the A-ring. Therefore, we synthesized and evaluated compounds containing other previously examined side chain units, [1,2,3]triazole, isoxazol-3-ylamino, and thioacetamide, as well as thiocarbamate on the A-ring. Evaluation of *in vitro* and *in vivo* antibacterial activities indicated that several of the new compounds are more potent than linezolid (**1**). It was confirmed that a thiocarbamate side chain unit at C-5 of the A-ring

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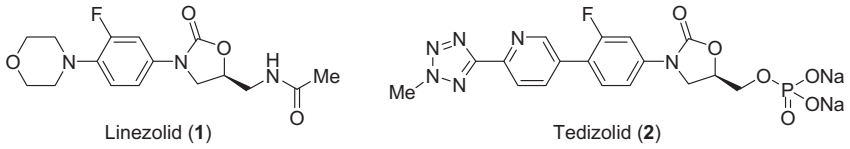


Fig. 1. Linezolid (**1**) and Tedizolid (**2**).

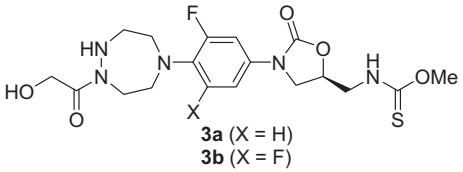


Fig. 2. Potent oxazolidinone analogs, **3a** and **3b**, having [1,2,5]triazepane bearing a hydroxyacetyl group as the C-ring unit.

is optimum for potent *in vitro* and *in vivo* antibacterial activities in these compounds. Initial safety evaluation showed that **11a** and **17a** had low inhibitory activity towards four cytochrome P450 (CYP) isoforms, like our previously reported compounds **3a** and **3b**, while their inhibitory activity towards monoamine oxidase (MAO)-A,B was markedly lower than that of **3a** and **3b**.

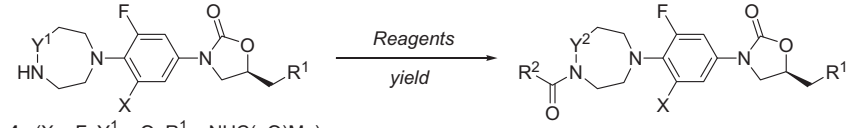
2. Results and discussion

2.1. Chemistry

The oxazolidinone family of antibiotics is composed of an A-ring (oxazolidinone), B-ring (phenyl), and C-ring (an appropriate heterocycle, such as morpholine or piperazine), with a C-5 side chain unit in the A-ring substructure [11]. Here, we focused on seven-membered [1,2,5]triazepane or [1,2,5]oxadiazepane heterocycles modified with amide or urea functionality as the C-ring unit. We previously examined the hydroxyacetamide functionality, and in this work we examined three other types of amide functional groups. The oxazolidinone intermediates **4**–**8** were prepared in accordance with our previous report [10]. Since the choice of C-5 side chain unit in the A-ring strongly influences *in vitro* antibacterial activity, we mainly adopted thiocarbamate [12], thioacetamide [13], [1,2,3]triazole [14] and isoxazol-3-ylamino [15] units, in contrast to typical acetamide [16]. For the amide functionality on the seven-membered heterocycle, we chose orthodox formamide **9**, acetamide **10**, and difluoroacetamide **11**. As shown in Table 1, formamide **9** and difluoroacetamide **11** were obtained by deprotection of the *tert*-butoxycarbonyl (Boc) group in appropriate intermediates under acidic conditions, followed by condensation with the appropriate carboxylic acid using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)/1-hydroxybenzotriazole (HOBt). Acetamide **10** was also obtained by Ac_2O/pyridine treatment, followed by deprotection.

Furthermore, oxazolidinones (**12**–**15**) bearing a fused-type C-ring were also synthesized in the [1,2,5]triazepane heterocycle series, as shown in Table 2. As simple structures with no substituent on the terminal pyridine ring, we synthesized compound

Table 1
Synthesis of oxazolidinone analogs bearing amide functionalities **9**–**11**.

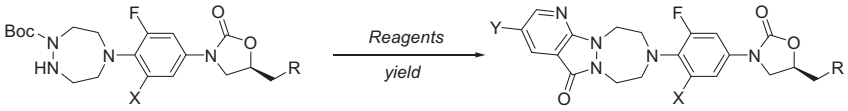


4c (X = F, Y^1 = O, R^1 = NHC(=O)Me)
5c (X = F, Y^1 = O, R^1 = NHC(=S)Me)
6a (X = H, Y^1 = NBoc, R^1 = NHC(=S)OMe)
6b (X = F, Y^1 = NBoc, R^1 = NHC(=S)OMe)
7b (X = F, Y^1 = NBoc, R^1 = [1,2,3]triazol-1-yl)
8b[a] (X = F, Y^1 = NBoc)

Substrate[b]	Reagents[c]	X	Y^2	R^1	R^2	Product	Yield (%)
6a	a	H	NH	NHC(=S)OMe	H	**9a**	53
7b	a	F	NH	[1,2,3]Triazol-1-yl	H	**9b**	55
8b[a]	a	F	NH	Isoxazol-3-ylamino	H	**9c**	31
4c	b	F	O	NHC(=O)Me	Me	**10a**	96
6a	b	H	NH	NHC(=S)OMe	Me	**10b**	71
5c	b	F	O	NHC(=S)Me	Me	**10c**	98
6b	b	F	NH	NHC(=S)OMe	Me	**10d**	75
7b	b	F	NH	[1,2,3]Triazol-1-yl	Me	**10e**	85
6a	c	H	NH	NHC(=S)OMe	CHF_2	**11a**	58
7b	c	F	NH	[1,2,3]Triazol-1-yl	CHF_2	**11b**	45
8b[a]	c	F	NH	Isoxazol-3-ylamino	CHF_2	**11c**	30

[a] R^1 of compound **8b** = *tert*-butoxycarbonyl-isoxazol-3-yl-amino.
[b] Substrates **4c**, **5c**, **6a**, **6b**, **7b**, and **8b** are known compounds, see Ref. [10].
[c] a) i) *conc*. HCl, 1,4-dioxane; ii) EDCI, HOBt, *i*-Pr_2NEt, HCO_2H, DMF; b) i) Ac_2O, pyridine, CH_2Cl_2; ii) *conc*. HCl, 1,4-dioxane (except for synthesis of **10a** and **10c**); iii) EDCI, HOBt, *i*-Pr_2NEt, CH_3CO_2H, DMF; c) i) *conc*. HCl, 1,4-dioxane; ii) EDCI, HOBt, *i*-Pr_2NEt, CHF_2CO_2H, DMF.

Table 2
Synthesis of oxazolidinone analogs bearing fused ring structure **12**–**15**.



4a (X = H, R = NHC(=O)Me)
4b (X = F, R = NHC(=O)Me)
6a (X = H, R = NHC(=S)OMe)
6b (X = F, R = NHC(=S)OMe)
7a (X = H, R = [1,2,3]triazol-1-yl)
7b (X = F, R = [1,2,3]triazol-1-yl)

Substrate[a]	Reagents[b]	X	R	Y	Product	Yield (%)
4a	a	H	NHC(=O)Me	H	**12a**	87
4b	a	F	NHC(=O)Me	H	**12b**	100
6a	a	H	NHC(=S)OMe	H	**12c**	90
6b	a	F	NHC(=S)OMe	H	**12d**	88
7a	a	H	[1,2,3]Triazol-1-yl	H	**12e**	84
7b	a	F	[1,2,3]Triazol-1-yl	H	**12f**	90
4b	b	F	NHC(=O)Me	Cl	**13**	76
4b	c	F	NHC(=O)Me	Br	**14**	85
4b	d	F	NHC(=O)Me	NH_2	**15a**	45
7b	d	F	[1,2,3]Triazol-1-yl	NH_2	**15b**	48

[a] Substrates **4a**, **4b**, **6a**, **6b**, **7a**, and **7b** are known compounds, see Ref. [10].
[b] a) i) 2-Chloronicotinoyl chloride, pyridine, CH_2Cl_2; ii) CF_3CO_2H, CH_2Cl_2; b) i) 2,5-dichloronicotinoyl chloride, pyridine, CH_2Cl_2; ii) CF_3CO_2H, CH_2Cl_2; c) i) 5-bromo-2-chloronicotinoyl chloride, pyridine, CH_2Cl_2; ii) CF_3CO_2H, CH_2Cl_2; d) i) *conc.* HCl, 1,4-dioxane; ii) EDCI, HOBt, *i*-Pr_2NEt, 5-*t*-butoxycarbonylamino-2-chloronicotinic acid, DMF; iii) CF_3CO_2H, CH_2Cl_2.

12 with six kinds of combinations of B ring (monofluorophenyl or difluorophenyl) and C-5 side chain unit in the A-ring (acetamide, thiocarbamate, and [1,2,3]triazole). Furthermore, in order to examine the effect of substitution on the pyridine ring, we chose Cl (**13**), Br (**14**), and NH_2 (**15**) as substituents. Compounds **12**–**15** were synthesized via conversion of the appropriate intermediate to 2-chloronicotinic acid amide, followed by acid treatment.

Then, we examined the synthesis of oxazolidinones **16**–**19** bearing a sterically simple urea functionality on the seven-membered heterocycle (Table 3). In order to evaluate antibacterial potential, the orthodox urea **16** was modified with four kinds of C-5 side chain unit of the A-ring in place of conventional acetamide. The analogs **17**–**19** bearing the other types of urea functionality on the seven-membered heterocycle were synthesized mainly with a thiocarbamate side chain in the A-ring. Ureas **16**–**19** were obtained by triphosgene/Et_3N treatment of the appropriate intermediate, followed by deprotection of the Boc group.

On the other hand, pyridine- and benzene-insertion types of oxazolidinone antibacterials have recently been synthesized and evaluated [6,17]. Because compound **2**, which is currently undergoing clinical trial, resembles these oxazolidinones, we decided to synthesize similar analogs. As the terminal hetero ring substructure (D-ring), we focused on the [1,2,5]oxadiazepane ring, and as the C-5 side chain of the A-ring, we selected both acetamide and [1,2,3]triazole. As shown in Scheme 1, commercially available 5-bromo-2-hydroxypyridine (**20**) was converted to triflate **21**, followed by treatment with [1,2,5]oxadiazepane-2-carboxylic acid *tert*-butyl ester [18] in hexamethylphosphoric triamide to afford the seven-membered heterocycle **22** in good yield. Suzuki–Miyaura coupling reaction of the known boronic acid ester [19,20] with compound **22** afforded the oxazolidinone intermediates **23a** and **23b**, respectively. Deprotection of the Boc group in **23** gave amine **24**, which was converted to the hydroxyacetamide compounds **25a** and **25b** in two steps using standard techniques.

2.2. Pharmacology

All the new synthesized oxazolidinones bearing seven-membered heterocycles, **9**–**19** and **24** and **25**, were evaluated for *in vitro* antibacterial activity against Gram-positive (*S. aureus*, *E. faecalis*, *Enterococcus faecium*, and *Streptococcus pneumoniae*) and Gram-negative (*Moraxella catarrhalis* and *Haemophilus influenzae*) pathogens using the conventional agar-dilution method. Linezolid-resistant *S. aureus* NRS271 (a clinical isolate) was also used. As shown in Table 4, the oxazolidinones bearing a formamide functionality on the seven-membered heterocycle **9** generally showed 4- to 16-fold more potent antibacterial activity than linezolid (**1**). Thiocarbamate **9a** exhibited clinically appropriate minimum inhibitory concentration (MIC) values (2–4 μg/mL) against Gram-negative strains, like the previously reported potent analogs **3a** and **3b**. The analog **10a** with acetamide functionality on the seven-membered heterocycle showed *in vitro* activities slightly weaker than those of the above formamide, but similar to those of linezolid, even with the orthodox acetamide-type C-5 side chain in the A-ring. The difluoroacetamide derivatives **11** also exhibited good antibacterial activity. In particular, compound **11a** bearing a thiocarbamate-type C-5 side chain in the A-ring showed the strongest antibacterial activity (0.125 μg/mL) against *S. aureus* SR20549, as well as sufficient *in vitro* activity toward Gram-negative strains, and its antibacterial activity pattern was similar to those of **3a** and **3b**. The *in vitro* antibacterial activities of analogs **12** bearing a fused ring as a C-ring substructure were investigated with various combinations of B-ring unit and C-5 side chain in the A-ring. Though the analog **12a**, which has the same structure as **1**, except for the C-ring scaffold, exhibited nearly the same levels of *in vitro* antibacterial activity as **1**, compound **12b**, in which the B-ring monofluorophenyl was replaced with difluorophenyl, showed 2-fold greater *in vitro* antibacterial activity compared to **12a**. The analogs **12c** and **12d** bearing thiocarbamate as the C-5 side chain

Table 3
Synthesis of oxazolidinone analogs bearing urea functionalities **16**–**19**.

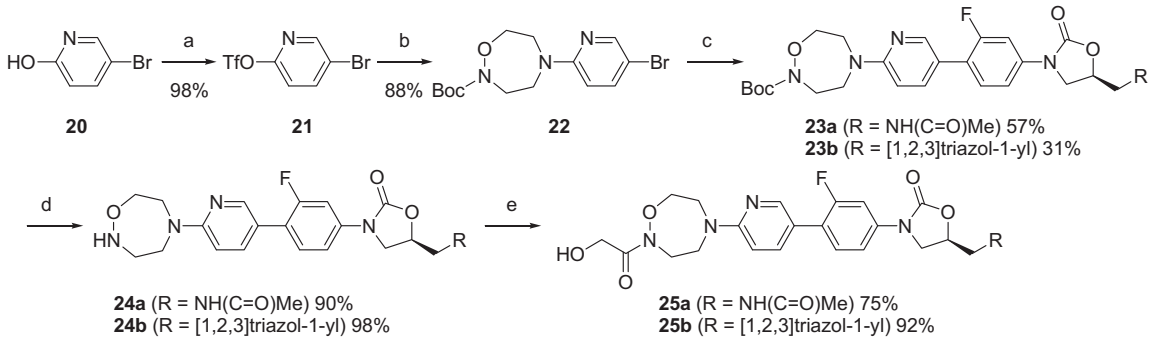
16-19

5a (X = H, Y^1 = NBoc, R^1 = NHC(=S)Me)
5b (X = F, Y^1 = NBoc, R^1 = NHC(=S)Me)
5c (X = F, Y^1 = O, R^1 = NHC(=S)Me)
6a (X = H, Y^1 = NBoc, R^1 = NHC(=S)OMe)
6b (X = F, Y^1 = NBoc, R^1 = NHC(=S)OMe)
6c (X = F, Y^1 = O, R^1 = NHC(=S)OMe)
7b (X = F, Y^1 = NBoc, R^1 = [1,2,3]triazol-1-yl)
7c (X = F, Y^1 = O, R^1 = [1,2,3]triazol-1-yl)
8b[a] (X = F, Y^1 = NBoc)

Substrate[b]	Reagents[c]	X	Y^2	R^1	R^2	Product	Yield (%)
5a	a	H	NH	NH(C=S)Me	H	**16a**	37
5b	a	F	NH	NH(C=S)Me	H	**16b**	66
5c	a	F	O	NH(C=S)Me	H	**16c**	99
6a	a	H	NH	NH(C=S)OMe	H	**16d**	89
6b	a	F	NH	NH(C=S)OMe	H	**16e**	83
6c	a	F	O	NH(C=S)OMe	H	**16f**	89
7b	a	F	NH	[1,2,3]Triazol-1-yl	H	**16g**	70
7c	a	F	O	[1,2,3]Triazol-1-yl	H	**16h**	94
8b[a]	a	F	NH	Isoxazol-3-ylamino	H	**16i**	94
6a	b	H	NH	NH(C=S)OMe	Me	**17a**	81
6b	b	F	NH	NH(C=S)OMe	Me	**17b**	83
6c	b	F	O	NH(C=S)OMe	Me	**17c**	99
7c	b	F	O	[1,2,3]Triazol-1-yl	Me	**17d**	62
6a	c	H	NH	NH(C=S)OMe	OH	**18a**	86
7b	c	F	NH	[1,2,3]Triazol-1-yl	OH	**18b**	69
7c	c	F	O	[1,2,3]Triazol-1-yl	OH	**18c**	79
6a	d	H	NH	NH(C=S)OMe	OMe	**19a**	80
6b	d	F	NH	NH(C=S)OMe	OMe	**19b**	70
6c	d	F	O	NH(C=S)OMe	OMe	**19c**	92

[a] R^1 of compound **8b** = *tert*-butoxycarbonyl-isoxazol-3-yl-amino.
[b] Substrates **5a**, **5b**, **5c**, **6a**, **6b**, **6c**, **7b**, **7c**, and **8b** are known compounds, see Ref. [10].
[c] a) i) triphosgene, Et_3N, THF, then NH_4OH; ii) *conc*. HCl, 1,4-dioxane (except for synthesis of **16c**, **16f**, and **16h**); b) i) triphosgene, Et_3N, THF, then CH_3NH_2; ii) *conc*. HCl, 1,4-dioxane (except for synthesis of **17c** and **17d**); c) i) triphosgene, Et_3N, THF, then hydroxylamine hydrochloride; ii) *conc*. HCl, 1,4-dioxane (except for synthesis of **18c**); d) i) triphosgene, Et_3N, THF, then *O*-methylhydroxylamine hydrochloride; ii) *conc*. HCl, 1,4-dioxane (except for synthesis of **19c**).

unit in the A-ring exhibited superior antibacterial activity against Gram-positive strains, and were also active against the linezolid-resistant strain, like **3a** and **3b**. The antibacterial activities of the analogs **12e** and **12f** bearing a [1,2,3]triazole side chain unit were similar to those of acetamides **12a** and **12b**, respectively. On the other hand, analogs **13**–**15** with a halogen or amino substituent on the terminal pyridine ring did not show enhanced antibacterial activity compared to non-substituted **12b** or **12f**. The most basic compounds **16** bearing an urea functionality on the C-ring were also investigated with various structural combinations,



20 **21** **22**
23a (R = NH(C=O)Me) 57%
23b (R = [1,2,3]triazol-1-yl) 31%
24a (R = NH(C=O)Me) 90%
24b (R = [1,2,3]triazol-1-yl) 98%
25a (R = NH(C=O)Me) 75%
25b (R = [1,2,3]triazol-1-yl) 92%

Scheme 1. Synthesis of pyridine insertion-type oxazolidinone analogs **24** and **25**. Reagents: (a) Tf_2O, pyridine; (b) [1,2,5]oxadiazepane-2-carboxylic acid *tert*-butyl ester, *i*-Pr_2NEt, HMPA; (c) (*S*)-*N*-((3-(3-fluoro-4-(3,3,4,4-tetramethylborolan-1-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (for **23a**) or (5*R*)-3-(3-fluoro-4-(3,3,4,4-tetramethylborolan-1-yl) phenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (for **23b**), $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane, H_2O; (d) *conc*. HCl, 1,4-dioxane; (e) i) acetoxyacetyl chloride, pyridine, CH_2Cl_2; ii) K_2CO_3, MeOH.

Table 4
In vitro antibacterial activities of amide and fused-ring analogs **9**–**15**.

Compound	Minimum inhibitory concentration (μg/mL)							
	S. a.[a]	*S. a.*[b]	*S. a.*[c]	*E. f.*[d]	*E. f.*[e]	*M. c.*[f]	*S. p.*[g]	*H. i.*[h]
1	2	2	32	4	2	8	1	16
3a[i]	0.25	0.25	2	0.5	0.25	2	0.125	4
3b[i]	0.25	0.25	2	0.25	0.25	1	≦0.063	4
9a	0.25	0.25	4	0.25	0.25	2	0.063	4
9b	0.25	1	16	1	1	8	≦0.063	8
9c	0.5	1	16	1	1	8	0.25	16
10a	2	4	32	2	4	4	1	32
10b	0.5	1	8	0.5	0.5	4	0.063	16
10c	0.25	1	4	0.5	0.5	2	0.125	8
10d	0.5	1	4	1	0.5	2	0.125	32
10e	1	2	16	2	2	16	1	32
11a	0.125	0.5	4	0.25	0.25	2	0.063	4
11b	0.5	1	16	1	1	8	0.125	16
11c	0.5	1	8	0.5	0.5	4	0.125	16
12a	2	1	16	2	2	16	0.5	32
12b	1	0.5	8	1	1	4	0.25	16
12c	0.25	0.25	2	0.5	0.25	2	0.125	16
12d	0.25	0.25	2	0.5	0.25	1	0.125	>64
12e	2	4	64	4	4	32	1	32
12f	0.5	2	8	1	1	8	0.5	32
13	1	1	8	2	1	4	0.25	64
14	1	1	8	2	1	4	0.25	64
15a	1	0.5	8	2	2	8	0.25	32
15b	1	1	16	2	2	16	0.25	32

[a] *Staphylococcus aureus* SR20549.
[b] *Staphylococcus aureus* Smith.
[c] Linezolid-resistant *Staphylococcus aureus* NRS271.
[d] *Enterococcus faecalis* SR1004.
[e] *Enterococcus faecium* SR7940.
[f] *Moraxella catarrhalis* SR26840.
[g] *Streptococcus pneumoniae* SR26207.
[h] *Haemophilus influenzae* SR27914.
[i] See Ref. [10].

except for the acetamide side chain, which seemed unfavorable for antibacterial activity.

As shown in Table 5, analogs **16a**–**f** having thioacetamide or thiocarbamate as the C-5 side chain moiety exhibited 4- to 16-fold more potent *in vitro* antibacterial activity than **1**, and the antibacterial activity was almost equivalent to those of the potent analogs **3a** and **3b**. In particular, **16e** and **16f** showed clinically appropriate levels of antibacterial activity against Gram-negative and linezolid-resistant strains. Although derivatives **16g**–**i** with a [1,2,3]triazole or an isoxazol-3-ylamino C-5 side chain in the A-ring also showed greater antibacterial activity than **1**, they were less potent than the compounds bearing a thiocarbonyl C-5 side chain in the A-ring. The MIC values of compound **17** indicated that methyl substitution on the terminal urea functionality had little or no effect on the antibacterial activity. The analogs **18** having a hydroxamic acid-type terminal unit on the C-ring also exhibited moderate antibacterial activities, though these were slightly lower as compared to the basic **16** series. The conversion of hydroxyl group to a methoxy group slightly decreased the antibacterial activity (**18a** vs **19a**).

As shown in Table 6, the pyridine insertion-type derivatives **24a** and **24b** with [1,2,5]oxadiazepane as the D-ring exhibited 2-fold greater antibacterial activities than **1**, but without any especially noteworthy feature. The antibacterial activity of analog **25** with a hydroxyacetamide group on the seven-membered heterocycle showed no change from those of non-substituted **24a** and **24b**. Thus, we have found several potent *in vitro* active oxazolidinone analogs without complicated structural ornamentation on the C-ring unit. The present synthesis and evaluation of oxazolidinone analogs with various substituent groups on our seven-membered heterocyclic [1,2,5]triazepane or [1,2,5]oxadiazepane C-ring structure yielded the following results. Broadly speaking, there was little

Table 5
In vitro antibacterial activities of urea analogs **16**–**19**.

Compound	Minimum inhibitory concentration (μg/mL)							
	S. a.[a]	*S. a.*[b]	*S. a.*[c]	*E. f.*[d]	*E. f.*[e]	*M. c.*[f]	*S. p.*[g]	*H. i.*[h]
1	2	2	32	4	2	8	1	16
3a[i]	0.25	0.25	2	0.5	0.25	2	0.125	4
3b[i]	0.25	0.25	2	0.25	0.25	1	≦0.063	4
16a	0.25	0.25	8	0.5	0.5	4	0.063	4
16b	0.125	0.25	4	0.25	0.25	1	0.063	4
16c	0.25	0.5	4	0.25	0.5	2	0.063	8
16d	0.25	0.25	4	0.25	0.125	2	≦0.063	4
16e	0.25	0.25	2	0.5	0.125	0.5	≦0.063	16
16f	0.25	0.25	2	0.25	0.125	1	≦0.063	8
16g	1	1	32	2	4	4	0.5	16
16h	1	2	32	4	4	8	1	16
16i	0.5	1	16	1	1	8	0.125	16
17a	0.25	0.5	8	0.5	0.25	2	0.25	16
17b	0.25	0.25	2	0.25	0.25	1	≦0.063	8
17c	0.5	0.5	4	1	0.5	2	0.125	32
17d	2	8	32	4	2	16	1	32
18a	0.5	1	16	1	1	4	≦0.063	4
18b	2	4	64	8	8	8	0.5	16
18c	2	2	64	4	4	8	0.5	16
19a	1	1	16	0.5	0.5	4	0.25	16
19b	0.5	0.5	4	0.5	0.25	2	0.25	16
19c	0.5	1	8	1	0.5	2	0.125	16

[a] *Staphylococcus aureus* SR20549.
[b] *Staphylococcus aureus* Smith.
[c] Linezolid-resistant *Staphylococcus aureus* NRS271.
[d] *Enterococcus faecalis* SR1004.
[e] *Enterococcus faecium* SR7940.
[f] *Moraxella catarrhalis* SR26840.
[g] *Streptococcus pneumoniae* SR26207.
[h] *Haemophilus influenzae* SR27914.
[i] See Ref. [10].

difference between compounds containing [1,2,5]triazepane and [1,2,5]oxadiazepane structures. As for the B-ring unit, a difluorophenyl group seemed to afford higher activity than a monofluorophenyl group, and a thiocarbonyl-type C-5 side chain in the A-ring was also favorable for potent *in vitro* antibacterial activity.

As the next step, selected potent *in vitro*-active analogs were tested for *in vivo* therapeutic effect via intravenous administration in a lethal systemic mouse infection model employing *S. aureus* SR3637. The results are summarized in Table 7. The MIC values of all the selected compounds against *S. aureus* SR3637 were less than 0.5 μg/mL. Formamides **9a**, **b** and acetamide **10b** exhibited similar levels of therapeutic effect to **1**. Because the *in vivo* effects of these

Table 6
In vitro antibacterial activities of pyridine insertion-type analogs **24** and **25**.

Compound	Minimum inhibitory concentration (μg/mL)							
	S. a.[a]	*S. a.*[b]	*S. a.*[c]	*E. f.*[d]	*E. f.*[e]	*M. c.*[f]	*S. p.*[g]	*H. i.*[h]
1	2	2	32	4	2	8	1	16
3a[i]	0.25	0.25	2	0.5	0.25	2	0.125	4
3b[i]	0.25	0.25	2	0.25	0.25	1	≦0.063	4
24a	1	2	8	1	1	16	0.125	16
24b	1	2	8	2	1	8	0.25	32
25a	1	2	8	1	1	16	0.125	16
25b	1	2	8	2	1	8	0.25	32

[a] *Staphylococcus aureus* SR20549.
[b] *Staphylococcus aureus* Smith.
[c] Linezolid-resistant *Staphylococcus aureus* NRS271.
[d] *Enterococcus faecalis* SR1004.
[e] *Enterococcus faecium* SR7940.
[f] *Moraxella catarrhalis* SR26840.
[g] *Streptococcus pneumoniae* SR26207.
[h] *Haemophilus influenzae* SR27914.
[i] See Ref. [10].

Table 7
In vivo antibacterial efficacies (ED_{50}) of selected oxazolidinones in a systemic mouse infection model.

Compound	MIC (μg/mL)	Therapeutic effect ED_{50} (mg/kg)
3a[a]	0.25	0.94 (**1**: 3.26)
3b[a]	0.25	0.77 (**1**: 2.13)
9a	0.25	2.95 (**1**: 3.31)
9b	0.25	2.50 (**1**: 1.94)
10b	0.5	2.85 (**1**: 3.31)
11a	0.25	0.77 (**1**: 2.13)
12c	0.25	3.17 (**1**: 2.13)
12d	0.25	9.83 (**1**: 4.98)
16c	0.25	5.71 (**1**: 2.02)
16e	0.25	1.23 (**1**: 2.13)
17a	0.5	0.86 (**1**: 2.07)
17b	0.25	3.17 (**1**: 2.07)
19b	0.5	3.05 (**1**: 2.07)

[a] See Ref. [10].

analogs did not fully reflect the *in vitro* activities, these compounds may have non-optimal pharmacokinetic or metabolic properties. However, difluoroacetamide **11a** had a 3-fold stronger therapeutic effect than **1**. The analogs bearing fused ring structure, **12c** and **12d**, showed moderate efficacy. The urea analog **16c** showed poor *in vivo* antibacterial potential, possibly due to chemical instability of the thioamide C-5 side chain moiety. On the other hand, compound **16e**, having a more stable thiocarbamate side chain unit, showed a good *in vivo* therapeutic effect. Compound **17a** showed a superior *in vivo* antibacterial activity to **1**, although **17b**, which is structurally rather similar, showed only a weak therapeutic effect. This result may indicate that the hydrophobicity of the oxazolidinone molecule influences the pharmacokinetic profile.

Thus, among the analogs examined, **11a**, **16e**, and **17a** showed promising *in vivo* activity, comparable to that of our previously reported hydroxyacetamides **3a** and **3b**. In order to further evaluate **11a** and **17a** as candidate antibiotics from the viewpoint of safety, as we discussed previously [10], we examined their inhibitory activities towards four CYP isozymes and MAO-A and -B. The results are shown in Table 8. The thiocarbamates **11a** and **17a** had similar levels of CYP-inhibitory activity ($IC_{50} > 20$ mM for the four selected isoforms) to linezolid (**1**), **3a**, and **3b**, and this profile is considered satisfactory for this class of antibiotics. Importantly, the thiocarbamates **11a** and **17a** showed remarkably improved values of MAO-A, B inhibition index compared to **3a** and **3b**. In particular, these two compounds hardly inhibited MAO-B. Thus, compounds **11a** and **17a** appear to be superior to **3a** and **3b** in terms of their safety profile.

3. Conclusion

Oxazolidinones bearing a seven-membered heterocycle [1,2,5] triazepane or [1,2,5]oxadiazepane substituted with an amide or urea functionality as the C-ring were synthesized and their *in vitro* antibacterial activities were evaluated. Examination of compounds with various combinations of partial structures resulted in the identification of several compounds with potent *in vitro* antibacterial activities. Selected compounds were tested in an *in vivo* mouse model employing *S. aureus* SR3637, and among them, **11a**, **16e**, and **17a** showed a potent *in vivo* therapeutic effect similar to that of our previously reported potent oxazolidinone analogs **3a** and **3b**. Our results indicate that a thiocarbamate side chain unit at C-5 of the A-ring is optimum for potent *in vitro* and *in vivo* antibacterial activities, regardless of the kind of substituent at the nitrogen atom on the C-ring. Compounds **11a** and **16a** showed markedly weaker inhibitory activity toward MAO-A and -B as compared to **3a** and **3b**, while all of these compounds showed similar levels of CYP-inhibitory activity ($IC_{50} > 20$ mM) towards four selected isoforms. Therefore, **11a** and **16a** may be better drug candidates than **3a** and **3b** from the viewpoint of safety profile. Thus, we consider that our substituted seven-membered heterocycles are promising structural units to replace conventional heterocyclic units, such as piperazine or morpholine, in the search for new, highly potent oxazolidinone antibiotics.

Table 8
Values of CYP450 and MAO-A, B inhibition index of potent *in vivo* active analogs **11a** and **17a**.

Compound	CYP450 isoform, IC_{50} (μM)				MAO inhibition (%)	
	1A2	2C9	2D6	3A4	A	B
3a[a]	>20	>20	>20	>20	48.2	10.1
3b[a]	>20	>20	>20	>20	12.4	10.6
11a	>20	>20	>20	>20	9.2	0.1
17a	>20	>20	>20	>20	3.4	3.1

4. Experimental protocols

4.1. Chemistry

Melting points were determined with a Yanagimoto micro melting point apparatus (hot plate) and are uncorrected. Elemental analyses were determined by a Yanaco CHN MT-5 instrument and were within ±0.4% of the theoretical values. Low-resolution electron ionization mass spectra (EI-LRMS) and high-resolution electron ionization mass spectra (EI-HRMS) were recorded on a JEOL JMS-AX505HA. Low-resolution electrospray ionization mass spectra (ESI-LRMS) were recorded on a Waters 3100 Mass Detector. High-resolution electrospray ionization mass spectra (ESI-HRMS) were recorded on a Thermo Fisher Scientific LTQ-Orbitrap. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were measured with a Varian Mercury at 300 MHz and at 75 MHz, respectively. The chemical shifts are recorded in ppm, and coupling constants (*J*) in Hz. ^{1}H NMR and ^{13}C NMR chemical shifts were calculated on the basis of tetramethylsilane (0 ppm for ^{1}H NMR in $CDCl_3$ or CD_3OD/$CDCl_3$) and residual solvent (77 ppm for ^{13}C NMR in $CDCl_3$ or CD_3OD/$CDCl_3$, 2.49 ppm for ^{1}H NMR in DMSO-d_6, and 39.5 ppm for ^{13}C NMR in DMSO-d_6) as internal standards. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br; broad peak. Column chromatography was carried out with silica gel [Fuji Davison BW200] as an absorbent. Thin layer chromatography (TLC) was carried out on Merck Silica gel 60 PF_{254}. Solutions were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate and the solvent was removed by rotary evaporation under reduced pressure.

4.1.1. (*S*)-*N*-((3-(3-Fluoro-4-(1-formyl[1,2,5]triazepan-5-yl) phenyl)-2-oxo-5-oxazolidinyl)methyl)-*O*-methylthiocarbamate (**9a**)

To a solution of **6a** (323.0 mg, 0.668 mmol) in 1,4-dioxane (3 mL) was added dropwise concentrated hydrochloric acid (1.0 mL). The mixture was stirred for 2 h at ambient temperature, and then concentrated in vacuo. The residue was used for the next reaction without further purification. Formic acid (90.2 mg, 1.960 mmol) was added to a mixture of the residue, EDCI (140.3 mg, 0.732 mmol), HOBt (18.6 mg, 0.138 mmol) and *i*-Pr_2NEt (112.5 mg, 0.870 mmol) in DMF (3 mL), and the whole was stirred for 16 h at ambient temperature. The reaction was quenched by the addition of 10% potassium carbonate aqueous solution (20 mL), and the mixture was extracted with ethyl acetate. The organic solution was dried and evaporated. Silica gel (10 g) column chromatography of the residue using $CHCl_3$/MeOH (99:1 to 99:3) as the eluent afforded **9a** (146.2 mg, 53%). Amorphous solid; ^{1}H NMR ($CDCl_3$)

δ = 3.10–4.12 (12H, m, $-CH_2-$), 4.00 (3H, s, $-OCH_3$), 4.84–4.96 (1H, m, oxazolidinone-H5), 6.85 (0.6H, t, J = 9.1 Hz, Ar-H6), 6.89 (0.4H, t, J = 9.1 Hz, Ar-H6), 7.00 (0.6H, dd, J = 2.4, 9.1 Hz, Ar-H5), 7.03 (0.4H, dd, J = 2.4, 9.1 Hz, Ar-H5), 7.39 (1H, dd, J = 2.4, 15.3 Hz, Ar-H6), 7.88 (0.6H, s, $-CH=O$), and 8.33 (0.4H, s, $-CH=O$); ^{13}C NMR ($CDCl_3$) δ = 47.58 (0.6C), 47.69 (0.4C), 48.75 (1C), 49.75 (1C), 51.10 (0.4C), 51.52 (0.6C), 52.03 (1C), 53.94 (0.4C), 54.06 (0.6C), 57.51 (1C), 71.17 (1C), 107.88 (0.4C, d, J_{C-F} = 26.6 Hz), 108.06 (0.6C, d, J_{C-F} = 26.6 Hz), 114.20 (0.4C), 114.40 (0.6C), 118.30 (0.6C), 119.08 (0.4C), 130.89 (0.6C, d, J_{C-F} = 12.8 Hz), 131.72 (0.4C, d, J_{C-F} = 12.8 Hz), 134.68 (0.6C, d, J_{C-F} = 8.8 Hz), 135.99 (0.4C, d, J_{C-F} = 8.8 Hz), 153.38 (0.6C, d, J_{C-F} = 245 Hz), 154.22 (1C), 154.26 (0.4H, d, J_{C-F} = 245 Hz), 160.54 (0.6C), 165.13 (0.4C), and 192.75 (1C); ESI-MS (m/z): 412 (M^+). HRMS-ESI (m/z): Calcd. for $C_{17}H_{23}FN_5O_4S$ (M^+ + H): 412.1449; Found 412.1450.

4.1.2. 5(R)-3-(4-(1-Formyl[1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**9b**)

Compound **9b** (148.7 mg, 55%) was prepared from **7b** (318.1 mg, 0.663 mmol) in the same manner as described for **7a**. White powder (EtOH); mp 124–126 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.00–3.06 (0.8H, m), 3.15–3.22 (1.2H, m, $-CH_2-$), 3.26–3.42 (3H, m, $-CH_2-$), 3.48–3.55 (0.8H, m, $-CH_2-$), 3.58–3.66 (1.2H, m, $-CH_2-$), 3.72–3.78 (1H, m, $-CH_2-$), 3.86–3.96 (1H, m, $-CH_2-$), 4.16 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.80 (1H, dd, J = 5.0, 14.8 Hz, $-CHH-$[1,2,3]triazole), 4.84 (1H, dd, J = 3.8, 14.8 Hz, $-CHH-$[1,2,3]triazole), 5.05–5.16 (1H, m, oxazolidinone-H5), 7.01 (0.8H, d, J = 10.7 Hz, Ar-H2 and H6), 7.03 (1.2H, d, J = 10.7 Hz, Ar-H2 and H6), 7.74 (1H, s, [1,2,3]triazole-H), 7.89 (1H, s, [1,2,3]triazole-H), 8.02 (0.4H, s, $-CH=O$), and 8.32 (0.6H, s, $-CH=O$); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 46.97 (1C), 49.53 (1C), 51.12 (1C), 51.71 (0.6C), 51.92 (0.4C), 52.67 (0.6C), 53.11 (0.4C), 55.28 (0.6C), 56.12 (0.4C), 70.46 (1C), 102.45 (2C, d, J_{C-F} = 31.0 Hz), 124.99 (1C, t, J_{C-F} = 15 Hz), 125.24 (1C), 133.47 (1C, t, J_{C-F} = 14 Hz), 133.79 (1C), 153.28 (1C), 157.90 (0.8C, dd, J_{C-F} = 8.3, 244 Hz), 158.26 (1.2C, dd, J_{C-F} = 8.3, 244 Hz), 160.79 (0.4C), and 165.33 (0.6C); LRMS-EI (m/z): 407 (M^+). HRMS-EI (m/z): Calcd. for $C_{17}H_{19}F_2N_7O_3$ (M^+): 407.1517; Found 407.1526.

4.1.3. 5(S)-(Isoxazol-3-ylaminomethyl)-3-(3,5-difluoro-4-(1-formyl[1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**9c**)

Compound **9c** (78.9 mg, 31%) was prepared from **8b** (357.5 mg, 0.601 mmol) in the same manner as described for **9a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 3.00–3.06 (1H, m, $-CH_2-$), 3.18–3.41 (4H, m, $-CH_2-$), 3.48–3.54 (1H, m, $-CH_2-$), 3.56–3.67 (2H, m, $-CH_2-$), 3.69–3.85 (3H, m, $-CH_2-$), 4.03 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.39 (1H, t, J = 6.5 Hz, $-NH-$isoxazole), 4.89–5.00 (1H, m, oxazolidinone-H5), 5.87 (1H, d, J = 1.8 Hz, isoxazole-H), 7.09 (1.2H, d, J = 10.8 Hz, Ar-H2 and H6), 7.11 (0.8H, d, J = 10.8 Hz, Ar-H2 and H6), 8.04 (0.6H, s, $-CH=O$), 8.07 (1H, d, J = 1.8 Hz, isoxazole-H), and 8.36 (0.4H, s, $-CH=O$); ^{13}C NMR ($CDCl_3$) δ = 46.43 (1C), 47.47 (1C), 48.72 (0.6C), 49.55 (0.4C), 51.52 (0.6C), 52.38 (0.4C), 52.96 (0.6C), 53.38 (0.4C), 55.54 (0.6C), 56.42 (0.4C), 71.46 (1C), 96.38 (1C), 102.31 (2C, d, J_{C-F} = 30.4 Hz),124.73 (0.6C, t, J_{C-F} = 14.3 Hz), 125.02 (0.4C, t, J_{C-F} = 14.3 Hz), 133.68 (0.4C, t, J_{C-F} = 13.6 Hz), 134.32 (0.6C, t, J_{C-F} = 13.6 Hz), 154.08 (1C), 158.07 (0.8C, dd, J_{C-F} = 8.3, 245 Hz), 158.17 (1C), 158.49 (1.2C, dd, J_{C-F} = 8.3, 245 Hz), 160.60 (1C), 163.65 (0.6C), and 165.17 (0.4C); LRMS-EI (m/z): 422 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{20}F_2N_6O_4$ (M^+): 422.1514; Found 422.1506.

4.1.4. (S)-N-((3-(3,5-Difluoro-4-(2-acetyl[1,2,5]oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**10a**)

To a solution of **4c** (99.2 mg, 0.268 mmol) and Et_3N (0.2 mL, 1.423 mmol) in CH_2Cl_2 (3 mL) was added Ac_2O (0.1 mL, 1.058 mmol). The mixture was stirred for 30 min at ambient temperature. The reaction was quenched by the addition of 10% potassium carbonate aqueous solution (10 mL), and the mixture was extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. Silica gel (8 g) column chromatography of the residue using $CHCl_3$/MeOH (99:1 to 96:4) as the eluent afforded **10a** (105.4 mg, 96%). Colorless needles (EtOH); mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ = 2.03 (3H, s, $CH_3-C=O$), 2.19 (3H, s, $CH_3-C=O$), 3.38–3.45 (4H, m, $-CH_2-$), 3.62–3.70 (2H, m, $-CH_2-$), 3.74 (1H, dd, J = 6.7, 9.1 Hz, oxazolidinone-H4), 3.90 (2H, t, J = 5.3 Hz, $-CH_2-$), 3.99 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.12 (2H, t, J = 4.9 Hz, $-CH_2-$), 4.73–4.83 (1H, m, oxazolidinone-H5), 6.36 (1H, t, J = 6.0 Hz, -NH-C=O), and 7.10 (2H, d, J = 10.8 Hz, Ar-H2 and H6); ^{13}C NMR ($CDCl_3$) δ = 19.88 (1C), 22.83 (1C), 41.79 (1C), 47.40 (1C), 49.43 (1C), 52.34 (1C), 54.39 (1C), 71.96 (1C), 76.72 (1C), 102.35 (2C, d, J_{C-F} = 30.2 Hz), 124.53 (1C, t, J_{C-F} = 15.5 Hz), 133.98 (1C, t, J_{C-F} = 12.1 Hz), 154.03 (1C), 158.20 (2C, dd, J_{C-F} = 8.9, 246 Hz), and 171.31 (2C); LRMS-EI (m/z): 412 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{22}F_2N_4O_5$ (M^+): 412.1558; Found 412.1568. Anal. Calcd for $C_{18}H_{22}F_2N_4O_5$: C, 52.42; H, 5.38; N, 13.59. Found: C, 52.30; H, 5.34; N, 13.57.

4.1.5. (S)-N-((3-(3-Fluoro-4-(1-acetyl[1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**10b**)

To a solution of **6a** (264.8 mg, 0.548 mmol) and Et_3N (0.5 mL, 3.558 mmol) in CH_2Cl_2 (3 mL) was added Ac_2O (0.3 mL, 3.174 mmol). The mixture was stirred for 30 min at ambient temperature. The reaction was quenched by the addition of 10% potassium carbonate aqueous solution (10 mL), and the mixture was diluted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue was used for the next reaction without further purification. To a solution of the residue in 1,4-dioxane (3 mL) was added concentrated hydrochloric acid (0.5 mL). The mixture was stirred for 2 h at ambient temperature. The reaction was quenched by the addition of 10% potassium carbonate aqueous solution (10 mL), and the mixture was extracted with 5% MeOH/$CHCl_3$. The organic solution was dried and evaporated. Silica gel (10 g) column chromatography of the residue using $CHCl_3$/MeOH (99:1 to 99:2) as the eluent afforded **10b** (164.8 mg, 71%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.96 (1.5H, s, $CH_3-C=O$), 2.20 (1.5H, s, $CH_3-C=O$), 3.06–4.14 (12H, m, $-CH_2-$), 4.01 (3H, s, $-OCH_3$), 4.85–4.96 (1H, m, oxazolidinone-H5), 6.88 (1H, br t, J = 6 Hz, $-NH-C=S$), 6.88 (0.5H, t, J = 9.1 Hz, Ar-H5), 6.89 (0.5H, t, J = 9.1 Hz, Ar-H5), 6.99 (0.5H, dd, J = 2.4, 9.1 Hz, Ar-H6), 7.03 (0.5H, dd, J = 2.4, 9.1 Hz, Ar-H6), 7.39 (0.5H, dd, J = 2.4, 14.8 Hz, Ar-H2), and 7.43 (0.5H, dd, J = 2.4, 14.8 Hz, Ar-H2); ^{13}C NMR ($CDCl_3$) δ = 20.67 (1C), 47.62 (1C), 49.49 (0.5C), 49.56 (0.5C), 50.44 (0.5C), 50.73 (0.5C), 51.19 (1C), 51.77 (0.5C), 51.85 (0.5C), 53.66 (0.5C), 53.91 (0.5C), 57.50 (1C), 71.15 (1C), 107.88 (1C, d, J_{C-F} = 26.6 Hz), 114.23 (1C), 118.44 (0.5C), 118.89 (0.5C), 131.02 (0.5C, d, J_{C-F} = 12.2 Hz), 131.54 (0.5C, d, J_{C-F} = 12.2 Hz), 135.20 (0.5C, d, J_{C-F} = 8.3 Hz), 136.23 (0.5C, d, J_{C-F} = 8.3 Hz), 153.63 (1C, d, J_{C-F} = 241 Hz), 154.23 (1C), 168.74 (0.5C), 173.68 (0.5C), and 192.75 (1C); LRMS-EI (m/z): 425 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{24}FN_5O_4S$ (M^+): 425.1533; Found 425.1483.

4.1.6. (S)-N-((3-(3,5-Difluoro-4-(2-acetyl[1,2,5]oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)thioacetamide (**10c**)

Compound **10c** (111.1 mg, 98%) was prepared from **5c** (101.6 mg, 0.263 mmol) in the same manner as described for **10a**. White powder (EtOH); mp 121–123 °C; ^{1}H NMR ($CDCl_3$) δ = 2.19 (3H, s, $CH_3-C=O$), 2.60 (3H, s, $CH_3-C=S$), 3.38–3.46 (4H, m, $-CH_2-$), 3.80 (1H, dd, J = 6.9, 9.1 Hz, oxazolidinone-H4), 3.90 (2H, t, J = 5.6 Hz, $-CH_2-$), 4.04 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.09–4.15 (3H, m, $-CH_2-$), 4.24 (1H, ddd, J = 2.9, 5.8,

14.4 Hz, −CHH−NH−C═S), 4.94–5.04 (1H, m, oxazolidinone-H5), 7.08 (2H, d, J = 10.9 Hz, Ar-H2 and H6), and 8.24 (1H, br t, J = 6 Hz, −NH−C═S); ^{13}C NMR ($CDCl_3$) δ = 19.96 (1C), 33.74 (1C), 47.57 (1C), 47.89 (1C), 49.50 (1C), 52.33 (1C), 54.44 (1C), 71.15 (1C), 76.88 (1C), 102.52 (2C, d, J_{C-F} = 29.8 Hz), 124.75 (1C, t, J_{C-F} = 13.3 Hz), 133.73 (1C, t, J_{C-F} = 12.7 Hz), 154.08 (1C), 158.18 (2C, dd, J_{C-F} = 8.9, 246 Hz), 171.50 (1C), and 203.85 (1C); LRMS-ESI (m/z): 429 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{18}H_{23}F_2N_4O_4S$ (M^+ + H): 429.1403; Found 429.1404.

4.1.7. (S)-N-((3-(3,5-Difluoro-4-(1-acetyl[1,2,5]triazepan-5-yl) phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**10d**)

Compound **10d** (174.6 mg, 75%) was prepared from **6b** (262.8 mg, 0.524 mmol) in the same manner as described for **10b**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 2.12 (1.2H, s, CH$_3$−C═O), 2.22 (1.8H, s, CH$_3$−C═O), 2.96–4.16 (12H, m, −CH$_2$−), 4.01 (3H, s, −OCH$_3$), 4.87–4.98 (1H, m, oxazolidinone-H5), 6.86 (0.4H, br t, J = 6 Hz, −NH−C═S), 6.89 (0.6H, br t, J = 9.1 Hz, −NH−C═S), and 7.10 (2H, d, J = 10.8 Hz, Ar-H2 and H6); ^{13}C NMR ($CDCl_3$) δ = 20.75 (1C), 47.41 (2C), 50.54 (1C), 51.67 (0.6C), 52.38 (0.4C), 52.83 (0.6C), 53.26 (0.4C), 55.30 (0.6C), 55.91 (0.4C), 57.53 (1C), 71.23 (1C), 102.37 (2C, d, J_{C-F} = 29.9 Hz), 125.08 (0.4C, t, J_{C-F} = 13.7 Hz), 125.41 (0.6C, t, J_{C-F} = 13.7 Hz), 133.82 (0.4C, t, J_{C-F} = 14.0 Hz), 134.19 (0.6C, t, J_{C-F} = 14.0 Hz), 153.85 (1C), 158.21 (0.8C, dd, J_{C-F} = 8.8, 246 Hz), 158.48 (1.2C, dd, J_{C-F} = 8.8, 246 Hz), 168.68 (0.4C), 173.76 (0.6C), and 192.87 (1C); LRMS-EI (m/z): 443 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{23}F_2N_5O_4S$ (M^+): 443.1439; Found 443.1449.

4.1.8. 5(R)-3-(4-(1-Acetyl[1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**10e**)

Compound **10e** (185.2 mg, 85%) was prepared from **7b** (247.2 mg, 0.516 mmol) in the same manner as described for **10b**. Colorless needles (EtOH); mp 161–162.5 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 2.13 (1.2H, m, CH$_3$−C═O), 2.22 (1.8H, s, CH$_3$−C═O), 2.96–3.03 (0.8H, m, −CH$_2$−), 3.09–3.16 (1.2H, m, −CH$_2$−), 3.25–3.38 (3H, m, −CH$_2$−), 3.50 (0.8H, t, J = 5.8 Hz, −CH$_2$−), 3.69 (1.2H, t, J = 5.8 Hz, −CH$_2$−), 3.78–3.85 (1H, m, −CH$_2$−), 3.91 (1H, dd, J = 5.9, 9.1 Hz, oxazolidinone-H4), 4.17 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.81 (1H, dd, J = 4.8, 14.6 Hz, −CHH−[1,2,3] triazole), 4.85 (1H, dd, J = 3.9, 14.6 Hz, −CHH−[1,2,3]triazole), 5.11 (1H, dddd, J = 3.9, 4.8, 5.9, 9.1 Hz, oxazolidinone-H5), 7.03 (2H, d, J = 10.6 Hz, Ar-H2 and H6), 7.74 (1H, s, [1,2,3]triazole-H), and 7.90 (1H, s, [1,2,3]triazole-H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 20.14 (1C), 46.93 (1C), 50.27 (0.6C), 50.37 (0.4C), 51.30 (0.6C), 51.68 (1C), 51.93 (0.4C), 52.16 (0.6C), 52.84 (0.4C), 55.02 (0.6C), 55.51 (0.4C), 70.46 (1C), 102.41 (2C, d, J_{C-F} = 30.4 Hz), 125.07 (0.6C, t, J_{C-F} = 15.3 Hz), 125.23 (0.4C, t, J_{C-F} = 15.3 Hz), 125.24 (1C), 133.26 (0.6C, t, J_{C-F} = 14.3 Hz), 133.34 (0.4C, t, J_{C-F} = 14.3 Hz), 133.72 (1C), 153.31 (1C), 158.03 (0.8C, dd, J_{C-F} = 9.1, 245 Hz), 158.25 (1.2C, dd, J_{C-F} = 9.1, 245 Hz), 169.07 (0.4C), and 174.26 (0.6C); LRMS-EI (m/z): 421 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{21}F_2N_7O_3$ (M^+): 421.1674; Found 421.1664. Anal. Calcd for $C_{18}H_{21}F_2N_7O_3$: C, 51.30; H, 5.02; N, 23.27. Found: C, 51.29; H, 5.02; N, 23.23.

4.1.9. (S)-N-((3-(3-Fluoro-4-(1-(difluoroacetyl)[1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**11a**)

Compound **11a** (171.6 mg, 58%) was prepared from **6a** (310.7 mg, 0.643 mmol) in the same manner as described for **9a**, except that difluoroacetic acid was used instead of formic acid. White powder (EtOH); mp 133–135 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.20–3.26 (2H, m, −CH$_2$−), 3.33–3.39 (2H, m, −CH$_2$−), 3.43–3.49 (2H, m, −CH$_2$−), 3.81–4.15 (6H, m, −CH$_2$−), 4.00 (3H, s, CH$_3$O−), 4.88–4.99 (1H, m, oxazolidinone-H5), 6.65 (1H, t, J = 53.4 Hz, CHF$_2$−C═O), 6.95 (1H, t, J = 9.1 Hz, Ar-H5), 7.06 (1H, dd, J = 2.2, 9.1 Hz, Ar-H6), 7.40 (1H, dd, J = 2.2, 14.7 Hz, Ar-H2), and 8.56 (1H, br t, J = 6 Hz, −NH−C═O); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 47.27 (1C), 47.70 (1C), 50.00 (1C), 50.19 (1C), 50.95 (1C), 53.62 (1C), 57.03 (1C), 71.34 (1C), 105.98 (1C, t, J_{C-F} = 242 Hz), 107.83 (1C, d, J_{C-F} = 26.0 Hz), 114.28 (1C), 119.14 (1C), 131.73 (1C, d, J_{C-F} = 14.1 Hz), 136.04 (1C, d, J_{C-F} = 9.4 Hz), 154.27 (1C, d, J_{C-F} = 247 Hz), 154.78 (1C), 164.33 (1C, t, J_{C-F} = 26.9 Hz), and 192.78 (1C); LRMS-EI (m/z): 461 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{22}F_3N_5O_4S$ (M^+): 461.1345; Found 461.1347. Anal. Calcd for $C_{18}H_{22}F_3N_5O_4S$: C, 46.85; H, 4.81; N, 15.18. Found: C, 46.82; H, 4.78; N, 15.15.

4.1.10. 5(R)-3-(4-(1-(Difluoroacetyl)[1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**11b**)

Compound **11b** (131.0 mg, 45%) was prepared from **7b** (303.0 mg, 0.632 mmol) in the same manner as described for **11a**. Colorless needles (EtOH); mp 157.5–159.5 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.14–3.21 (2H, m, −CH$_2$−), 3.25–3.32 (2H, m, −CH$_2$−), 3.36–3.43 (2H, m, −CH$_2$−), 3.82–3.89 (2H, m, −CH$_2$−), 3.92 (1H, dd, J = 5.9, 9.1 Hz, oxazolidinone-H4), 4.18 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.81 (1H, dd, J = 5.0, 14.8 Hz, −CHH−[1,2,3]-triazole), 4.85 (1H, dd, J = 3.8, 14.8 Hz, −CHH−[1,2,3]triazole), 5.11 (1H, dddd, J = 3.8, 5.0, 5.9, 9.1 Hz, oxazolidinone-H5), 6.67 (1H, t, J = 54.3 Hz, CHF$_2$−C═O), 7.04 (2H, d, J = 10.6 Hz, Ar-H2 and H6), 7.74 (1H, d, J = 0.9 Hz, [1,2,3]triazole-H), and 7.91 (1H, d, J = 0.9 Hz, [1,2,3]triazole-H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 46.92 (1C), 50.97 (1C), 51.32 (1C), 51.69 (1C), 51.84 (1C), 55.03 (1C), 70.49 (1C), 102.39 (2C, d, J_{C-F} = 30.4 Hz), 106.01 (1C, t, J_{C-F} = 242 Hz), 124.80 (1C, t, J_{C-F} = 14.3 Hz), 125.29 (1C), 133.60 (1C, t, J_{C-F} = 12.8 Hz), 133.71 (1C), 153.34 (1C), 158.27 (2C, dd, J_{C-F} = 9.4, 247 Hz), and 164.30 (1C, t, J_{C-F} = 26.6 Hz); LRMS-EI (m/z): 457 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{19}F_4N_7O_3$ (M^+): 457.1486; Found 457.1500.

4.1.11. 5(S)-(Isoxazol-3-ylaminomethyl)-3-(3,5-difluoro-4-(1-(difluoroacetyl)[1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**11c**)

Compound **11c** (80.9 mg, 30%) was prepared from **8b** (342.7 mg, 0.576 mmol) in the same manner as described for **11a**. White powder (EtOH); mp 122–124 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.15–3.22 (2H, m, −CH$_2$−), 3.26–3.33 (2H, m, −CH$_2$−), 3.37–3.43 (2H, m, −CH$_2$−), 3.56 (1H, dd, J = 5.6, 14.7 Hz, −CHH−NH−isoxazole), 3.64 (1H, dd, J = 3.6, 14.7 Hz, −CHH−NH−isoxazole), 3.78–3.89 (3H, m, −CH$_2$−), 4.06 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.87–4.98 (1H, m, oxazolidinone-H5), 5.92 (1H, d, J = 1.8 Hz, isoxazole-H), 6.66 (1H, t, J = 53.4 Hz, CHF$_2$−C═O), 7.14 (2H, d, J = 10.8 Hz, Ar-H2 and H6), and 8.07 (1H, d, J = 1.8 Hz, isoxazole-H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 46.11 (1C), 47.45 (1C), 51.08 (1C), 51.57 (1C), 51.90 (1C), 55.16 (1C), 71.58 (1C), 96.23 (1C), 102.28 (2C, d, J_{C-F} = 30.4 Hz), 106.10 (1C, t, J_{C-F} = 243 Hz), 124.51 (1C, t, J_{C-F} = 14.4 Hz), 134.42 (1C, t, J_{C-F} = 12.3 Hz), 154.42 (1C), 158.04 (1C), 158.44 (2C, dd, J_{C-F} = 8.8, 246 Hz), 163.66 (1C), and 164.31 (1C, t, J_{C-F} = 26.6 Hz); LRMS-EI (m/z): 472 (M^+). HRMS-EI (m/z): Calcd. for $C_{19}H_{20}F_4N_6O_4$ (M^+): 472.1482; Found 472.1467.

4.1.12. (S)-N-((3-(3-Fluoro-4-(10-oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**12a**)

To a solution of **4a** (218.7 mg, 0.484 mmol) and pyridine (0.1 mL, 1.241 mmol) in CH_2Cl_2 (2 mL) was added 2-chloronicotinoyl chloride (130.8 mg, 0.743 mmol). The mixture was stirred for 1 h at ambient temperature, and then concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the residue in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.5 mL). The mixture was stirred for 18 h at ambient temperature, then neutralized with 10%

potassium carbonate aqueous solution (10 mL), and extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. Silica gel (8 g) column chromatography of the residue using $CHCl_3$/MeOH (98:2 to 94:6) as the eluent afforded **12a** (190.7 mg, 87%). Colorless needles (EtOH); mp 212.5–213.5 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 2.01 (3H, s, C<u>H</u>$_3$–C=O), 3.41–3.54 (4H, m, –CH_2–), 3.53–3.68 (2H, m, –CH_2–), 3.78 (1H, dd, J = 6.6, 9.1 Hz, oxazolidinone-H4), 4.08 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.41–4.54 (4H, m, –CH_2–), 4.73–4.83 (1H, m, oxazolidinone-H5), 7.05 (1H, t, J = 8.8 Hz, Ar-H5), 7.11 (1H, dd, J = 2.4, 8.8 Hz, Ar-H6), 7.15 (1H, dd, J = 4.7, 7.9 Hz, fused ring-H2), 7.49 (1H, dd, J = 2.4, 14.1 Hz, Ar-H2), 7.97 (1H, t, J = 5.9 Hz, –N<u>H</u>–C=O), 8.21 (1H, dd, J = 1.5, 7.9 Hz, fused ring-H1), and 8.57 (1H, dd, J = 1.5, 4.7 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 21.94 (1C), 41.68 (1C), 44.47 (1C), 47.59 (1C), 48.15 (1C), 53.58 (1C), 53.71 (1C), 71.83 (1C), 107.39 (1C, d, J_{C-F} = 26.6 Hz), 108.31 (1C), 113.90 (1C), 116.90 (1C), 120.92 (1C), 133.23 (1C), 133.41 (1C, d, J_{C-F} = 10.0 Hz), 136.09 (1C, d, J_{C-F} = 9.4 Hz), 152.72 (1C), 153.95 (1C), 154.66 (1C), 155.26 (1C, d, J_{C-F} = 246 Hz), 157.94 (1C), and 172.06 (1C); LRMS-EI (m/z): 454 (M^+). HRMS-EI (m/z): Calcd. for $C_{22}H_{23}FN_6O_4$ (M^+): 454.1765; Found 454.1768.

4.1.13. (S)-N-((3-(3,5-Difluoro-4-(10-oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**12b**)

Compound **12b** (114.4 mg, 100%) was prepared from **4b** (113.9 mg, 0.243 mmol) in the same manner as described for **12a**. Colorless needles (EtOH); mp 204–206 °C; ^{1}H NMR ($CDCl_3$) δ = 2.03 (3H, s, C<u>H</u>$_3$–C=O), 3.38–3.51 (4H, m, –CH_2–), 3.57–3.73 (2H, m, –CH_2–), 3.74 (1H, dd, J = 6.8, 9.1 Hz, oxazolidinone-H4), 4.00 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.37–4.48 (4H, m, –CH_2–), 4.73–4.84 (1H, m, oxazolidinone-H5), 6.00 (1H, br t, J = 6 Hz, –N<u>H</u>–C=O), 7.07 (1H, dd, J = 4.7, 7.6 Hz, fused ring-H2), 7.14 (2H, d, J = 10.9 Hz, Ar-H2 and H6), 8.18 (1H, dd, J = 1.8, 7.6 Hz, fused ring-H1), and 8.53 (1H, dd, J = 1.8, 4.7 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$) δ = 22.89 (1C), 41.89 (1C), 45.48 (1C), 47.44 (1C), 49.33 (1C), 54.56 (1C), 54.72 (1C), 71.99 (1C), 102.35 (2C, d, J_{C-F} = 29.4 Hz), 108.93 (1C), 116.80 (1C), 124.72 (1C, t, J_{C-F} = 14.6 Hz), 133.29 (1C), 134.97 (1C, t, J_{C-F} = 13.6 Hz), 152.74 (1C), 153.98 (1C), 154.73 (1C), 158.11 (1C), 158.70 (2C, dd, J_{C-F} = 8.3, 246 Hz), and 171.31 (1C); LRMS-EI (m/z): 472 (M^+). HRMS-EI (m/z): Calcd. for $C_{22}H_{22}F_2N_6O_4$ (M^+): 472.1671; Found 472.1689.

4.1.14. (S)-N-((3-(3-Fluoro-4-(10-oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**12c**)

Compound **12c** (228.3 mg, 90%) was prepared from **6a** (253.4 mg, 0.524 mmol) in the same manner as described for **12a**. Colorless needles (EtOH); mp 203–205 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.42–3.54 (4H, m, –CH_2–), 3.87–4.07 (3H, m, –CH_2–), 4.00 (3H, s, –OC<u>H</u>$_3$), 4.09 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.41–4.54 (4H, m, –CH_2–), 4.90–5.00 (1H, m, oxazolidinone-H5), 7.05 (1H, t, J = 8.8 Hz, Ar-H5), 7.12 (1H, dd, J = 2.3, 8.8 Hz, Ar-H6), 7.15 (1H, dd, J = 4.7, 7.9 Hz, fused ring-H2), 7.47 (1H, dd, J = 2.4, 13.8 Hz, Ar-H2), 8.21 (1H, dd, J = 1.8, 7.9 Hz, fused ring-H1), and 8.57 (1H, dd, J = 1.8, 4.7 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 44.50 (1C), 47.24 (1C), 47.58 (1C), 48.15 (1C), 53.59 (1C), 53.75 (1C), 57.00 (1C), 71.34 (1C), 107.53 (1C, d, J_{C-F} = 26.0 Hz), 108.35 (1C), 114.05 (1C), 116.92 (1C), 120.94 (1C), 133.27 (1C), 133.41 (1C, d, J_{C-F} = 10.6 Hz), 136.15 (1C, d, J_{C-F} = 9.9 Hz), 152.74 (1C), 153.97 (1C), 154.63 (1C), 155.28 (1C, d, J_{C-F} = 246 Hz), 158.00 (1C), and 192.82 (1C); LRMS-EI (m/z): 486 (M^+). HRMS-EI (m/z): Calcd. for $C_{22}H_{23}FN_6O_4S$ (M^+): 486.1486; Found 486.1506.

4.1.15. (S)-N-((3-(3,5-Difluoro-4-(10-oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**12d**)

Compound **12d** (230.1 mg, 88%) was prepared from **6b** (258.8 mg, 0.516 mmol) in the same manner as described for **12a**. Colorless needles (EtOH); mp 220–223 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.40–3.54 (4H, m, –CH_2–), 3.86–4.12 (4H, m, –CH_2–), 4.01 (3H, s, C<u>H</u>$_3$O–), 4.38–4.54 (4H, m, –CH_2–), 4.91–5.01 (1H, m, oxazolidinone-H5), 7.15 (1H, dd, J = 4.8, 7.9 Hz, fused ring-H2), 7.18 (2H, d, J = 10.7 Hz, Ar-H2 and H6), 8.22 (1H, dd, J = 1.7, 7.9 Hz, fused ring-H1), and 8.56 (1H, dd, J = 1.7, 4.8 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 45.31 (1C), 47.09 (1C), 47.25 (1C), 48.85 (1C), 54.21 (1C), 54.45 (1C), 57.03 (1C), 71.35 (1C), 102.24 (2C, d, J_{C-F} = 29.4 Hz), 108.16 (1C), 116.79 (1C), 124.30 (1C, t, J_{C-F} = 14.6 Hz), 133.27 (1C), 134.89 (1C, t, J_{C-F} = 13.6 Hz), 152.71 (1C), 153.60 (1C), 154.23 (1C), 157.75 (1C), 158.42 (2C, dd, J_{C-F} = 8.5, 243 Hz), and 192.86 (1C); LRMS-EI (m/z): 504 (M^+). HRMS-EI (m/z): Calcd. for $C_{22}H_{22}F_2N_6O_4S$ (M^+): 504.1391; Found 504.1413. Anal. Calcd for $C_{22}H_{22}F_2N_6O_4S$: C, 52.37; H, 4.40; N, 16.66. Found: C, 52.15; H, 4.45; N, 16.40.

4.1.16. 5(R)-3-(4-(10-Oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)-3-fluorophenyl)-5-(1,2,3-tri-azol-1-ylmethyl)oxazolidin-2-one (**12e**)

Compound **12e** (84.2 mg, 84%) was prepared from **7a** (99.3 mg, 0.215 mmol) in the same manner as described for **12a**. Colorless needles (EtOH); mp 166.5–168.5 °C; ^{1}H NMR ($CDCl_3$) δ = 3.37–3.50 (4H, m, –CH_2–), 3.92 (1H, dd, J = 5.9, 9.1 Hz, oxazolidinone-H4), 4.14 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.37–4.47 (4H, m, –CH_2–), 4.80 (2H, d, J = 4.4 Hz, –C<u>H</u>$_2$–[1,2,3]triazole), 5.07 (1H, ddt, J = 5.9, 9.1, 4.4 Hz, oxazolidinone-H5), 6.92–7.00 (2H, m, Ar-H5 and H6), 7.08 (1H, dd, J = 4.7, 7.6 Hz, fused ring-H2), 7.33 (1H, dd, J = 2.2, 13.5 Hz, Ar-H2), 7.75 (1H, d, J = 0.9 Hz, [1,2,3]triazole-H), 7.79 (1H, d, J = 0.9 Hz, [1,2,3]triazole-H), 8.17 (1H, dd, J = 1.8, 7.6 Hz, fused ring-H1), and 8.54 (1H, dd, J = 1.8, 4.7 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$) δ = 44.65 (1C), 47.35 (1C), 48.69 (1C), 51.95 (1C), 53.75 (1C), 53.85 (1C), 70.37 (1C), 107.89 (1C, d, J_{C-F} = 25.4 Hz), 109.15 (1C), 114.30 (1C), 116.95 (1C), 120.93 (1C), 125.04 (1C), 132.80 (1C, d, J_{C-F} = 8.8 Hz), 133.30 (1C), 134.33 (1C), 136.75 (1C, d, J_{C-F} = 10.0 Hz), 152.75 (1C), 153.32 (1C), 155.17 (1C), 155.36 (1C, d, J_{C-F} = 245 Hz), and 158.34 (1C); LRMS-EI (m/z): 464 (M^+). HRMS-EI (m/z): Calcd. for $C_{22}H_{21}FN_8O_3$ (M^+): 464.1721; Found 464.1710.

4.1.17. 5(R)-3-(4-(10-Oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**12f**)

Compound **12f** (64.7 mg, 90%) was prepared from **7b** (71.4 mg, 0.149 mmol) in the same manner as described for **12a**. Colorless needles (EtOH); mp 209–211 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.40–3.52 (4H, m, –CH_2–), 3.93 (1H, dd, J = 6.1, 9.1 Hz, oxazolidinone-H4), 4.18 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.39–4.52 (4H, m, –CH_2–), 4.81 (1H, dd, J = 4.9, 14.8 Hz, –C<u>H</u>H–[1,2,3]triazole), 4.86 (1H, dd, J = 4.9, 14.8 Hz, –CH<u>H</u>–[1,2,3]triazole), 5.12 (1H, ddt, J = 6.1, 9.1, 4.9 Hz, oxazolidinone-H5), 7.08 (2H, d, J = 10.8 Hz, Ar-H2 and H6), 7.14 (1H, dd, J = 4.8, 7.8 Hz, fused ring-H2), 7.75 (1H, br s, [1,2,3]triazole-H), 7.91 (1H, br s, [1,2,3]triazole-H), 8.21 (1H, dd, J = 1.5, 7.8 Hz, fused ring-H1), and 8.56 (1H, dd, J = 1.5, 4.8 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 45.32 (1C), 46.91 (1C), 48.89 (1C), 51.68 (1C), 54.18 (1C), 54.41 (1C), 70.48 (1C), 102.37 (2C, d, J_{C-F} = 29.9 Hz), 108.24 (1C), 116.80 (1C), 124.60 (1C, t, J_{C-F} = 14.7 Hz), 125.25 (1C), 133.26 (1C), 133.76 (1C), 134.30 (1C, t, J_{C-F} = 13.5 Hz), 152.72 (1C), 153.26 (1C), 153.80 (1C), 157.86 (1C), and 158.38 (2C, dd, J_{C-F} = 10.0, 248 Hz); LRMS-EI (m/z): 482 (M^+). HRMS-EI (m/z): Calcd. for $C_{22}H_{20}F_2N_8O_3$ (M^+): 482.1626;

Found 482.1627. Anal. Calcd for $C_{22}H_{20}F_2N_8O_3$: C, 54.77; H, 4.18; N, 23.23. Found: C, 54.57; H, 4.25; N, 22.97.

4.1.18. (S)-N-((3-(3,5-Difluoro-4-(2-chloro-10-oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)-phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**13**)

Compound **13** (102.9 mg, 76%) was prepared from **4b** (125.0 mg, 0.266 mmol) in the same manner as described for **12a**, except that 2,5-dichloronicotinoyl chloride was used instead of 2-chloronicotinoyl chloride. Colorless needles (EtOH); mp 247–249 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 2.01 (3H, s, C<u>H</u>$_3$–C=O), 3.40–3.52 (4H, m, –CH_2–), 3.56 (1H, dd, J = 5.6, 14.5 Hz, –C<u>H</u>H–NH–C=O), 3.61 (1H, dd, J = 4.1, 14.5 Hz, –CH<u>H</u>–NH–C=O), 3.75 (1H, dd, J = 6.7, 9.1 Hz, oxazolidinone-H4), 4.04 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.39–4.51 (4H, m, –CH_2–), 4.78 (1H, dddd, J = 4.1, 5.6, 6.7, 9.1 Hz, oxazolidinone-H5), 7.18 (2H, d, J = 10.6 Hz, Ar-H2 and H6), 8.17 (1H, d, J = 2.4 Hz, fused ring-H1), and 8.50 (1H, d, J = 2.4 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 22.07 (1C), 41.66 (1C), 45.52 (1C), 47.41 (1C), 48.99 (1C), 54.30 (1C), 54.46 (1C), 71.94 (1C), 102.24 (2C, d, J_{C-F} = 29.9 Hz), 108.70 (1C), 124.28 (1C, t, J_{C-F} = 14.7 Hz), 124.40 (1C), 132.18 (1C), 135.02 (1C, t, J_{C-F} = 14.0 Hz), 151.77 (2C), 154.32 (1C), 156.92 (1C), 158.45 (2C, dd, J_{C-F} = 8.8, 255 Hz), and 172.14 (1C); LRMS-EI (m/z): 506 (M^+). HRMS-EI (m/z): Calcd. for $C_{22}H_{21}ClF_2N_6O_4$ (M^+): 506.1281; Found 506.1289. Anal. Calcd for $C_{22}H_{21}ClF_2N_6O_4$: C, 52.13; H, 4.18; N, 16.58. Found: C, 51.93; H, 4.23; N, 16.42.

4.1.19. (S)-N-((3-(3,5-Difluoro-4-(2-bromo-10-oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**14**)

Compound **14** (140.7 mg, 85%) was prepared from **4b** (141.6 mg, 0.302 mmol) in the same manner as described for **12a**, except that 5-bromo-2-chloronicotinoyl chloride was used instead of 2-chloronicotinoyl chloride. Colorless needles (EtOH); mp 256–258 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 2.01 (3H, s, C<u>H</u>$_3$–C=O), 3.39–3.51 (4H, m, –CH_2–), 3.56 (1H, dd, J = 5.6, 14.4 Hz, –C<u>H</u>H–NH–C=O), 3.61 (1H, dd, J = 3.8, 14.4 Hz, –CH<u>H</u>–NH–C=O), 3.75 (1H, dd, J = 6.7, 9.1 Hz, oxazolidinone-H4), 4.04 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.38–4.52 (4H, m, –CH_2–), 4.78 (1H, dddd, J = 3.8, 5.6, 6.7, 9.1 Hz, oxazolidinone-H5), 7.18 (2H, d, J = 10.9 Hz, Ar-H2 and H6), 8.31 (1H, d, J = 2.2 Hz, fused ring-H1), and 8.58 (1H, d, J = 2.2 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 22.05 (1C), 41.68 (1C), 45.49 (1C), 47.41 (1C), 48.87 (1C), 54.34 (1C), 54.47 (1C), 71.94 (1C), 102.26 (2C, d, J_{C-F} = 29.9 Hz), 109.45 (1C), 111.66 (1C), 124.26 (1C, t, J_{C-F} = 14.5 Hz), 135.05 (1C, t, J_{C-F} = 14.0 Hz), 135.16 (1C), 151.88 (1C), 153.69 (1C), 154.33 (1C), 156.58 (1C), 158.52 (2C, dd, J_{C-F} = 8.3, 247 Hz), and 172.16 (1C); LRMS-EI (m/z): 550 (M^+). HRMS-EI (m/z): Calcd. for $C_{22}H_{21}BrF_2N_6O_4$ (M^+): 550.0776; Found 550.0802. Anal. Calcd for $C_{22}H_{21}BrF_2N_6O_4$: C, 47.93; H, 3.84; N, 15.24. Found: C, 47.94; H, 3.91; N, 15.27.

4.1.20. (S)-N-((3-(3,5-Difluoro-4-(2-amino-10-oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)pheny-l)-2-oxo-5-oxazolidinyl)methyl)acetamide (**15a**)

To a solution of **4b** (316.9 mg, 0.675 mmol) in 1,4-dioxane (3 mL) was added concentrated hydrochloric acid (0.5 mL). The mixture was stirred for 1 h at ambient temperature and then concentrated in vacuo. The residue was used for the next reaction without further purification. To a mixture of the residue, EDCI (155.0 mg, 0.809 mmol), HOBt (15.8 mg, 0.117 mmol) and i-Pr_2NEt (132.1 mg, 1.022 mmol) in DMF (3 mL) was added 5-*tert*-butoxycarbonylamino-2-chloronicotinic acid (221.1 mg, 0.811 mmol). The mixture was stirred for 19 h at ambient temperature, then 10% citric acid aqueous solution (10 mL) was added, and the whole was extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. The residue was used for the next reaction without further purification. To a solution of the residue in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (1.0 mL). The mixture was stirred for 7 h at ambient temperature, then neutralized with 10% potassium carbonate aqueous solution (15 mL), and extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. Silica gel (10 g) column chromatography of the residue using $CHCl_3$/MeOH (95:5 to 90:10) as the eluent afforded **15a** (149.0 mg, 45%). Amorphous powder; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 2.02 (3H, s, C<u>H</u>$_3$–C=O), 3.36–3.54 (4H, m, –CH_2–), 3.56–3.64 (2H, m, –CH_2–), 3.76 (1H, dd, J = 6.7, 9.1 Hz, oxazolidinone-H4), 4.06 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.24–4.36 (4H, m, –CH_2–), 4.75–4.85 (1H, m, oxazolidinone-H5), 7.17 (2H, d, J = 10.8 Hz, Ar-H2 and H6), 7.47 (1H, d, J = 2.6 Hz, fused ring-H1), 8.04 (1H, t, J = 5.9 Hz, –N<u>H</u>–C=O), and 8.16 (1H, d, J = 2.6 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 21.99 (1C), 41.71 (1C), 45.69 (1C), 47.35 (1C), 50.60 (1C), 53.60 (1C), 54.03 (1C), 71.85 (1C), 102.15 (2C, d, J_{C-F} = 29.8 Hz), 109.21 (1C), 116.15 (1C), 124.37 (1C, t, J_{C-F} = 15.5 Hz), 134.67 (1C, t, J_{C-F} = 13.6 Hz), 139.21 (1C), 142.59 (1C), 150.29 (1C), 154.32 (1C), 158.39 (2C, dd, J_{C-F} = 8.9, 246 Hz), 158.61 (1C), and 172.25 (1C); LRMS-ESI (m/z): 488 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{22}H_{24}F_2N_7O_4$ (M^+ + H): 488.1852; Found 488.1855.

4.1.21. 5(R)-3-(4-(2-Amino-10-oxo-5,6,8,9-tetrahydro-10H-4,4b,7,9a-tetraazabenzo[a]azulen-7-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**15b**)

Compound **15b** (152.1 mg, 48%) was prepared from **7b** (305.7 mg, 0.638 mmol) in the same manner as described for **15a**. Amorphous powder; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.34–3.52 (4H, m, –CH_2–), 3.93 (1H, dd, J = 5.9, 9.1 Hz, oxazolidinone-H4), 4.19 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.23–4.35 (4H, m, –CH_2–), 4.82 (1H, dd, J = 5.0, 14.8 Hz, –C<u>H</u>H–[1,2,3]triazole), 4.87 (1H, dd, J = 3.9, 14.8 Hz, –CH<u>H</u>–[1,2,3]triazole), 5.14 (1H, dddd, J = 3.9, 5.0, 5.9, 9.1 Hz, oxazolidinone-H5), 7.07 (2H, d, J = 10.7 Hz, Ar-H2 and H6), 7.46 (1H, d, J = 2.6 Hz, fused ring-H1), 7.75 (1H, d, J = 0.9 Hz, [1,2,3]triazole-H), 7.92 (1H, d, J = 0.9 Hz, [1,2,3]triazole-H), and 8.16 (1H, d, J = 2.6 Hz, fused ring-H3); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 45.70 (1C), 46.90 (1C), 50.62 (1C), 51.68 (1C), 53.56 (1C), 53.99 (1C), 70.48 (1C), 102.35 (2C, d, J_{C-F} = 29.9 Hz), 109.25 (1C), 116.19 (1C), 124.68 (1C, t, J = 15.2 Hz), 125.28 (1C), 133.79 (1C), 134.05 (1C, t, J = 13.1 Hz), 139.17 (1C), 142.59 (1C), 150.30 (1C), 153.27 (1C), 158.32 (2C, dd, J_{C-F} = 8.9, 246 Hz), and 158.66 (1C); LRMS-ESI (m/z): 498 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{22}H_{22}F_2N_9O_3$ (M^+ + H): 498.1808; Found 498.1809.

4.1.22. (S)-N-((3-(3-Fluoro-4-(1-carbamoyl-[1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)thioacetamide (**16a**)

To a solution of **5a** (95.4 mg, 0.204 mmol) and triphosgene (30.6 mg, 0.103 mmol) in tetrahydrofuran (4 mL) was added dropwise Et_3N (0.09 mL, 0.640 mmol) at 0 °C. The mixture was stirred for 10 min at the same temperature, and then concentrated NH_3 aqueous solution (0.2 mL) was added. Stirring was continued for 20 h at ambient temperature. The mixture was diluted with water (10 mL) and then extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. The residue was used for the next reaction without further purification. To a solution of the residue in 1,4-dioxane (2 mL) was added concentrated hydrochloric acid (0.2 mL). The mixture was stirred for 1 h at ambient temperature. The reaction was quenched by the addition of 10% potassium carbonate aqueous solution (5 mL), and the mixture was extracted with 10% MeOH/$CHCl_3$. The organic solution was dried, and evaporated. Silica gel (8 g) column chromatography of the residue using $CHCl_3$/MeOH (97:3 to 92:8) as the eluent afforded **16a** (30.8 mg, 37%). White powder (EtOH); mp 176.5–178.5 °C (dec.); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 2.57 (3H, s, C<u>H</u>$_3$–C=S), 3.15–3.23 (2H,

m, $-CH_2-$), 3.36–3.44 (4H, m, $-CH_2-$), 3.80–3.88 (3H, m, $-CH_2-$), 3.93–4.04 (1H, m, $-CH_2-$), 4.10 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.12–4.22 (1H, m, $-CH_2-$), 4.94–5.04 (1H, m, oxazolidinone-H5), 6.94 (1H, t, J = 9.1 Hz, Ar-H5), 7.04 (1H, dd, J = 2.4, 9.1 Hz, Ar-H6), and 7.40 (1H, dd, J = 2.4, 14.7 Hz, Ar-H2); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 32.63 (1C), 47.94 (2C), 48.95 (1C), 49.93 (1C), 51.56 (1C), 53.51 (1C), 71.00 (1C), 107.90 (1C, d, J_{C-F} = 29.3 Hz), 114.32 (1C), 118.82 (1C), 130.99 (1C, d, J_{C-F} = 12.8 Hz), 136.42 (1C, d, J_{C-F} = 8.9 Hz), 154.07 (1C, d, J_{C-F} = 244 Hz), 154.85 (1C), 160.63 (1C), and 203.23 (1C); LRMS-EI (m/z): 410 (M^+). HRMS-EI (m/z): Calcd. for $C_{17}H_{23}FN_6O_3S$ (M^+): 410.1536; Found 410.1539.

4.1.23. (S)-N-((3-(3,5-Difluoro-4-(1-carbamoyl-[1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)thioacetamide (**16b**)

Compound **16b** (109.4 mg, 66%) was prepared from **5b** (186.3 mg, 0.384 mmol) in the same manner as described for **16a**. White powder (EtOH); mp 181.5–183.5 °C (dec.); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 2.57 (3H, s, C<u>H</u>$_3$–C=S), 3.11–3.18 (2H, m, $-CH_2-$), 3.27–3.38 (4H, m, $-CH_2-$), 3.73–3.80 (2H, m, $-CH_2-$), 3.83 (1H, dd, J = 6.8, 9.1 Hz, oxazolidinone-H4), 3.97–4.05 (1H, m, $-CH_2-$), 4.08 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.15 (1H, dd, J = 3.4, 14.4 Hz, –C<u>H</u>H–NH–C=S), 4.95–5.06 (1H, m, oxazolidinone-H5), and 7.11 (2H, d, J = 10.8 Hz, Ar-H2 and H6); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 32.70 (1C), 47.55 (1C), 47.76 (1C), 49.97 (1C), 50.88 (1C), 53.20 (1C), 54.88 (1C), 70.97 (1C), 102.32 (2C, d, J_{C-F} = 29.9 Hz), 125.13 (1C, t, J_{C-F} = 14.7 Hz), 133.66 (1C, t, J_{C-F} = 12.8 Hz), 154.28 (1C), 158.30 (2C, dd, J_{C-F} = 8.6, 245 Hz), 160.68 (1C), and 203.33 (1C); LRMS-ESI (m/z): 428 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{23}F_2N_6O_3S$ (M^+ + H): 429.1515; Found 429.1515.

4.1.24. (S)-N-((3-(3,5-Difluoro-4-(2-carbamoyl-[1,2,5]oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)thioacetamide (**16c**)

Compound **16c** (143.5 mg, 99%) was prepared from **5c** (130.7 mg, 0.338 mmol) in the same manner as described for **16a**, except that hydrochloric acid treatment was omitted. Colorless needles (EtOH); mp 182–184 °C (dec.); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 2.57 (3H, s, C<u>H</u>$_3$–C=S), 3.39–3.51 (4H, m, $-CH_2-$), 3.77–3.87 (3H, m, $-CH_2-$), 3.93–4.21 (5H, m, $-CH_2-$), 4.95–5.06 (1H, m, oxazolidinone-H5), and 7.12 (2H, d, J = 10.7 Hz, Ar-H2 and H6); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 32.74 (1C), 47.49 (1C), 47.82 (1C), 50.34 (1C), 53.22 (1C), 54.24 (1C), 70.98 (1C), 75.03 (1C), 102.36 (2C, d, J_{C-F} = 30.4 Hz), 124.66 (1C, t, J_{C-F} = 14.4 Hz), 133.23 (1C, t, J_{C-F} = 13.8 Hz), 154.33 (1C), 157.81 (2C, dd, J_{C-F} = 8.8, 245 Hz), 160.30 (1C), and 203.38 (1C); LRMS-ESI (m/z): 430 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{22}F_2N_5O_4S$ (M^+ + H): 430.1355; Found 430.1355.

4.1.25. (S)-N-(((3-[3-Fluoro-4-(1-carbamoyl-[1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**16d**)

Compound **16d** (172.4 mg, 89%) was prepared from **6a** (220.6 mg, 0.456 mmol) in the same manner as described for **16a**. White powder (EtOH); mp 166–168 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.15–3.22 (2H, m, $-CH_2-$), 3.35–3.43 (4H, m, $-CH_2-$), 3.60–3.76 (3H, m, $-CH_2-$), 3.80–4.11 (3H, m, $-CH_2-$), 4.00 (3H, s, –OC<u>H</u>$_3$), 4.87–4.98 (1H, m, oxazolidinone-H5), 6.93 (1H, t, J = 9.1 Hz, Ar-H5), 7.03 (1H, dd, J = 2.4, 9.1 Hz, Ar-H6), and 7.38 (1H, dd, J = 2.4, 14.8 Hz, Ar-H2); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 47.38 (1C), 47.63 (1C), 48.91 (1C), 49.90 (1C), 51.47 (1C), 53.46 (1C), 57.10 (1C), 71.30 (1C), 107.78 (1C, d, J_{C-F} = 27.1 Hz), 114.22 (1C), 118.68 (1C), 131.08 (1C, d, J_{C-F} = 10.5 Hz), 136.27 (1C, d, J_{C-F} = 9.4 Hz), 153.96 (1C, d, J_{C-F} = 244 Hz), 154.77 (1C), 160.54 (1C), and 192.75 (1C); LRMS-ESI (m/z): 427 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{24}FN_6O_4S$ (M^+ + H): 427.1558; Found 427.1559.

4.1.26. (S)-N-((3-(3,5-Difluoro-4-(1-carbamoyl-[1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**16e**)

Compound **16e** (151.7 mg, 83%) was prepared from **6b** (205.4 mg, 0.410 mmol) in the same manner as described for **16a**. White powder (EtOH); mp 178.5–180.5 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.11–3.18 (2H, m, $-CH_2-$), 3.28–3.37 (4H, m, $-CH_2-$), 3.74–3.80 (2H, m, $-CH_2-$), 3.87 (1H, dd, J = 6.8, 9.1 Hz, oxazolidinone-H4), 3.93–4.11 (3H, m, $-CH_2-$), 4.00 (3H, s, –OC<u>H</u>$_3$), 4.89–5.00 (1H, m, oxazolidinone-H5), and 7.12 (2H, d, J = 10.8 Hz, Ar-H2 and H6); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 47.06 (1C), 47.23 (1C), 49.90 (1C), 50.83 (1C), 53.10 (1C), 54.84 (1C), 57.05 (1C), 71.28 (1C), 102.22 (2C, d, J_{C-F} = 30.4 Hz), 124.99 (1C, t, J_{C-F} = 14.3 Hz), 133.68 (1C, t, J_{C-F} = 13.2 Hz), 154.30 (1C), 158.23 (2C, dd, J_{C-F} = 8.9, 246 Hz), 160.72 (1C), and 192.75 (1C); LRMS-ESI (m/z): 445 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{23}F_2N_6O_4S$ (M^+ + H): 445.1464; Found 445.1464. Anal. Calcd for $C_{17}H_{22}F_2N_6O_4S$: C, 45.94; H, 4.99; N, 18.91. Found: C, 45.68; H, 4.97; N, 18.60.

4.1.27. (S)-N-((3-(3,5-Difluoro-4-(2-carbamoyl-[1,2,5]oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**16f**)

Compound **16f** (126.7 mg, 89%) was prepared from **6c** (128.8 mg, 0.320 mmol) in the same manner as described for **16c**. Colorless needles (EtOH); mp 163.5–165 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.42 (2H, t, J = 5.3 Hz, $-CH_2-$), 3.46 (2H, t, J = 5.3 Hz, $-CH_2-$), 3.80 (2H, t, J = 5.3 Hz, $-CH_2-$), 3.87 (1H, dd, J = 7.0, 9.1 Hz, oxazolidinone-H4), 3.94–4.16 (5H, m, $-CH_2-$), 4.00 (3H, s, –OC<u>H</u>$_3$), 4.90–5.01 (1H, m, oxazolidinone-H5), and 7.13 (2H, d, J = 10.8 Hz, Ar-H2 and H6); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 47.08 (1C), 47.24 (1C), 50.31 (1C), 53.19 (1C), 54.23 (1C), 57.07 (1C), 71.32 (1C), 74.99 (1C), 102.32 (2C, d, J_{C-F} = 30.4 Hz), 124.56 (1C, t, J_{C-F} = 14.4 Hz), 133.37 (1C, t, J_{C-F} = 13.3 Hz), 154.34 (1C), 157.80 (2C, dd, J_{C-F} = 8.3, 246 Hz), 160.33 (1C), and 192.82 (1C); LRMS-ESI (m/z): 446 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{22}F_2N_5O_5S$ (M^+ + H): 446.1304; Found 446.1302. Anal. Calcd for $C_{17}H_{21}F_2N_5O_5S$: C, 45.84; H, 4.75; N, 15.72. Found: C, 45.88; H, 4.75; N, 15.73.

4.1.28. 5(R)-3-(4-(1-Carbamoyl-[1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**16g**)

Compound **16g** (137.0 mg, 70%) was prepared from **7b** (223.4 mg, 0.466 mmol) in the same manner as described for **16a**. White powder (CH_2Cl_2/EtOH); mp 193–195 °C; ^{1}H NMR (DMSO-d_6) δ = 2.90–2.99 (2H, m, $-CH_2-$), 3.12–3.27 (4H, m, $-CH_2-$), 3.55–3.63 (2H, m, $-CH_2-$), 3.85 (1H, dd, J = 5.8, 9.4 Hz, oxazolidinone-H4), 4.18 (1H, t, J = 9.4 Hz, oxazolidinone-H4), 4.81 (2H, d, J = 5.0 Hz, $-CH_2-$[1,2,3]triazole), 5.04 (1H, t, J = 5.9 Hz, N<u>H</u>), 5.13 (1H, ddt, J = 5.8, 9.4, 5.0 Hz, oxazolidinone-H5), 6.05 (2H, br s, N<u>H</u>$_2$), 7.19 (2H, d, J = 11.1 Hz, Ar-H2 and H6), 7.75 (1H, s, [1,2,3]triazole-H), and 8.15 (1H, s, [1,2,3]triazole-H); ^{13}C NMR (DMSO-d_6) δ = 46.98 (1C), 49.12 (1C), 51.28 (1C), 51.61 (1C), 52.64 (1C), 54.97 (1C), 70.82 (1C), 102.25 (2C, d, J_{C-F} = 30.4 Hz), 124.70 (1C, t, J_{C-F} = 16.6 Hz), 125.79 (1C), 133.33 (1C), 133.85 (1C, t, J_{C-F} = 14.0 Hz), 153.27 (1C), 157.68 (2C, dd, J_{C-F} = 8.8, 244 Hz), and 159.37 (1C); LRMS-ESI (m/z): 423 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{21}F_2N_8O_3$ (M^+ + H): 423.1699; Found 423.1699.

4.1.29. 5(R)-3-(4-(2-Carbamoyl-[1,2,5]oxadiazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**16h**)

Compound **16h** (98.0 mg, 94%) was prepared from **7c** (93.0 mg, 0.245 mmol) in the same manner as described for **16c**. White powder (CH_2Cl_2/EtOH); mp 179–181 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.38–3.49 (4H, m, $-CH_2-$), 3.80 (2H, t, J = 5.9 Hz, $-CH_2-$), 3.91 (1H, dd, J = 6.2, 9.1 Hz, oxazolidinone-H4), 4.10 (2H,

t, J = 5.3 Hz, $-CH_2-$), 4.18 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.81 (1H, dd, J = 5.0, 14.7 Hz, $-C\underline{H}H-$[1,2,3]triazole), 4.86 (1H, dd, J = 3.8, 14.7 Hz, $-CH\underline{H}-$[1,2,3]triazole), 5.12 (1H, dddd, J = 3.8, 5.0, 6.2, 9.1 Hz, oxazolidinone-H5), 7.04 (2H, d, J = 10.8 Hz, Ar-H2 and H6), 7.74 (1H, s, [1,2,3]triazole-H), and 7.92 (1H, s, [1,2,3]triazole-H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 46.92 (1C), 50.32 (1C), 51.71 (1C), 53.18 (1C), 54.18 (1C), 70.47 (1C), 74.96 (1C), 102.46 (2C, d, J_{C-F} = 30.9 Hz), 124.84 (1C, t, J_{C-F} = 14.0 Hz), 125.29 (1C), 132.79 (1C, t, J_{C-F} = 12.1 Hz), 133.76 (1C), 153.35 (1C), 157.76 (2C, dd, J_{C-F} = 8.8, 246 Hz), and 160.31 (1C); LRMS-ESI (m/z): 424 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{20}F_2N_7O_4$ (M^+ + H): 424.1539; Found 424.1538.

4.1.30. 5(S)-(Isoxazol-3-yl-aminomethyl)-3-(3,5-difluoro-4-(1-carbamoyl-[1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**16i**)

Compound **16i** (139.4 mg, 94%) was prepared from **6c** (200.9 mg, 0.338 mmol) in the same manner as described for **16a**. White powder (EtOH); mp 161–162.5 °C; ^1H NMR ($CDCl_3$ + CD_3OD) δ = 3.10–3.18 (2H, m, $-CH_2-$), 3.26–3.39 (4H, m, $-CH_2-$), 3.57 (1H, d, J = 5.6, 14.7 Hz, $-C\underline{H}H-$NH–isoxazole), 3.63 (1H, dd, J = 4.0, 14.7 Hz, $-CH\underline{H}-$NH–isoxazole), 3.73–3.81 (2H, m, $-CH_2-$), 3.83 (1H, dd, J = 6.7, 9.1 Hz, oxazolidinone-H4), 4.07 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.93 (1H, dddd, J = 4.0, 5.6, 6.7, 9.1 Hz, oxazolidinone-H5), 5.94 (1H, d, J = 1.8 Hz, isoxazole-H), 7.13 (2H, d, J = 10.7 Hz, Ar-H2 and H6), and 8.07 (1H, d, J = 1.8 Hz, isoxazole-H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 46.13 (1C), 47.50 (1C), 50.06 (1C), 50.98 (1C), 53.29 (1C), 55.01 (1C), 71.62 (1C), 96.33 (1C), 102.31 (2C, d, J_{C-F} = 30.9 Hz), 125.04 (1C, t, J_{C-F} = 14.6 Hz), 134.03 (1C, t, J_{C-F} = 13.9 Hz), 154.57 (1C), 158.09 (1C), 158.42 (2C, dd, J_{C-F} = 9.4, 246 Hz), 160.86 (1C), and 163.74 (1C); LRMS-EI (m/z): 437 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{21}F_2N_7O_4$ (M^+): 437.1623; Found 437.1621. Anal. Calcd for $C_{18}H_{21}F_2N_7O_4$: C, 49.43; H, 4.84; N, 22.42. Found: C, 49.07; H, 4.93; N, 22.11.

4.1.31. (S)-N-((3-(3-Fluoro-4-(1-(methylcarbamoyl)-[1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**17a**)

To a solution of **6a** (229.8 mg, 0.475 mmol) and triphosgene (70.0 mg, 0.236 mmol) in tetrahydrofuran (5 mL) was added dropwise Et_3N (0.20 mL, 1.423 mmol) at 0 °C. The mixture was stirred for 10 min at the same temperature, and then 40% methylamine aqueous solution (0.2 mL) was added. Stirring was continued for 2 h at ambient temperature. The mixture was diluted with water (10 mL) and extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. The residue was used for the next reaction without further purification. To a solution of the residue in 1,4-dioxane (3 mL) was added concentrated hydrochloric acid (0.4 mL). The mixture was stirred for 1 h at ambient temperature. The reaction was quenched by the addition of 10% potassium carbonate aqueous solution (10 mL), and the mixture was extracted with 10% MeOH/$CHCl_3$. The organic solution was dried, and evaporated. Silica gel (10 g) column chromatography of the residue using $CHCl_3$/MeOH (98:2 to 95:5) as the eluent afforded **17a** (172.4 mg, 89%). Amorphous powder; ^1H NMR ($CDCl_3$ + CD_3OD) δ = 2.78 (3H, s, $C\underline{H}_3-$NH–C=O), 3.11–3.18 (2H, m, $-CH_2-$), 3.34–3.43 (4H, m, $-CH_2-$), 3.78–4.15 (6H, m, $-CH_2-$), 4.00 (3H, s, $-OC\underline{H}_3$), 4.87–4.98 (1H, m, oxazolidinone-H5), 6.93 (1H, t, J = 9.1 Hz, Ar-H5), 7.03 (1H, dd, J = 2.4, 9.1 Hz, Ar-H6), and 7.38 (1H, dd, J = 2.4, 14.7 Hz, Ar-H2); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 26.03 (1C), 47.24 (1C), 47.68 (1C), 49.17 (1C), 49.79 (1C), 51.74 (1C), 53.46 (1C), 56.99 (1C), 71.26 (1C), 107.82 (1C, d, J_{C-F} = 27.1 Hz), 114.27 (1C), 118.64 (1C), 131.00 (1C, d, J_{C-F} = 10.2 Hz), 136.30 (1C, d, J_{C-F} = 8.8 Hz), 153.91 (1C, d, J_{C-F} = 244 Hz), 154.78 (1C), 160.03 (1C), and 192.70 (1C); LRMS-ESI (m/z): 441 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{18}H_{26}FN_6O_4S$ (M^+ + H): 441.1715; Found 441.1715.

4.1.32. (S)-N-((3-(3,5-Difluoro-4-(1-(methylcarbamoyl)[1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**17b**)

Compound **17b** (168.5 mg, 83%) was prepared from **6b** (221.1 mg, 0.441 mmol) in the same manner as described for **17a**. Colorless prisms (EtOH); mp 175.5–177.5 °C; ^1H NMR ($CDCl_3$ + CD_3OD) δ = 2.80 (3H, s, $C\underline{H}_3-$NH–C=O), 3.06–3.14 (2H, m, $-CH_2-$), 3.26–3.38 (4H, m, $-CH_2-$), 3.72–3.81 (2H, m, $-CH_2-$), 3.87 (1H, dd, J = 6.9, 9.1 Hz, oxazolidinone-H4), 3.93–4.12 (3H, m, $-CH_2-$), 4.00 (3H, s, $-OC\underline{H}_3$), 4.89–5.00 (1H, m, oxazolidinone-H5), and 7.12 (2H, d, J = 10.8 Hz, Ar-H2 and H6); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 26.08 (1C), 47.10 (1C), 47.27 (1C), 50.29 (1C), 50.71 (1C), 53.58 (1C), 54.85 (1C), 57.08 (1C), 71.31 (1C), 102.27 (2C, d, J_{C-F} = 30.4 Hz), 125.13 (1C, t, J_{C-F} = 14.4 Hz), 133.64 (1C, t, J_{C-F} = 13.3 Hz), 154.32 (1C), 158.25 (2C, dd, J_{C-F} = 9.2, 246 Hz), 160.22 (1C), and 192.81 (1C); LRMS-ESI (m/z): 459 (M^+ + H). HRMS-ESI (v): Calcd. for $C_{18}H_{25}F_2N_6O_4S$ (M^+ + H): 459.1621; Found 459.1620. Anal. Calcd for $C_{18}H_{24}F_2N_6O_4S$: C, 47.15; H, 5.28; N, 18.33. Found: C, 47.17; H, 5.34; N, 18.05.

4.1.33. (S)-N-((3-(3,5-Difluoro-4-(2-(methylcarbamoyl)-[1,2,5]oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**17c**)

Compound **17c** (138.7 mg, 99%) was prepared from **6c** (122.2 mg, 0.304 mmol) in the same manner as described for **17a**, except that hydrochloric acid treatment was omitted. Colorless prisms (EtOH); mp 162.5–164.5 °C; ^1H NMR ($CDCl_3$) δ = 2.85 (3H, d, J = 4.8 Hz, $C\underline{H}_3-$NH–C=O), 3.39 (2H, t, J = 5.3 Hz, $-CH_2-$), 3.46 (2H, t, J = 5.3 Hz, $-CH_2-$), 3.75–3.81 (2H, m, $-CH_2-$), 3.83 (1H, dd, J = 7.0, 9.1 Hz, oxazolidinone-H4), 3.97–4.09 (5H, m, $-CH_2-$), 4.00 (3H, s, $-OC\underline{H}_3$), 4.88–4.99 (1H, m, oxazolidinone-H5), 5.87 (1H, q, J = 4.8 Hz, $C\underline{H}_3-N\underline{H}-$C=O), 7.08 (2H, d, J = 10.8 Hz, Ar-H2 and H6), and 7.32 (1H, t, J = 6.3 Hz, $-N\underline{H}-$C=S); ^{13}C NMR ($CDCl_3$) δ = 26.65 (1C), 47.27 (1C), 47.41 (1C), 51.60 (1C), 54.04 (1C), 54.36 (1C), 57.59 (1C), 71.18 (1C), 74.22 (1C), 102.42 (2C, d, J_{C-F} = 30.9 Hz), 124.85 (1C, t, J_{C-F} = 14.1 Hz), 133.24 (1C, t, J_{C-F} = 13.6 Hz), 153.84 (1C), 157.86 (2C, dd, J = 9.1, 245 Hz), 160.33 (1C), and 192.84 (1C); LRMS-EI (m/z): 459 (M^+). HRMS-EI (m/z): Calcd. for $C_{18}H_{23}F_2N_5O_5S$ (M^+): 459.1388; Found 459.1389. Anal. Calcd for $C_{18}H_{23}F_2N_5O_5S$: C, 47.05; H, 5.05; N, 15.24. Found: C, 47.12; H, 5.06; N, 14.97.

4.1.34. 5(R)-3-(4-(2-Methylcarbamoyl[1,2,5]oxadiazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethy-l)oxazolidin-2-one (**17d**)

Compound **17d** (97.5 mg, 62%) was prepared from **7c** (137.5 mg, 0.362 mmol) in the same manner as described for **17c**. Amorphous solid; ^1H NMR ($CDCl_3$) δ = 2.85 (3H, d, J = 4.8 Hz, $C\underline{H}_3-$NH–C=O), 3.40 (2H, br t, J = 5 Hz, $-CH_2-$), 3.46 (2H, br t, J = 5 Hz, $-CH_2-$), 3.79 (2H, br t, J = 5 Hz, $-CH_2-$), 3.89 (1H, dd, J = 6.2, 9.1 Hz, oxazolidinone-H4), 4.02 (2H, br t, J = 5 Hz, $-CH_2-$), 4.10 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.78 (2H, d, J = 4.1 Hz, $-C\underline{H}_2-$[1,2,3]triazole), 5.06 (1H, ddt, J = 6.2, 9.1, 4.1 Hz, oxazolidinone-H5), 5.81 (1H, q, J = 4.8 Hz, $CH_3-N\underline{H}-$C=O), 6.92 (2H, d, J = 10.7 Hz, Ar-H2 and H6), 7.75 (1H, br s, [1,2,3]triazole-H), and 7.77 (1H, br s, [1,2,3]triazole-H); ^{13}C NMR ($CDCl_3$) δ = 26.56 (1C), 47.12 (1C), 51.52 (1C), 51.84 (1C), 53.93 (1C), 54.25 (1C), 70.38 (1C), 74.14 (1C), 102.58 (2C, d, J_{C-F} = 29.8 Hz), 125.04 (1C), 125.08 (1C, t, J_{C-F} = 14.3 Hz), 132.62 (1C, t, J_{C-F} = 13.6 Hz), 134.20 (1C), 153.02 (1C), 157.76 (2C, dd, J_{C-F} = 9.4, 248 Hz), and 160.20 (1C); LRMS-EI (v): 437 (M^+). HRMS-EI (v): Calcd. for $C_{18}H_{21}F_2N_7O_4$ (M^+): 437.1623; Found 437.1617.

*4.1.35. (S)-N-((3-(3-Fluoro-4-(1-(hydroxycarbamoyl)[1,2,5] triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**18a**)*

To a solution of **6a** (251.2 mg, 0.519 mmol) and triphosgene (76.2 mg, 0.257 mmol) in tetrahydrofuran (5 mL) was added dropwise Et_3N (0.44 mL, 3.131 mmol) at 0 °C. The mixture was stirred for 10 min at the same temperature, and then hydroxyammonium chloride (117.8 mg, 2.559 mmol) was added. Stirring was continued for 7.5 h at ambient temperature. The mixture was diluted with water (10 mL) and extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. The residue was used for the next reaction without further purification. To a solution of the residue in 1,4-dioxane (3 mL) was added concentrated hydrochloric acid (0.4 mL). The mixture was stirred for 1.5 h at ambient temperature. The reaction was quenched by the addition of 10% potassium carbonate aqueous solution (5 mL), and the mixture was extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. Silica gel (10 g) column chromatography of the residue using $CHCl_3$/MeOH (97:3 to 90:10) as the eluent afforded **18a** (196.9 mg, 86%). White powder ($CHCl_3$/MeOH); mp 191–193.5 °C (dec.); ^{1}H NMR (DMSO-d_6) δ = 2.89–3.00 (2H, m, $-CH_2-$), 3.22–3.42 (4H, m, $-CH_2-$), 3.59–3.80 (5H, m, $-CH_2-$), 3.87 (3H, s, $-OCH_3$), 4.08 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.80–4.91 (1H, m, oxazolidinone-H5), 4.99 (1H, t, J = 6.0 Hz, NH), 6.98 (1H, t, J = 9.7 Hz, Ar-H5), 7.09 (1H, dd, J = 2.1, 9.7 Hz, Ar-H6), 7.40 (1H, dd, J = 2.1, 15.5 Hz, Ar-H2), 8.09 (1H, br s, $-NH-OH$), 8.90 (1H, s, $-NH-OH$), and 9.50 (1H, br t, J = 6 Hz, NH); ^{13}C NMR (DMSO-d_6) δ = 47.33 (1C), 47.60 (1C), 48.53 (1C), 49.68 (1C), 50.31 (1C), 53.30 (1C), 56.71 (1C), 70.24 (1C), 107.14 (1C, d, J_{C-F} = 24.9 Hz), 114.42 (1C), 118.53 (1C), 131.09 (1C, d, J_{C-F} = 10.6 Hz), 134.95 (1C, d, J_{C-F} = 9.1 Hz), 152.88 (1C, d, J_{C-F} = 241 Hz), 153.89 (1C), 160.27 (1C), and 191.69 (1C); LRMS-ESI (m/z): 443 (M^+ + H). HRMS-ESI (v): Calcd. for $C_{17}H_{24}FN_6O_5S$ (M^+ + H): 443.1507; Found 443.1510. Anal. Calcd for $C_{17}H_{23}FN_6O_5S$: C, 46.15; H, 5.24; N, 18.99. Found: C, 46.05; H, 5.19; N, 18.83.

*4.1.36. 5(R)-3-(4-(1-(Hydroxycarbamoyl)[1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**18b**)*

Compound **18b** (134.1 mg, 69%) was prepared from **7b** (212.7 mg, 0.444 mmol) in the same manner as described for **18a**. White powder (CH_2Cl_2/MeOH); mp 182–184 °C (dec.); ^{1}H NMR (DMSO-d_6) δ = 2.87–2.98 (2H, m, $-CH_2-$), 3.11–3.19 (2H, m, $-CH_2-$), 3.21–3.29 (2H, m, $-CH_2-$), 3.54–3.63 (2H, m, $-CH_2-$), 3.79–3.89 (1H, m, oxazolidinone-H4), 4.19 (1H, t, J = 9.4 Hz, oxazolidinone-H4), 4.82 (2H, br s, $-CH_2-$[1,2,3]triazole), 4.99 (1H, t, J = 5.8 Hz, NH), 5.08–5.19 (1H, m, oxazolidinone-H5), 7.19 (2H, d, J = 11.1 Hz, Ar-H2 and H6), 7.75 (1H, s, [1,2,5]triazole-H), 8.12 (1H, s, [1,2,5]triazole-H), 8.15 (1H, s, $-NH-OH$), and 8.91 (1H, s, $-NH-OH$); ^{13}C NMR (DMSO-d_6) δ = 46.97 (1C), 49.85 (1C), 51.30 (1C), 51.59 (1C), 52.28 (1C), 54.98 (1C), 70.82 (1C), 102.26 (2C, d, J_{C-F} = 29.8 Hz), 124.60 (1C, t, J_{C-F} = 14.7 Hz), 125.77 (1C), 133.31 (1C), 133.89 (1C, t, J_{C-F} = 14.3 Hz), 153.26 (1C), 157.67 (2C, dd, J_{C-F} = 8.9, 244 Hz), and 160.44 (1C); LRMS-ESI (m/z): 439 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{21}F_2N_8O_4$ (M^+ + H): 439.1648; Found 439.1650.

*4.1.37. 5(R)-3-(4-(2-(Hydroxycarbamoyl)[1,2,5]oxadiazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**18c**)*

Compound **18c** (82.8 mg, 79%) was prepared from **7c** (90.8 mg, 0.239 mmol) in the same manner as described for **18a**, except that hydrochloric acid treatment was omitted. Amorphous powder; ^{1}H NMR (DMSO-d_6) δ = 3.30–3.48 (3H, m, $-CH_2-$), 3.65 (1H, br t, J = 5 Hz, $-CH_2-$), 3.76 (1H, br t, J = 5 Hz, $-CH_2-$), 3.85 (1H, dd, J = 5.9, 9.3 Hz, oxazolidinone-H4), 3.99–4.11 (2H, m, $-CH_2-$), 4.19 (1H, t, J = 9.3 Hz, oxazolidinone-H4), 4.35 (1H, t, J = 5.0 Hz, $-CH_2-$), 4.82 (2H, d, J = 5.0 Hz, $-CH_2-$[1,2,3]triazole), 5.08–5.19 (1H, m, oxazolidinone-H5), 7.22 (2H, d, J = 11.0 Hz, Ar-H2 and H6), 7.75 (1H, s, [1,2,3]triazole-H), and 8.15 (1H, s, [1,2,3]triazole-H); ^{13}C NMR (DMSO-d_6) δ = 46.97 (1C), 50.48 (0.5C), 51.25 (0.5C), 51.58 (1C), 52.53 (0.5C), 52.92 (0.5C), 54.37 (0.5C), 55.97 (0.5C), 70.82 (1C), 75.73 (0.5C), 75.91 (0.5C), 102.26 (2C, d, J_{C-F} = 30.4 Hz), 123.95 (0.5C, t, J_{C-F} = 14.3 Hz), 124.04 (0.5C, t, J_{C-F} = 14.3 Hz), 125.77 (1C), 133.32 (1C), 134.18 (0.5C, t, J_{C-F} = 13.7 Hz), 134.22 (0.5C, t, J_{C-F} = 13.7 Hz), 153.26 (1C), 154.45 (0.5C), 157.51 (2C, dd, J_{C-F} = 9.1, 243 Hz), and 157.94 (0.5C); LRMS-ESI (m/z): 440 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{17}H_{20}F_2N_7O_5$ (M^+ + H): 440.1488; Found 440.1493.

*4.1.38. (S)-N-((3-(3-Fluoro-4-(1-(methoxycarbamoyl)[1,2,5] triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**19a**)*

To a solution of **6a** (244.1 mg, 0.505 mmol) and triphosgene (75.9 mg, 0.256 mmol) in tetrahydrofuran (5 mL) was added dropwise Et_3N (0.43 mL, 3.060 mmol) at 0 °C. The mixture was stirred for 10 min at the same temperature, and then *O*-methylhydroxylamine hydrochloride (206.5 mg, 2.472 mmol) was added. Stirring was continued for 24 h at ambient temperature. The mixture was diluted with water (10 mL) and extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. The residue was used for the next reaction without further purification. To a solution of the residue in 1,4-dioxane (3 mL) was added concentrated hydrochloric acid (0.4 mL), and the mixture was stirred for 2 h at ambient temperature. The reaction was quenched by the addition of 10% potassium carbonate aqueous solution (10 mL), and the mixture was extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. Silica gel (10 g) column chromatography of the residue using $CHCl_3$/MeOH (98:2 to 96:4) as the eluent afforded **19a** (184.5 mg, 80%). White powder (EtOH); mp 146–148 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.11–3.19 (2H, m, $-CH_2-$), 3.32–3.44 (4H, m, $-CH_2-$), 3.72 (3H, s, $-NH-OCH_3$), 3.77–4.16 (6H, m, $-CH_2-$), 4.00 (3H, s, $-OCH_3$), 4.88–4.99 (1H, m, oxazolidinone-H5), 6.93 (1H, t, J = 9.1 Hz, Ar-H5), 7.04 (1H, dd, J = 2.5, 9.1 Hz, Ar-H6), 7.39 (1H, dd, J = 2.5, 14.7 Hz, Ar-H2), and 8.58 (1H, br t, J = 6 Hz, $-NH-C=S$); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 47.36 (1C), 47.65 (1C), 49.31 (1C), 49.89 (1C), 51.20 (1C), 53.45 (1C), 57.02 (1C), 63.99 (1C), 71.26 (1C), 107.79 (1C, d, J_{C-F} = 27.6 Hz), 114.23 (1C), 118.78 (1C), 131.21 (1C, d, J_{C-F} = 9.6 Hz), 136.14 (1C, d, J_{C-F} = 8.8 Hz), 154.00 (1C, d, J_{C-F} = 247 Hz), 154.77 (1C), 160.25 (1C), and 192.74 (1C); LRMS-ESI (m/z): 457 (M^+ + H). HRMS-ESI (m/z): Calcd. for $C_{18}H_{26}FN_6O_5S$ (M^+ + H): 457.1664; Found 457.1662. Anal. Calcd for $C_{18}H_{25}FN_6O_5S$: C, 47.36; H, 5.52; N, 18.41. Found: C, 47.39; H, 5.50; N, 18.28.

*4.1.39. (S)-N-((3-(3,5-Difluoro-4-(1-(methoxycarbamoyl)[1,2,5] triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)-methyl)-O-methylthiocarbamate (**19b**)*

Compound **19b** (205.2 mg, 70%) was prepared from **6b** (309.7 mg, 0.617 mmol) in the same manner as described for **19a**. White powder (EtOH); mp 176–180 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ = 3.08–3.14 (2H, m, $-CH_2-$), 3.25–3.39 (4H, m, $-CH_2-$), 3.71–3.80 (2H, m, $-CH_2-$), 3.74 (3H, s, $-NH-OCH_3$), 3.87 (1H, dd, J = 6.8, 9.1 Hz, oxazolidinone-H4), 3.94–4.01 (2H, m, $-CH_2-$), 4.00 (3H, s, $-OCH_3$), 4.06 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.90–5.01 (1H, m, oxazolidinone-H5), 7.13 (2H, d, J = 10.8 Hz, Ar-H2 and H6), and 8.59 (1H, br t, J = 6 Hz, $-NH-C=S$); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 47.27 (2C), 50.37 (1C), 50.85 (1C), 52.80 (1C), 54.87 (1C), 57.03 (1C), 63.99 (1C), 71.29 (1C), 102.27 (2C, d, J_{C-F} = 29.8 Hz), 124.88 (1C, t, J_{C-F} = 14.2 Hz), 133.84 (1C, t, J_{C-F} = 12.8 Hz), 154.30 (1C),

158.29 (2C, dd, J_{C-F} = 9.1, 246 Hz), 160.38 (1C), and 192.89 (1C); LRMS-ESI (*m*/*z*): 475 (M^+ + H). HRMS-ESI (*m*/*z*): Calcd. for $C_{18}H_{25}F_2N_6O_5S$ (M^+ + H): 475.1570; Found 475.1571.

4.1.40. (S)-N-((3-(3,5-Difluoro-4-(2-(methoxycarbamoyl)[1,2,5]oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**19c**)

Compound **19c** (112.3 mg, 92%) was prepared from **6c** (102.9 mg, 0.256 mmol) in the same manner as described for **19a**, except that hydrochloric acid treatment was omitted. White powder (Et_2O/EtOH); mp 159–161 °C; ^1H NMR ($CDCl_3$ + CD_3OD) δ = 3.39–3.48 (4H, m, $-CH_2-$), 3.73–3.82 (2H, m, $-CH_2-$), 3.76 (3H, s, $-NH-OC\underline{H}_3$), 3.87 (1H, dd, *J* = 6.7, 9.1 Hz, oxazolidinone-H4), 3.94–4.04 (3H, m, $-CH_2-$), 4.00 (3H, s, $-OC\underline{H}_3$), 4.07 (2H, t, *J* = 4.7 Hz, $-CH_2-$), 4.90–5.01 (1H, m, oxazolidinone-H5), 7.13 (2H, d, *J* = 10.8 Hz, Ar-H2 and H6), and 8.55 (1H, br t, *J* = 6 Hz, $-N\underline{H}-C=S$); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ = 47.27 (2C), 50.79 (1C), 53.03 (1C), 54.25 (1C), 57.05 (1C), 64.01 (1C), 71.31 (1C), 75.26 (1C), 102.35 (2C, d, J_{C-F} = 30.4 Hz), 124.48 (1C, t, J_{C-F} = 14.3 Hz), 133.52 (1C, t, J_{C-F} = 12.8 Hz), 154.32 (1C), 157.84 (2C, dd, J_{C-F} = 9.1, 246 Hz), 159.70 (1C), and 192.87 (1C); LRMS-ESI (*m*/*z*): 476 (M^+ + H). HRMS-ESI (*m*/*z*): Calcd. for $C_{18}H_{24}F_2N_5O_6S$ (M^+ + H): 476.1410; Found 476.1413. Anal. Calcd for $C_{18}H_{23}F_2N_5O_6S$: C, 45.47; H, 4.88; N, 14.73. Found: C, 45.54; H, 4.83; N, 14.56.

4.1.41. Trifluoromethanesulfonic acid 5-bromo-pyridin-2-yl ester (**21**)

To a solution of **20** (1.9267 g, 11.07 mmol) in pyridine (11 mL) was added dropwise triflic anhydride (2.05 mL, 12.18 mmol) at 0 °C, and the mixture was stirred for 10 min at the same temperature and then for 20 min at ambient temperature. The reaction mixture was diluted with Et_2O (50 mL), the organic layer was washed with 1 M $CuSO_4$ aqueous solution, H_2O, and brine, and dried. Evaporation of the solvent followed by silica gel (50 g) column chromatography of the residue using Et_2O/*n*-hexane (10:90) as the eluent afforded **21** (3.3320 g, 98%). Colorless oil; ^1H NMR ($CDCl_3$) δ = 7.11 (1H, d, *J* = 8.5 Hz, pyridine-H3), 8.00 (1H, dd, *J* = 2.6, 8.5 Hz, pyridine-H4), and 8.46 (1H, d, *J* = 2.6 Hz, pyridine-H6); ^{13}C NMR ($CDCl_3$) δ = 116.68 (1C), 118.56 (1C, q, J_{C-F} = 320 Hz), 120.45 (1C), 143.45 (1C), 149.68 (1C), and 154.50 (1C); LRMS-EI (*m*/*z*): 305 (M^+). HRMS-EI (*m*/*z*): Calcd. for $C_6H_3BrF_3NO_3S$ (M^+): 304.8969; Found 304.8966.

4.1.42. 5-(5-Bromopyridin-2-yl)[1,2,5]oxadiazepane-2-carboxylic acid tert-butyl ester (**22**)

To a solution of **21** (1.5571 g, 5.088 mmol) and *i*-Pr_2NEt (1.3410 g, 10.38 mmol) in hexamethylphosphoric triamide (5 mL) was added [1,2,5]oxadiazepane-2-carboxylic acid *tert*-butyl ester (1.5509 g, 7.668 mmol) at ambient temperature. The solution was stirred for 15 h at 100 °C, then cooled and diluted with H_2O (30 mL). The resulting mixture was extracted with AcOEt, and the organic solution was dried and evaporated. Silica gel (50 g) column chromatography of the residue using *n*-hexane/AcOEt (85:15 to 75:25) as the eluent afforded **22** (1.6018 g, 88%). Colorless prisms (Et_2O/*n*-hexane); mp 102.5–104.5 °C; ^1H NMR ($CDCl_3$) δ = 1.43 (9H, s, *t*-$C_4\underline{H}_9-$), 3.80 (4H, s, $-CH_2-$), 3.88 (2H, t, *J* = 5.3 Hz, $-CH_2-$), 4.09 (2H, t, *J* = 5.3 Hz, $-CH_2-$), 6.45 (1H, d, *J* = 9.1 Hz, pyridine-H3), 7.51 (1H, dd, *J* = 2.6, 9.1 Hz, pyridine-H4), and 8.16 (1H, d, *J* = 2.6 Hz, pyridine-H6); ^{13}C NMR ($CDCl_3$) δ = 28.22 (3C), 47.38 (1C), 47.74 (1C), 48.40 (1C), 71.32 (1C), 81.32 (1C), 106.90 (1C), 107.18 (1C), 139.71 (1C), 148.76 (1C), 155.10 (1C), and 155.78 (1C); LRMS-EI (*m*/*z*): 357 (M^+). HRMS-EI (*m*/*z*): Calcd. for $C_{14}H_{20}BrN_3O_3$ (M^+): 357.0688; Found 357.0677. Anal. Calcd for $C_{14}H_{20}BrN_3O_3$: C, 46.94; H, 5.63; N, 11.73. Found: C, 46.87; H, 5.54; N, 11.66.

4.1.43. (S)-N-((3-(3-Fluoro-4-(2-(2-(tert-butoxycarbonyl)[1,2,5]oxadiazepan-5-yl)pyridin-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**23a**)

A suspension of **22** (503.4 mg, 1.405 mmol), (*S*)-*N*-(3-((3-fluoro-4-(3,3,4,4-tetramethylborolan-1-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (637.9 mg, 1.687 mmol), $Pd(PPh_3)_4$ (168.3 mg, 0.146 mmol), and sodium carbonate (447.2 mg, 4.219 mmol) in 1,4-dioxane (4 mL) and H_2O (1 mL) was refluxed for 1.5 h. After cooling, the reaction mixture was diluted with H_2O (30 mL). The resulting mixture was extracted with AcOEt, and the organic solution was washed with brine, dried and evaporated. Silica gel (20 g) column chromatography of the residue using $CHCl_3$/MeOH (98:1 to 97:3) as the eluent afforded **23a** (426.5 mg, 57%). Amorphous solid; ^1H NMR ($CDCl_3$) δ = 1.43 (9H, s, *t*-$C_4\underline{H}_9-$), 2.04 (3H, s, $C\underline{H}_3-C=O$), 3.63–3.72 (2H, m, $-CH_2-$), 3.79–3.98 (7H, m, $-CH_2-$), 4.07 (1H, t, *J* = 9.1 Hz, oxazolidinone-H4), 4.14 (2H, t, *J* = 5.3 Hz, $-CH_2-$), 4.76–4.87 (1H, m, oxazolidinone-H5), 6.57 (1H, t, *J* = 6.2 Hz, $-N\underline{H}-C=O$), 6.61 (1H, d, *J* = 8.8 Hz, pyridine-H3), 7.24 (1H, dd, *J* = 2.2, 8.6 Hz, Ar-H6), 7.37 (1H, t, *J* = 8.6 Hz, Ar-H5), 7.49 (1H, dd, *J* = 2.2, 12.9 Hz, Ar-H2), 7.65 (1H, d, *J* = 8.8 Hz, pyridine-H4), and 8.31 (1H, s, pyridine-H6); ^{13}C NMR ($CDCl_3$) δ = 22.98 (1C), 28.22 (3C), 41.91 (1C), 47.30 (1C), 47.49 (1C), 48.01 (1C), 48.35 (1C), 71.61 (1C), 72.01 (1C), 81.33 (1C), 105.37 (1C), 106.45 (1C, d, J_{C-F} = 28.8 Hz), 113.76 (1C), 119.59 (1C), 122.00 (1C, d, J_{C-F} = 14.9 Hz), 129.79 (1C, d, J_{C-F} = 5.5 Hz), 137.69 (1C), 137.90 (1C, d, J_{C-F} = 12.8 Hz), 147.79 (1C), 154.20 (1C), 155.12 (1C), 156.43 (1C), 159.76 (1C, d, J_{C-F} = 247 Hz), and 171.17 (1C); LRMS-EI (*m*/*z*): 529 (M^+). HRMS-EI (*m*/*z*): Calcd. for $C_{26}H_{32}FN_5O_6$ (M^+): 529.2337; Found 529.2338.

4.1.44. 5(R)-3-(4-(2-(2-(tert-Butoxycarbonyl)[1,2,5]oxadiazepan-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(1,2,3-triazol-1-ylmethyl) oxazolidin-2-one (**23b**)

Compound **23b** (235.6 mg, 31%) was prepared from **22** (506.5 mg, 1.414 mmol) in the same manner as described for **23a**, except that (5*R*)-3-(3-fluoro-4-(3,3,4,4-tetramethylborolan-1-yl)phenyl)-5-(1,2,3-triazol-1-yl-methyl)oxazolidin-2-one was used instead of (*S*)-*N*-((3-(3-fluoro-4-(3,3,4,4-tetramethylborolan-1-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide. White powder (CH_2Cl_2/EtOH); mp 201–203 °C; ^1H NMR ($CDCl_3$) δ = 1.43 (9H, s, *t*-$C_4\underline{H}_9-$), 3.82–3.92 (4H, m, $-CH_2-$), 3.92–4.01 (3H, m, $-CH_2-$), 4.14 (2H, t, *J* = 5.3 Hz, $-CH_2-$), 4.19 (1H, t, *J* = 9.1 Hz, oxazolidinone-H4), 4.81 (2H, d, *J* = 4.2 Hz, $-C\underline{H}_2-$[1,2,3]triazole), 5.04–5.14 (1H, m, oxazolidinone-H5), 6.62 (1H, d, *J* = 8.8 Hz, pyridine-H3), 7.16 (1H, dd, *J* = 2.2, 8.5 Hz, Ar-H6), 7.36 (1H, t, *J* = 8.5 Hz, Ar-H5), 7.38 (1H, dd, *J* = 2.2, 12.6 Hz, Ar-H2), 7.65 (1H, d, *J* = 8.8 Hz, pyridine-H4), 7.76 (1H, br s, [1,2,3]triazole-H), 7.80 (1H, br s, [1,2,3]triazole-H), and 8.31 (1H, br s, pyridine-H6); ^{13}C NMR ($CDCl_3$) δ = 28.25 (3C), 47.33 (2C), 48.03 (1C), 48.39 (1C), 51.98 (1C), 70.44 (1C), 71.64 (1C), 81.32 (1C), 105.39 (1C), 106.72 (1C, d, J_{C-F} = 28.8 Hz), 114.02 (1C), 119.53 (1C), 122.51 (1C, d, J_{C-F} = 14.3 Hz), 124.99 (1C), 129.88 (1C, d, J_{C-F} = 5.0 Hz), 134.48 (1C), 137.37 (1C, d, J_{C-F} = 12.8 Hz), 137.71 (1C), 147.83 (1C), 153.15 (1C), 155.12 (1C), 156.52 (1C), and 159.75 (1C, d, J_{C-F} = 248 Hz); LRMS-EI (*m*/*z*): 539 (M^+). HRMS-EI (*m*/*z*): Calcd. for $C_{26}H_{30}FN_7O_5$ (M^+): 539.2293; Found 539.2285. Anal. Calcd for $C_{26}H_{30}FN_7O_5$: C, 57.88; H, 5.60; N, 18.17. Found: C, 57.66; H, 5.74; N, 17.98.

4.1.45. (S)-N-((3-(3-Fluoro-4-(2-([1,2,5]oxadiazepan-5-yl)pyridin-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**24a**)

To a solution of **23a** (111.3 mg, 0.210 mmol) in 1,4-dioxane (2 mL) was added concentrated hydrochloric acid (0.2 mL). The mixture was stirred for 1 h at ambient temperature, then neutralized with 10% potassium carbonate aqueous solution, and extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. Silica gel (8 g) column chromatography of the residue using

$CHCl_3$/MeOH (97:3 to 95:5) as the eluent afforded **24a** (81.3 mg, 90%). White powder (CH_2Cl_2/EtOH); mp 178–180 °C; ^{1}H NMR ($CDCl_3 + CD_3OD$) $\delta = 2.02$ (3H, s, C<u>H</u>$_3$–C=O), 3.22 (2H, t, $J = 5.3$ Hz, –C<u>H</u>$_2$–), 3.55–3.65 (2H, m, –C<u>H</u>$_2$–), 3.81 (1H, dd, $J = 6.8$, 9.1 Hz, oxazolidinone-H4), 3.87 (2H, t, $J = 5.3$ Hz, –C<u>H</u>$_2$–), 3.91–4.03 (4H, m, –C<u>H</u>$_2$–), 4.10 (1H, t, $J = 9.1$ Hz, oxazolidinone-H4), 4.75–4.85 (1H, m, oxazolidinone-H5), 6.66 (1H, d, $J = 8.8$ Hz, pyridine-H3), 7.25 (1H, dd, $J = 2.1$, 8.5 Hz, Ar-H6), 7.39 (1H, t, $J = 8.5$ Hz, Ar-H5), 7.50 (1H, dd, $J = 2.1$, 12.9 Hz, Ar-H2), 7.66 (1H, d, $J = 8.8$ Hz, pyridine-H4), 7.86 (1H, br t, $J = 6$ Hz, –N<u>H</u>–C=O), and 8.28 (1H, s, pyridine-H6); ^{13}C NMR ($CDCl_3 + CD_3OD$) $\delta = 22.13$ (1C), 41.75 (1C), 47.44 (1C), 48.43 (1C), 49.10 (1C), 49.99 (1C), 68.99 (1C), 71.95 (1C), 105.54 (1C), 106.25 (1C, d, $J_{C-F} = 29.3$ Hz), 113.69 (1C), 118.93 (1C), 121.74 (1C, d, $J_{C-F} = 11.6$ Hz), 129.49 (1C, d, $J_{C-F} = 5.0$ Hz), 137.60 (2C), 147.25 (1C), 154.56 (1C), 156.78 (1C), 159.46 (1C, d, $J_{C-F} = 248$ Hz), and 172.12 (1C); LRMS-EI (m/z): 429 (M^+). HRMS-EI (m/z): Calcd. for $C_{21}H_{24}FN_5O_4$ (M^+): 429.1812; Found 429.1810.

4.1.46. 5(R)-3-(4-(2-[1,2,5]Oxadiazepan-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**24b**)

Compound **24b** (158.0 mg, 98%) was prepared from **23b** (199.0 mg, 0.369 mmol) in the same manner as described for **24a**. White powder (CH_2Cl_2/EtOH); mp 189.5–191.5 °C; ^{1}H NMR ($CDCl_3 + CD_3OD$) $\delta = 3.22$ (2H, t, $J = 5.3$ Hz, –C<u>H</u>$_2$–), 3.87 (2H, t, $J = 5.3$ Hz, –C<u>H</u>$_2$–), 3.92–4.04 (5H, m, –C<u>H</u>$_2$–), 4.24 (1H, t, $J = 9.1$ Hz, oxazolidinone-H4), 4.82 (1H, dd, $J = 5.0$, 14.7 Hz, –C<u>H</u>H–[1,2,3]triazole), 4.86 (1H, dd, $J = 3.8$, 14.7 Hz, –CH<u>H</u>–[1,2,3]triazole), 5.08–5.18 (1H, m, oxazolidinone-H5), 6.67 (1H, d, $J = 8.8$ Hz, pyridine-H3), 7.17 (1H, dd, $J = 2.1$, 8.5 Hz, Ar-H6), 7.37 (1H, t, $J = 8.5$ Hz, Ar-H5), 7.40 (1H, dd, $J = 2.1$, 13.0 Hz, Ar-H2), 7.66 (1H, d, $J = 8.8$ Hz, pyridine-H4), 7.75 (1H, s, [1,2,3]triazole-H), 7.92 (1H, s, [1,2,3]triazole-H), and 8.26 (1H, s, pyridine-H6); ^{13}C NMR ($CDCl_3 + CD_3OD$) $\delta = 47.04$ (1C), 48.42 (1C), 49.09 (1C), 49.96 (1C), 51.80 (1C), 68.97 (1C), 70.57 (1C), 105.58 (1C), 106.44 (1C, d, $J_v = 28.8$ Hz), 113.89 (1C), 118.85 (1C), 122.12 (1C, d, $J_{C-F} = 10.6$ Hz), 125.26 (1C), 129.53 (1C, d, $J_{C-F} = 5.0$ Hz), 133.80 (1C), 137.07 (1C, d, $J_{C-F} = 13.3$ Hz), 137.65 (1C), 147.22 (1C), 153.53 (1C), 156.82 (1C), and 159.40 (1C, d, $J_{C-F} = 247$ Hz); LRMS-EI (m/z): 439 (M^+). HRMS-EI (m/z): Calcd. for $C_{21}H_{22}FN_7O_3$ (M^+): 439.1768; Found 439.1780.

4.1.47. (S)-N-((3-(3-Fluoro-4-(2-(2-(hydroxyacetyl)[1,2,5]oxadiazepan-5-yl)pyridin-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**25a**)

To a solution of compound **24a** (126.0 mg, 0.293 mmol) and pyridine (234.1 mg, 2.960 mmol) in CH_2Cl_2 (5 mL) was added acetoxyacetyl chloride (211.1 mg, 1.546 mmol). The mixture was stirred for 2 h, and then a small amount of EtOH was added and the solution was concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the residue in MeOH (3 mL) was added potassium carbonate (406.7 mg, 2.943 mmol). The mixture was stirred for 30 min at ambient temperature, diluted by the addition of H_2O (5 mL), and extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated. Silica gel (8 g) column chromatography of the residue using $CHCl_3$/MeOH (99:1 to 92:8) as the eluent afforded **25a** (107.3 mg, 75%). White powder (EtOH); mp 151–153 °C; ^{1}H NMR ($CDCl_3 + CD_3OD$) $\delta = 2.02$ (3H, s, C<u>H</u>$_3$–C=O), 3.56–3.66 (2H, m, –C<u>H</u>$_2$–), 3.83 (1H, dd, $J = 6.7$, 9.1 Hz, oxazolidinone-H4), 3.91–4.22 (9H, m, –C<u>H</u>$_2$–), 4.34 (2H, br s, –C<u>H</u>$_2$–OH), 4.76–4.87 (1H, m, oxazolidinone-H5), 6.70 (1H, d, $J = 8.8$ Hz, pyridine-H3), 7.28 (1H, dd, $J = 2.1$, 8.5 Hz, Ar-H6), 7.40 (1H, t, $J = 8.5$ Hz, Ar-H5), 7.53 (1H, dd, $J = 2.1$, 12.9 Hz, Ar-H2), 7.71 (1H, d, $J = 8.8$ Hz, pyridine-H4), 8.02 (1H, br t, $J = 6$ Hz, –N<u>H</u>–C=O), and 8.30 (1H, s, pyridine-H6); ^{13}C NMR ($CDCl_3 + CD_3OD$) $\delta = 21.98$ (1C), 41.72 (1C), 45.83 (1C), 47.07 (1C), 47.42 (1C), 47.68 (1C), 59.44 (1C), 71.92 (1C), 74.74 (1C), 105.41 (1C), 106.21 (1C, d, $J_{C-F} = 27.7$ Hz), 113.68 (1C), 119.88 (1C), 121.32 (1C, d, $J_{C-F} = 13.2$ Hz), 129.53 (1C, d, $J_{C-F} = 5.0$ Hz), 137.85 (2C), 147.27 (1C), 154.56 (1C), 155.66 (1C), 159.42 (1C, d, $J_{C-F} = 248$ Hz), 172.18 (1C), and 173.58 (1C); LRMS-EI (m/z): 487 (M^+). HRMS-EI (m/z): Calcd. for $C_{23}H_{26}FN_5O_6$ (M^+): 487.1867; Found 487.1856. Anal. Calcd for $C_{23}H_{26}FN_5O_6$: C, 56.67; H, 5.38; N, 14.37. Found: C, 56.28; H, 5.55; N, 14.67.

4.1.48. 5(R)-3-(4-(2-(2-(Hydroxyacetyl)[1,2,5]oxadiazepan-5-yl)pyridin-5-yl)-3-fluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**25b**)

Compound **25b** (79.1 mg, 92%) was prepared from **24b** (75.6 mg, 0.172 mmol) in the same manner as described for **25a**. White powder (CH_2Cl_2/EtOH); mp 138–139.5 °C; ^{1}H NMR ($CDCl_3 + CD_3OD$) $\delta = 3.90$–4.06 (6H, m, –C<u>H</u>$_2$–), 4.07–4.21 (3H, m, –C<u>H</u>$_2$–), 4.26 (1H, t, $J = 9.1$ Hz, oxazolidinone-H4), 4.33 (2H, br s, –C<u>H</u>$_2$–OH), 4.83 (1H, dd, $J = 5.3$, 15.0 Hz, –C<u>H</u>H–[1,2,3]triazole), 4.87 (1H, dd, $J = 3.8$, 15.0 Hz, –CH<u>H</u>–[1,2,3]triazole), 5.08–5.19 (1H, m, oxazolidinone-H5), 6.69 (1H, d, $J = 8.8$ Hz, pyridine-H3), 7.19 (1H, dd, $J = 2.2$, 8.5 Hz, Ar-H6), 7.38 (1H, t, $J = 8.5$ Hz, Ar-H5), 7.42 (1H, dd, $J = 2.2$, 12.7 Hz, Ar-H2), 7.69 (1H, d, $J = 8.8$ Hz, pyridine-H4), 7.75 (1H, br s, [1,2,3]triazole-H), 7.94 (1H, br s, [1,2,3]triazole-H), and 8.28 (1H, s, pyridine-H6); ^{13}C NMR ($CDCl_3 + CD_3OD$) $\delta = 45.81$ (1C), 47.02 (2C), 47.67 (1C), 51.74 (1C), 59.43 (1C), 70.57 (1C), 74.71 (1C), 105.40 (1C), 106.36 (1C, d, $J_{C-F} = 30.4$ Hz), 113.84 (1C), 119.75 (1C), 122.66 (1C, d, $J_{C-F} = 14.4$ Hz), 125.27 (1C), 129.55 (1C, d, $J_{C-F} = 5.0$ Hz), 133.71 (1C), 137.28 (1C, d, $J_{C-F} = 12.8$ Hz), 137.83 (1C), 147.31 (1C), 153.51 (1C), 155.72 (1C), 159.35 (1C, d, $J_{C-F} = 245$ Hz), and 173.62 (1C); LRMS-EI (m/z): 497 (M^+). HRMS-EI (m/z): Calcd. for $C_{23}H_{24}FN_7O_5$ (M^+): 497.1823; Found 497.1812.

4.2. Pharmacological evaluation

The *in vitro* antibacterial activity, *in vivo* therapeutic effect of selected compounds, and inhibitory activity of selected compounds towards four cytochrome P450 isozymes (CYP) and MAO-A, and -B were evaluated in the same way as reported previously [10].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.08.002.

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