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Antibacterial oxazolidinone analogues having a *N*-hydroxyacetyl-substituted seven-membered [1,2,5]triazepane or [1,2,5]oxadiazepane C-ring unit

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ABSTRACT

We synthesized a series of oxazolidinone analogues bearing a *N*-hydroxyacetyl-substituted [1,2,5]triazepane or [1,2,5]oxadiazepane C-ring unit as homologues of an earlier drug candidate, eperezolid. Several of these compounds exhibited potent *in vitro* antibacterial activities towards not only Gram-positive, but also Gram-negative and linezolid-resistant pathogens. Compounds **21a** and **21b**, bearing a thiocarbamate side chain, showed high *in vivo* activity against methicillin-resistant *Staphylococcus aureus* SR3637, together with a promising safety profile in terms of weak inhibition of monoamine oxidase and cytochrome P450 isozymes.

1. Introduction

Linezolid (**1**) is a new, completely synthetic class of antibiotic belonging to the oxazolidinone family, and is 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]. Though linezolid was the first member of the oxazolidinone family to be approved by the US Food and Drug Administration (FDA), eperezolid (**2**) [3] was also a potent drug candidate, developed in parallel with **1** (Fig. 1). Indeed, **2** exhibited more potent *in vitro* antibacterial activity and a better *in vivo* therapeutic effect than **1**, but concerns about its safety profile and pharmacokinetics in humans led to the selection of **1** as the preferred candidate for clinical application [4]. The oxazolidinone antibacterials **1** and **2** contain a six-membered saturated heterocycle (morpholine or piperazine, respectively) as the C-ring unit. Morpholine or piperazine moieties have been incorporated in a variety of recently reported pharmacologically active compounds [5–40], and their favourable balance of lipophilicity and hydrophilicity has led to their utilization as partial structural units for improvement of bioavailability or water-solubility of various lead compounds in medicinal-chemical research [41]. However, we were interested in developing a novel scaffold with favourable chemical and pharmaceutical properties for drug development. This led us to consider the seven-membered heterocycles [1,2,5]triazepane and [1,2,5]oxadiazepane as possible substitutes for the six-membered heterocycles morpholine in **1** and piperazine in **2**. Little work has been done on the synthesis of derivatives of these seven-membered heterocycles [42], and their potential as pharmacophores remains unexplored. Herein we report the synthesis and evaluation of a series of oxazolidinones in which the piperazine ring of **2** is replaced with [1,2,5]triazepane or [1,2,5]oxadiazepane [43].

2. Results and discussion

2.1. Chemistry

First of all, we planned to synthesize the title oxazolidinone analogues, in which the C-ring unit was changed to [1,2,5]triazepane or [1,2,5]oxadiazepane bearing a hydroxyacetyl functional group. The remaining structure was configured as follows, based

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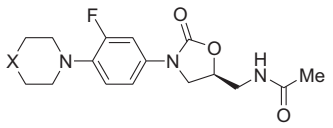
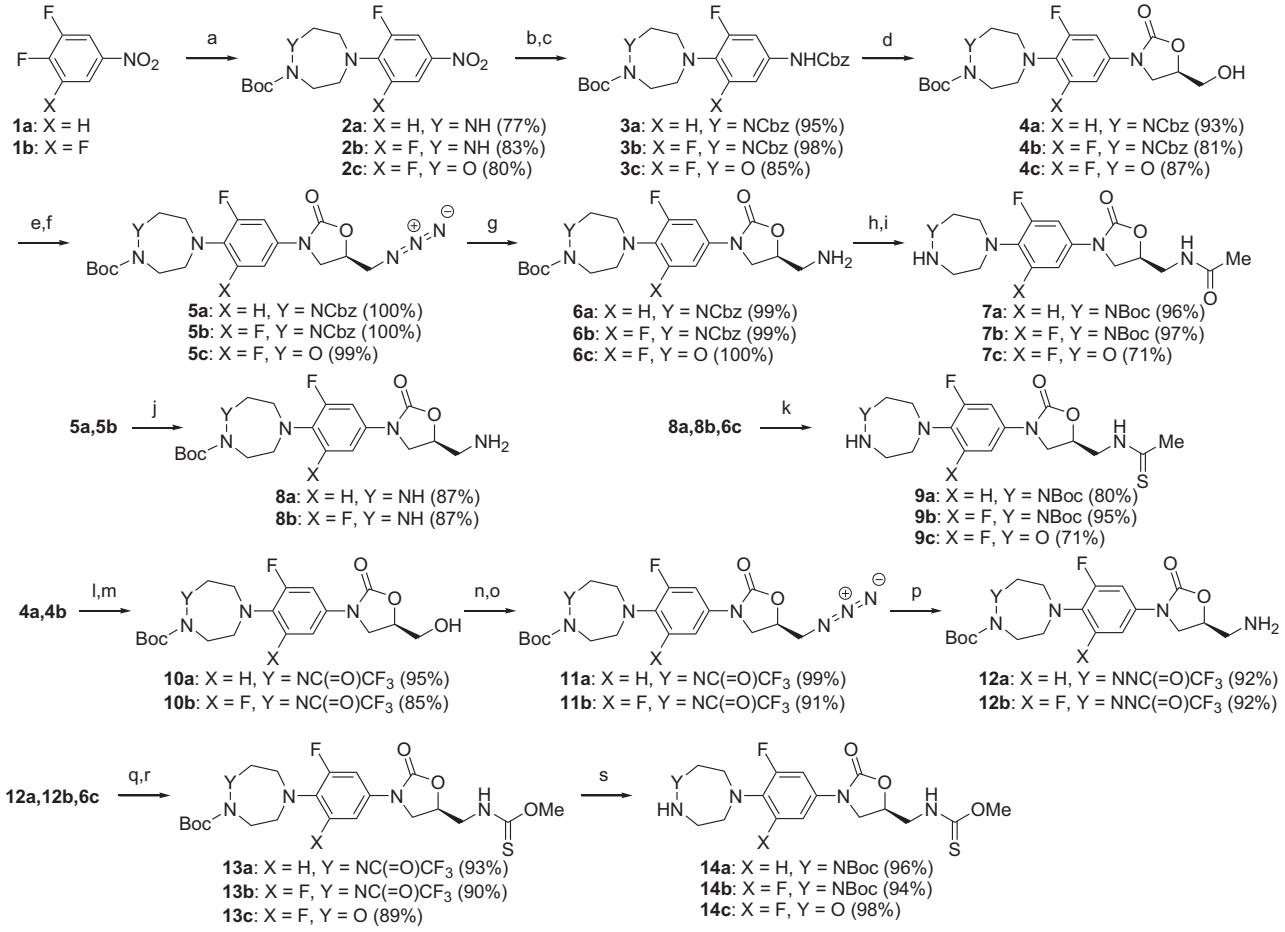


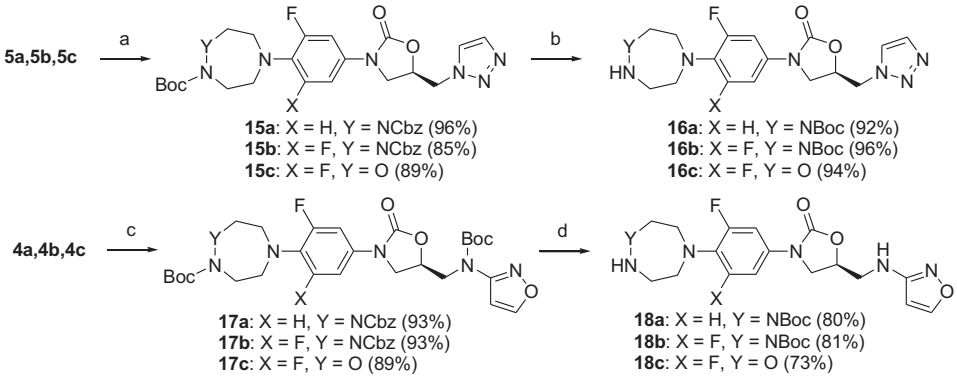
Fig. 1. Representative oxazolidinone antibacterial agents.

upon abundant related research. Two kinds of aromatic structures, 3-fluorophenyl or 3,5-difluorophenyl were selected as the B-ring aromatic unit [44]. As the side chain moiety at the C-5 position on the A-ring, we employed conventional acetamide [45], thioacetamide [46], thiocarbamate [47], [1,2,3]triazole [48], or isoxazolylaminomethyl [49]. The synthesis of our oxazolidinone intermediates is outlined in Schemes 1 and 2. Cyclization reaction to the seven-membered carbocycle was performed at the first stage of the synthetic process. Commercially available 3,4-difluoronitrobenzene (**1a**) or 3,4,5-trifluoronitrobenzene (**1b**) was used as a starting material for all our oxazolidinone analogues. Compound **1a** or **1b** was treated with [1,2,5]triazepane-1-carboxylic acid *tert*-butyl ester [43] or [1,2,5]oxadiazepane-2-car boxylic acid *tert*-butyl ester [43] in the presence of diisopropylethylamine to afford seven-membered heterocycles **2a**–**c**, respectively. Reduction of the nitro group in **2** to an amino group by catalytic hydrogenation, followed by protection of the amino group with benzyloxycarbonyl (Cbz) gave compounds **3a**–**c**. The carbamates **3a**–**c** were then subjected to cyclization to obtain oxazolidinones **4a**–**c**, respectively. The hydroxyl groups in **4a**–**c** were converted to azide using a standard method, and the azide was further transformed to amine, affording **6a**–**c**. The acetamidation of [1,2,5]triazepanes **6a** and **6b**, followed by deprotection of the Cbz group, afforded the oxazolidinone precursors **7a** and **7b** bearing the acetamide side chain unit. Acetamidation of [1,2,5]oxadiazepane **6c**, followed by deprotection of *tert*-butoxycarbonyl (Boc) group, gave oxazolidinone precursor **7c**. Catalytic hydrogenation of **5a** and **5b** afforded amines **8a** and **8b**, which were treated with ethyl dithioacetate in the presence of triethylamine to afford oxazolidinone precursors **9a** and **9b** bearing a thioamide side chain unit. For the synthesis of the oxazolidinone precursor bearing thiocarbamate, we changed the protective Cbz group to a trifluoroacetyl



[a] Reagents: (a) [1,2,5]triazepane-1-carboxylic acid *t*-butylester (for **2a** and **2b**) or [1,2,5]oxadiazepane-2-carboxylic acid *t*-butylester (for **2c**), *i*-Pr_2NEt; (b) 10%Pd/C, H_2; (c) CbzCl, Na_2CO_3; (d) *n*-BuLi, (*R*)-glycidylbutyrate; (e) MsCl, pyridine; (f) NaN_3; (g) Ph_3P, H_2O; (h) Ac_2O, pyridine; (i) 10%Pd/C, H_2 (for **7a** and **7b**) or CF_3CO_2H (for **7c**); (j) 10%Pd/C, H_2; (k) ethyl dithioacetate, Et_3N and CF_3CO_2H (for **9c**); (l) 10%Pd/C, H_2; (m) trichloroacetic acid anhydride, Et_3N, then NH_4OH; (n) MsCl, pyridine; (o) NaN_3; (p) Ph_3P, H_2O; (q) CS_2, Et_3N, $ClCO_2Et$; (r) MeONa; (s) LiOH (for **14a** and **14b**) or CF_3CO_2H (for **14c**).

Scheme 1.



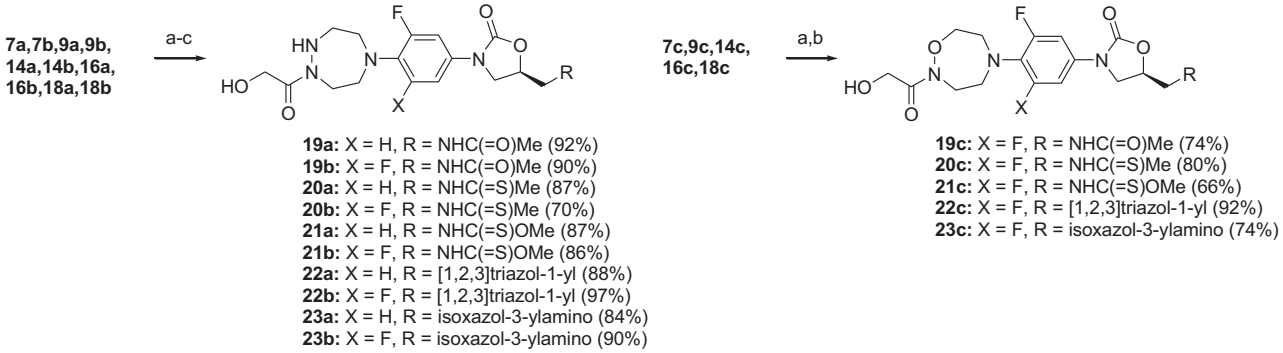
[a] Reagents: (a) 2,5-norbornadiene; (b) 10%Pd/C, H_2 (for **11a** and **11b**) or CF_3CO_2H (for **11c**); (c) isoxazol-3-yl-carbamic acid *t*-butyl ester, ADDP, *n*-Bu_3P; (d) 10% Pd/C, H_2 (for **18a** and **18b**) or CF_3CO_2H (for **18c**).

Scheme 2.

group at the N atom on the [1,2,5]triazepane ring. Namely, **4a** and **4b** were subjected to catalytic hydrogenation, then treated with trifluoroacetic acid anhydride/triethylamine to afford alcohols **10a** and **10b**. Compound **10** was converted to **12** using the same procedure as described for conversion of **4** to **6**. The amines **12a**, **12b**, and **6c** were converted to thioisocyanates, and then reaction with sodium methoxide gave thiocarbamates **13a**–**c**. Finally, the trifluoroacetyl group on [1,2,5]triazepanes **13a**,**b** was hydrolyzed to afford oxazolidinone precursors **14a** and **14b** bearing a thiocarbamate side chain unit. The Boc group of [1,2,5]oxadiazepane **13c** was also deprotected to afford **14c**. The azides **5a**–**c** were reacted with 2,5-norbornadiene under reflux to obtain [1,2,3]triazoles **15a**–**c** and appropriate deprotection reaction afforded oxazolidinone precursors **16a**–**c**, respectively, bearing the [1,2,3] triazole side chain unit. Mitsunobu reaction of alcohols **4a**–**c** with isoxazol-3-yl-carbamic acid *tert*-butyl ester gave compounds **17a**–**c**. The [1,2,5]triazepanes **17a** and **17b** were subjected to catalytic hydrogenation to obtain oxazolidinone precursors **18a** and **18b** bearing an isoxazol-3-ylamino group side chain unit. The [1,2,5] oxadiazepane **17c** was also deprotected to afford oxazolidinone precursor **18c**. Thus, we completed the preparation of oxazolidinone precursors **7a**–**c**, **9a**–**c**, **14a**–**c**, **16a**–**c**, and **18a**–**c**. As shown in Scheme 3, we obtained the target oxazolidinone analogues with a hydroxyacetyl group at a N atom of [1,2,5]triazepane and [1,2,5] oxadiazepane from the above **7**, **9**, **14**, **16** and **18**. Specifically, each precursor was reacted with acetoxyacetyl chloride in the presence of pyridine as base to form the acetoxyacetamide, followed by deacetylation using potassium carbonate; finally, deprotection of the Boc group at the N atom using trifluoroacetic acid afforded the desired oxazolidinone analogues **19a**–**c**, **20a**–**c**, **21a**–**c**, **22a**–**c**, and **23a**–**c**.

2.2. Evaluation of in vitro antibacterial activity

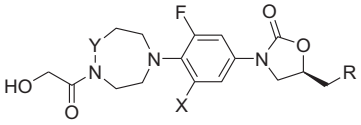
All the synthesized oxazolidinone analogues **19**, **20**, **21**, **22**, and **23** were evaluated for *in vitro* antibacterial activity against Gram-positive (*S. aureus*, *E. faecalis*, *Enterococcus faecium*, and *Streptococcus pneumoniae*) bacteria and Gram-negative (*Moraxella catarrhalis* and *Haemophilus influenzae*) bacteria using a conventional agar-dilution method. A clinical isolate of linezolid-resistant *S. aureus* NRS271 was also examined [50]. In addition, oxazolidinone precursors **7c**, **9c**, **14c**, **16c**, and **18c** having a [1,2,5]oxadiazepane ring as the C-ring unit were included as test compounds because their structures were considered to be homologous to that of linezolid (**1**). The individual minimum inhibitory concentrations (MICs, μg/mL) of the tested analogues against the above Gram-positive and Gram-negative pathogens are listed in Table 1, along with those of **1** and **2** as reference drugs. The oxazolidinone analogues **19a**–**c** bearing an acetamide side chain unit at the C-5 position on the A-ring exhibited almost the same level of *in vitro*



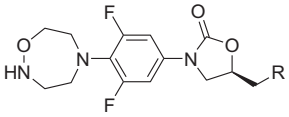
[a] Reagents: (a) acetoxyacetyl chloride, pyridine; (b) K_2CO_3; (c) CF_3CO_2H.

Scheme 3.

Table 1
In vitro antibacterial activity of synthesized oxazolidinone analogues.



19a,b,c-23a,b,c



7c,9c,14c,16c,18c

Compound	X	Y	R	Minimum inhibitory concentration (μg/mL)								ClogP[i]
				S. aureus[a]	*S. aureus*[b]	*S. aureus*[c]	*E. faecalis*[d]	*E. faecium*[e]	*M. catarrhalis*[f]	*S. pneumoniae*[g]	*H. influenzae*[h]	
1	–	–	–	2	2	32	4	2	8	1	16	0.5321
2	–	–	–	1	1	32	1	2	8	0.125	4	−1.0891
19a	H	NH	NHC(=O)Me	4	2	64	2	4	8	1	16	−0.7353
19b	F	NH	NHC(=O)Me	1	1	16	2	4	4	0.25	8	−0.5325
19c	F	O	NHC(=O)Me	2	2	32	4	2	8	1	16	0.2818
7c	–	–	NHC(=O)Me	1	1	16	2	1	4	0.25	16	0.1522
20a	H	NH	NHC(=S)Me	0.5	0.25	8	0.5	0.5	1	≤0.063	2	−0.1886
20b	F	NH	NHC(=S)Me	0.125	0.25	1	0.25	0.125	0.5	0.063	2	0.0142
20c	F	O	NHC(=S)Me	0.125	0.25	2	0.25	0.25	1	0.063	4	0.8285
9c	–	–	NHC(=S)Me	0.25	0.25	4	0.25	0.125	1	0.063	2	0.6989
21a	H	NH	NHC(=S)OMe	0.25	0.25	2	0.5	0.25	2	0.125	4	0.6584
21b	F	NH	NHC(=S)OMe	0.25	0.25	2	0.25	0.25	1	≤0.063	4	0.8612
21c	F	O	NHC(=S)OMe	0.25	0.25	2	0.5	0.25	1	0.125	4	1.6755
14c	–	–	NHC(=S)OMe	0.25	0.5	4	0.5	0.25	1	0.125	8	1.5459
22a	H	NH	[1,2,3]Triazol-1-yl	2	4	64	4	4	8	1	16	−0.6366
22b	F	NH	[1,2,3]Triazol-1-yl	1	2	16	1	1	4	0.5	8	−0.4338
22c	F	O	[1,2,3]Triazol-1-yl	1	2	16	2	2	8	1	16	0.3805
16c	–	–	[1,2,3]Triazol-1-yl	1	2	16	2	1	4	0.5	8	0.2509
23a	H	NH	Isoxazol-3-ylamino	1	2	64	2	2	16	0.5	32	0.5213
23b	F	NH	Isoxazol-3-ylamino	0.5	0.5	8	0.25	1	16	0.125	16	0.7241
23c	F	O	Isoxazol-3-ylamino	0.25	0.5	8	0.5	1	4	0.25	16	1.5384
18c	–	–	Isoxazol-3-ylamino	0.5	1	16	0.5	1	4	0.125	16	1.4088

[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] Clog*P* (hydrophobicity) was calculated using ChemDraw Ultra, version 7.0.

antibacterial activity as **1** or **2**, and no clear possibilities for further development were identified. Analogues **22a**–**c** with the [1,2,3] triazole type unit showed similar antibacterial activity to acetamide **19**. There seemed to be a tendency that analogues with the 3,5-difluorophenyl B-ring unit were a little more active than those with the 3-fluorophenyl B-ring unit (cf. **19a** vs **19b** and **22a** vs **22b**). On the other hand, thioacetamides **20a**–**c** and thiocarbamates **21a**–**c** showed 4- to 16-fold more potent *in vitro* antibacterial activity than the reference drugs **1** and **2**. Moreover, the MIC values reached clinically useful levels in almost all cases, not only towards typical Gram-positive bacteria, but also towards Gram-negative bacteria *M. catarrhalis* and *H. influenzae*, as well as linezolid-resistant *S. aureus* (1–4 μg/mL). The analogues **23a**–**c** having an isoxazol-3-ylamino side chain unit also showed excellent activity towards Gram-positive pathogens, though their antibacterial spectra did not extend to linezolid-resistant and Gram-negative strains. We found no clear correlation between overall lipophilicity of the test molecules and *in vitro* antibacterial activity, but Clog*P* values were all positive for potent analogues (less than 0.25 μg/mL MIC against *S. aureus* SR20549). As regards the B ring part, the analogues with a 3,5-difluorophenyl group were more active *in vitro* than the analogues with the less lipophilic 3-fluorophenyl group without exception. Thus, it may be necessary to consider the lipophilicity per partial structure, rather than the overall molecular lipophilicity to find compounds that are highly active *in vitro*.

2.3. Evaluation of in vivo therapeutic effect

Next, in order to examine the *in vivo* antibacterial activity of compounds with potent *in vitro* activity, selected compounds were tested for *in vivo* therapeutic effect in a lethal systemic mouse infection model with *S. aureus* SR3637, via both intravenous and oral routes. The results are shown in Table 2. The control eperezolid **2** exhibited a better *in vivo* therapeutic effect upon intravenous

Table 2
In vivo antibacterial efficacies (ED_{50}) of selected oxazolidinones in a systemic mouse infection model.

Compound	MIC[a] (μg/mL)	Therapeutic effect ED_{50} (mg/kg)	
		Administration route	
		iv[b]	po[c]
2	1	1.85 (**1**: 4.13)	4.76 (**1**: 4.11)
20a	0.25	2.95 (**1**: 1.73)	>10 (**1**: 2.02–2.83)
20b	0.125	2.95 (**1**: 1.73)	9.83 (**1**: 2.02–2.83)
21a	0.25	0.94 (**1**: 3.26)	1.05 (**1**: 2.10)
21b	0.25	0.77 (**1**: 2.13)	2.07 (**1**: 2.83)
22b	1	1.71 (**1**: 1.73)	–
23b	0.5	2.18 (**1**: 2.02)	2.83 (**1**: 4.11)
23c	0.25	>10 (**1**: 1.95)	–

[a] *Staphylococcus aureus* SR3637.
[b] Intravenous.
[c] Oral.

Table 3
CYP450 and MAO-A, B inhibition index of potent *in vivo* active analogues **21a** and **21b**.

Compound	CYP450 isoform, IC_{50} (μM)				MAO inhibition (%)	
	1A2	2C9	2D6	3A4	A	B
1	>20	>20	>20	>20	61.3	70.4
2	>20	>20	>20	>20	53.6	20.2
21a	>20	>20	>20	>20	48.2	10.1
21b	>20	>20	>20	>20	12.4	10.6

administration than did linezolid **1**, though it was less effective than **1** in the case of oral administration. In spite of their excellent MIC profile, thioamides **20a** and **20b** showed lower *in vivo* antibacterial efficacies compared to **1** via intravenous injection, and the therapeutic effects upon oral administration were far inferior to that of **1**. Those results may indicate that change of the acetamide side chain unit to thioacetamide worsened the pharmacokinetic profile or metabolic stability. Though the analogue **23b** with an isoxazol-3-ylamino side chain unit exhibited moderate *in vivo* therapeutic effect via both intravenous and oral routes, the ED_{50} values were insufficient. Also, [1,2,5]oxadiazepane **23c** did not show *in vivo* efficacy, like [1,2,5]triazepane **23b**. The reason for this is probably that the hydroxyacetyl group at the N atom of the [1,2,5]oxadiazepane ring is unstable in plasma owing to its chemically active Weinreb amide-type structure. On the other hand, the analogues **21a** and **21b** bearing a thiocarbamate side chain unit exhibited superior *in vivo* therapeutic efficacy to **1** and **2** via both intravenous and oral routes. Indeed, **21a** displayed a 3-fold greater *in vivo* therapeutic effect than **1** via intravenous administration, and a 2-fold greater effect via oral administration.

2.4. Evaluation of inhibition of four cytochrome P450 (CYP) isoforms and monoamine oxidases A and B (MAO-A and -B) by selected compounds

For further pharmacological and safety evaluation, we examined the inhibition of four CYP isoforms and MAO-A and -B by the compounds that showed potent *in vivo* antibacterial activity. The results are summarized in Table 3. Linezolid (**1**) is known to be a relatively potent inhibitor of MAO-A and MAO-B, although there is no report of any serious clinical side effect resulting from this activity. Nevertheless, it would be desirable to reduce this activity. To our gratification, the potent *in vivo*-active thiocarbamates **21a** and **21b** showed improved values of MAO-A, B inhibition index in comparison with both of the oxazolidinone progenitors **1** and **2**. Compounds **21a** and **21b** had similar levels of CYP inhibition potential ($IC_{50} > 20$ μM for the four selected isoforms) to **1** and **2**, and these levels are satisfactory from a safety point of view. Thus, our oxazolidinone analogues **21a** and **21b** appear to have pharmacokinetic properties that would be consistent with clinical application.

3. Conclusion

We designed and synthesized new oxazolidinone analogues in which the six-membered heterocyclic piperazine or morpholine partial structure is replaced with a seven-membered heterocycle, [1,2,5]triazepane or [1,2,5]oxadiazepane, as the C-ring. The *in vitro* and *in vivo* antibacterial potentials of these compounds were evaluated. Analogues **21a** and **21b** bearing a thiocarbamate side chain unit at C-5 of the oxazolidinone ring exhibited particularly potent *in vitro* and *in vivo* antibacterial activities, and a preliminary safety study indicated that they are not potent inhibitors of MAO-A, B or four CYP450 isoforms. Thus, our seven-membered heterocyclic units appeared to be effective partial structures for novel oxazolidinone antibiotics. Compounds **21a** and **21b** are considered to be promising antibiotic candidates, and further evaluation is under way.

4. Experimental protocols

4.1. Chemistry

Melting points were determined with a Yanagimoto micro melting point apparatus (hot plate) and are uncorrected. Low-resolution mass spectra (LRMS) were recorded on a Hitachi M-80B spectrometer. High-resolution mass spectra (HRMS) were recorded on a Hitachi M-80B spectrometer or 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 chloroform (77 ppm for ^{13}C NMR in $CDCl_3$ or $CD_3OD/CDCl_3$) 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 sulphate or anhydrous magnesium sulphate and the solvent was removed by rotary evaporation under reduced pressure.

*4.1.1. 5-(2-Fluoro-4-nitrophenyl) [1,2,5]triazepane-1-carboxylic acid tert-butyl ester (**2a**)*

To a solution of [1,2,5]triazepane-1-carboxylic acid *tert*-butyl ester **1** (267.6 mg, 1.330 mmol) and 3,4-difluoronitrobenzene (262.3 mg, 1.649 mmol) in acetonitrile (2 mL) was added isopropylethylamine (344.5 mg, 2.666 mmol) at ambient temperature, the solution was refluxed for 16 h. After cooling, concentration of the reaction mixture in vacuo followed by silica gel (15 g) column chromatography using *n*-hexane/AcOEt (80:20 to 40:60) as the eluent afforded **2a** (348.6 mg, 77%). Yellow prisms (EtOH); mp: 144–145 °C; ^{1}H NMR ($CDCl_3$) δ = 1.28 (9H, s, *t*-$C_4\underline{H}_9$), 3.13 (2H, t, J = 5.5 Hz, $-CH_2-$), 3.66–3.73 (4H, m, $-CH_2-$), 3.86 (2H, br t, J = 6 Hz, $-CH_2-$), 6.79 (1H, t, J = 9.1 Hz, Ar–H6), and 7.86–7.95 (2H, m, Ar–H3 and H5); EI-LRMS *m*/*z*: 340 (M^+).

*4.1.2. 5-(2,6-Difluoro-4-nitrophenyl) [1,2,5]triazepane-1-carboxylic acid tert-butyl ester (**2b**)*

Compound **2b** (385.7 mg, 83%) was prepared from **1** (261.3 mg, 1.298 mmol) in the same manner as described for **2a**. Yellow powder (MeOH); mp: 78–79 °C; ^{1}H NMR ($CDCl_3$) δ = 1.54 (9H, s, *t*-$C_4\underline{H}_9$), 3.12 (2H, t, J = 5.2 Hz, $-CH_2-$), 3.51 (2H, br t, J = 5 Hz, $-CH_2-$), 3.61–3.72 (4H, m, $-CH_2-$), and 7.77 (2H, d, J = 10.7 Hz, Ar–H3 and H5); EI-LRMS *m*/*z*: 358 (M^+).

*4.1.3. 5-(2,6-Difluoro-4-nitrophenyl) [1,2,5]oxadiazepane-2-carboxylic acid tert-butyl ester (**2c**)*

Compound **2c** (365.0 mg, 80%) was prepared from **1** (257.0 mg, 1.271 mmol) in the same manner as described for **2a**. Yellow needles (*n*-hexane); mp: 87–88 °C; ^{1}H NMR ($CDCl_3$) δ = 1.51 (9H, s, *t*-$C_4\underline{H}_9$), 3.62–3.72 (4H, m, $-CH_2-$), 3.84 (2H, t, J = 6.0 Hz, $-CH_2-$), 4.13 (2H, t, J = 5.1 Hz, $-CH_2-$), and 7.78 (2H, d, J = 10.5 Hz, Ar–H3 and H5); EI-LRMS *m*/*z*: 359 (M^+). EI-HRMS *m*/*z*: calcd. for $C_{15}H_{19}F_2N_3O_5$ (M^+): 359.1291; found 359.1278.

*4.1.4. 5-(4-Benzyloxycarbonylamino-2-fluorophenyl) [1,2,5] triazepane-1,2-dicarboxylic acid 1-benzyl ester 2-tert-butyl ester (**3a**)*

A suspension of **2a** (346.9 mg, 1.019 mmol) and 10% Pd/C (70.1 mg) in 95% MeOH (10 mL) was hydrogenated at 1 atm at

ambient temperature for 2 h, and then filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was dissolved in MeOH (10 mL) and H_2O (5 mL). To this solution was added sodium carbonate (270.1 mg, 2.548 mmol) and benzyl chloroformate (386.7 mg, 2.267 mmol). Stirring was continued for 30 min, then water (30 mL) was added and the mixture was extracted with AcOEt. The organic solution was dried and evaporated. Silica gel (20 g) column chromatography of the residue using *n*-hexane/AcOEt (80:20 to 60:40) as the eluent afforded **3a** (558.5 mg, 95%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.33–1.48 (9H, m, *t*-C_4H_9), 3.12–3.58 (6H, m, $-CH_2-$), 3.95–4.27 (2H, m, $-CH_2-$), 5.05–5.29 (4H, m, Ar–CH_2O), 6.65 (1H, br s, NH), 6.82 (1H, t, J = 9.1 Hz, Ar–H6), 6.86–6.94 (1H, m, Ar–H5), and 7.20–7.42 (11H, m, Ar–H); EI-LRMS *m*/*z*: 578 (M^+).

4.1.5. 5-(4-Benzyloxycarbonylamino-2,6-difluorophenyl) [1,2,5] triazepane-1,2-dicarboxylic acid 1-benzyl ester 2-tert-butyl ester (**3b**)

Compound **3b** (410.7 mg, 98%) was prepared from **2b** (251.1 mg, 0.701 mmol) in the same manner as described for **3a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.30–1.55 (9H, m, *t*-C_4H_9), 3.00–3.53 (6H, m, $-CH_2-$), 3.90–4.17 (2H, m, $-CH_2-$), 5.06–5.32 (4H, m, Ar–CH_2O), 6.77 (1H, br s, NH), 6.97 (2H, d, J = 10.2 Hz, Ar–H3 and H5), and 7.21–7.43 (10H, m, Ar–H); EI-LRMS *m*/*z*: 596 (M^+).

4.1.6. 5-(4-Benzyloxycarbonylamino-2,6-difluorophenyl) [1,2,5] oxadiazepane-2-carboxylic acid tert-butyl ester (**3c**)

Compound **3c** (3.1902 g, 85%) was prepared from **2c** (2.9011 g, 8.081 mmol) in the same manner as described for **3a**. Colourless prisms (*n*-hexane); mp: 100–101 °C; ^{1}H NMR ($CDCl_3$) δ = 1.50 (9H, s, *t*-C_4H_9), 3.33 (4H, t, J = 5.1 Hz, $-CH_2-$), 3.75 (2H, t, J = 5.1 Hz, $-CH_2-$), 4.05 (2H, t, J = 5.1 Hz, $-CH_2-$), 5.06–5.32 (4H, m, Ar–CH_2O), 7.00 (2H, d, J = 10.5 Hz, Ar–H3 and H5), 7.11 (1H, br s, NH), and 7.28–7.40 (5H, m, Ar–H); EI-LRMS *m*/*z*: 463 (M^+). EI-HRMS *m*/*z*: calcd. for $C_{23}H_{27}F_2N_3O_5$ (M^+): 463.1917; found 463.1904.

4.1.7. 5(R)-(Hydroxymethyl)-3-(3-fluoro-4-(1-(benzyloxycarbonyl)-2-(tert-butoxycarbonyl)[1,2,5]triazepan-5-yl) phenyl)oxazolidin-2-one (**4a**)

To a solution of **3a** (20.018 g, 34.60 mmol) in tetrahydrofuran (200 mL) at −78 °C under an argon atmosphere was added dropwise 1.58 M *n*-butyl lithium/*n*-hexane (24.0 mL, 37.92 mmol) over 10 min. Further (*R*)-glycidyl butyrate (5.4847 g, 38.04 mmol) in tetrahydrofuran (10 mL) was added dropwise to the reaction mixture over 10 min, followed by stirring for 1 h at the same temperature. Then the reaction mixture was allowed to come gradually to ambient temperature. Stirring was continued for 21 h, then water (300 mL) was added, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, and dried. Evaporation of the solvent followed by silica gel (250 g) column chromatography of the residue using *n*-hexane/AcOEt (1:1 to 0:1) and $CHCl_3$/MeOH (97:3 to 9:1) as eluents afforded **4a** (17.489 g, 93%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.32–1.52 (9H, m, *t*-C_4H_9), 2.46 (1H, br, OH), 3.16–3.60 (6H, m, $-CH_2-$), 3.69–3.80 (1H, m, $-CH_2-$), 3.87–4.27 (5H, m, $-CH_2-$), 4.67–4.77 (1H, m, oxazolidinone-H5), 5.05–5.28 (2H, m, Ar–CH_2O), 6.87 (1H, t, J = 9.1 Hz, Ar–H5), 7.02–7.13 (1H, m, Ar–H6), and 7.27–7.46 (6H, m, Ar–H); EI-LRMS *m*/*z*: 544 (M^+).

4.1.8. 5(R)-(Hydroxymethyl)-3-(3,5-difluoro-4-(1-(benzyloxycarbonyl)-2-(tert-butoxycarbonyl)[1,2,5]triazepan-5-yl) phenyl)oxazolidin-2-one (**4b**)

Compound **4b** (5.5651 g, 81%) was prepared from **3b** (7.2419 g, 12.14 mmol) in the same manner as described for **4a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.35–1.49 (9H, m, *t*-C_4H_9), 2.35 (1H, br, OH), 3.04–3.54 (6H, m, $-CH_2-$), 3.75 (1H, br d, J = 12 Hz, $-CH_2-$), 3.88–4.17 (5H, m, $-CH_2-$), 4.69–4.78 (1H, m, oxazolidinone-H5), 5.07–5.32 (2H, m, Ar–CH_2O), 7.12 (2H, d, J = 10.7 Hz, Ar–H2 and H6), and 7.28–7.40 (5H, m, Ar–H); EI-LRMS *m*/*z*: 562 (M^+).

4.1.9. 5(R)-(Hydroxymethyl)-3-(3,5-difluoro-4-(2-(tert-butoxycarbonyl)[1,2,5]oxadiazepan-5-yl)phenyl)oxazolidin-2-one (**4c**)

Compound **4c** (291.1 mg, 87%) was prepared from **3c** (363.2 mg, 0.784 mmol) in the same manner as described for **4a**. Colourless prisms (benzene/*n*-hexane); mp: 93–94 °C; ^{1}H NMR ($CDCl_3$) δ = 1.51 (9H, s, *t*-C_4H_9), 3.33–3.43 (4H, m, $-CH_2-$), 3.71–3.82 (3H, m, $-CH_2-$), 3.90–4.02 (3H, m, $-CH_2-$), 4.07 (2H, t, J = 5.1 Hz, $-CH_2-$), 4.70–4.80 (1H, m, oxazolidinone-H5), and 7.02 (2H, d, J = 10.5 Hz, Ar–H2 and H6); EI-LRMS *m*/*z*: 429 (M^+). EI-HRMS *m*/*z*: calcd. for $C_{19}H_{25}F_2N_3O_6$ (M^+): 429.1710; found 429.1710.

4.1.10. 5(R)-(Azidomethyl)-3-(3-fluoro-4-(1-(benzyloxycarbonyl)-2-(tert-butoxycarbonyl)[1,2,5]triazepan-5-yl)phenyl) oxazolidin-2-one (**5a**)

To a solution of **4a** (1.4713 g, 2.702 mmol) and triethylamine (0.56 mL, 3.985 mmol) in CH_2Cl_2 (14 mL) was added dropwise methanesulfonyl chloride (0.26 mL, 3.359 mmol) at 0 °C and the resulting mixture was stirred for 10 min at ambient temperature. The reaction mixture was quenched with H_2O (10 mL), and extracted with $CHCl_3$. The organic layer was washed with brine, dried, and evaporated to afford a residue, which was used without further purification. To a solution of the residue in *N*,*N*-dimethylformamide (10 mL) was added sodium azide (0.2641 g, 4.062 mmol), and the mixture was stirred for 4 h within the temperature range of 80–90 °C. The reaction mixture was then cooled and poured into water (20 mL). The aqueous layer was extracted with AcOEt and the combined organic layer was washed with H_2O and brine, and dried. Evaporation of the solvent followed by silica gel (40 g) column chromatography of the residue using *n*-hexane/AcOEt (70:30 to 40:60) as the eluent afforded **5a** (1.5380 g, 100%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.31–1.49 (9H, m, *t*-C_4H_9), 3.18–3.85 (9H, m, $-CH_2-$), 3.96–4.28 (3H, m, $-CH_2-$), 4.71–4.82 (1H, m, oxazolidinone-H5), 5.05–5.29 (2H, m, Ar–CH_2O), 6.88 (1H, t, J = 9.1 Hz, Ar–H5), 7.01–7.13 (1H, m, Ar–H6), and 7.28–7.45 (6H, m, Ar–H); EI-LRMS *m*/*z*: 569 (M^+).

4.1.11. 5(R)-(Azidomethyl)-3-(3,5-difluoro-4-(1-(benzyloxycarbonyl)-2-(tert-butoxycarbonyl)[1,2,5]triazepan-5-yl) phenyl)oxazolidin-2-one (**5b**)

Compound **5b** (2.2917 g, 100%) was prepared from **4b** (2.2025 g, 3.915 mmol) in the same manner as described for **5a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.35–1.53 (9H, m, *t*-C_4H_9), 3.04–3.50 (6H, m, $-CH_2-$), 3.58 (1H, dd, J = 4.4, 13.2 Hz, $-CHH-N_3$), 3.71 (1H, dd, J = 4.4, 13.2 Hz, $-CHH-N_3$), 3.78 (1H, dd, J = 6.3, 8.8 Hz, oxazolidinone-H4), 3.91–4.18 (2H, m, $-CH_2-$), 4.01 (1H, t, J = 8.8 Hz, oxazolidinone-H4), 4.78 (1H, ddt, J = 6.3, 8.8, 4.4 Hz, oxazolidinone-H5), 5.07–5.32 (2H, m, Ar–CH_2O), 7.12 (2H, d, J = 10.7 Hz, Ar–H2 and H6), and 7.27–7.40 (5H, m, Ar–H); EI-LRMS *m*/*z*: 587 (M^+).

4.1.12. 5(R)-(Azidomethyl)-3-(3,5-difluoro-4-(2-(tert-butoxycarbonyl)[1,2,5]oxadiazepan-5-yl)phenyl)oxazolidin-2-one (**5c**)

Compound **5c** (360.1 mg, 99%) was prepared from **4c** (406.0 mg, 0.802 mmol) in the same manner as described for **5a**. Colourless prisms (EtOH); mp: 72–73 °C; ^{1}H NMR ($CDCl_3$) δ = 1.51 (9H, s, *t*-C_4H_9), 3.34–3.45 (4H, m, $-CH_2-$), 3.59 (1H, dd, J = 4.5, 13.5 Hz, $-CHH-N_3$), 3.73 (1H, dd, J = 4.5, 13.5 Hz, $-CHH-N_3$), 3.74–3.85 (3H, m, $-CH_2-$ and oxazolidinone-H4), 4.03 (1H, t, J = 9.0 Hz,

oxazolidinone-H4), 4.04–4.14 (2H, m, $-CH_2-$), 4.76–4.86 (1H, m, oxazolidinone-H5), and 7.13 (2H, d, $J = 10.8$ Hz, Ar–H2 and H6); EI-LRMS m/z: 454 (M^+). EI-HRMS m/z: calcd. for $C_{19}H_{24}F_2N_6O_5$ (M^+): 454.1776; found 454.1776.

4.1.13. 5(S)-(Aminomethyl)-3-(3-fluoro-4-(1-(benzyloxycarbonyl)-2-(tert-butoxycarbonyl)[1,2,5]triazepan-5-yl) phenyl)oxazolidin-2-one (**6a**)

To a solution of **5a** (1.5380 g, 2.700 mmol) and triphenylphosphine (0.8661 g, 1.521 mmol) in tetrahydrofuran (14 mL) was added H_2O (0.5 mL, 27.78 mmol) at ambient temperature, and the resulting mixture was refluxed for 2 h. The reaction mixture was cooled and concentrated in vacuo. Silica gel (40 g) column chromatography of the residue using $CHCl_3$/MeOH (98:2 to 85:15) as the eluent afforded **6a** (1.4505 g, 99%). Amorphous solid; ^{1}H NMR ($CDCl_3$) $\delta = 1.33–1.49$ (9H, m, *t*-C_4H_9), 2.97 (1H, dd, $J = 5.8, 13.7$ Hz, $-CHH-NH_2$), 3.10 (1H, dd, $J = 4.1, 13.7$ Hz, $-CHH-NH_2$), 3.16–3.60 (6H, m, $-CH_2-$), 3.79 (1H, br t, $J = 8$ Hz, $-CH_2-$), 3.93–4.27 (3H, m, $-CH_2-$), 4.61–4.72 (1H, m, oxazolidinone-H5), 5.05–5.29 (2H, m, Ar–CH_2O), 6.88 (1H, t, $J = 9.1$ Hz, Ar–H5), 7.03–7.13 (1H, m, Ar–H6), and 7.25–7.48 (6H, m, Ar–H); EI-LRMS m/z: 543 (M^+).

4.1.14. 5(S)-(Aminomethyl)-3-(3,5-difluoro-4-(1-(benzyloxycarbonyl)-2-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl) phenyl)oxazolidin-2-one (**6b**)

Compound **6b** (1.8095 g, 99%) was prepared from **5b** (1.9033 g, 3.239 mmol) in the same manner as described for **6a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) $\delta = 1.35–1.53$ (9H, m, *t*-C_4H_9), 2.96 (1H, dd, $J = 5.5, 13.7$ Hz, $-CHH-NH_2$), 3.04–3.54 (6H, m, $-CH_2-$), 3.12 (1H, dd, $J = 4.0, 13.7$ Hz, $-CHH-NH_2$), 3.80 (1H, br t, $J = 8$ Hz, $-CH_2-$), 3.90–4.17 (2H, m, $-CH_2-$), 3.96 (1H, t, $J = 9.1$ Hz, oxazolidinone-H4), 4.62–4.73 (1H, m, oxazolidinone-H5), 5.08–5.32 (2H, m, Ar–CH_2O), 7.13 (2H, br d, $J = 10.7$ Hz, Ar–H2 and H6), and 7.26–7.40 (5H, m, Ar–H); EI-LRMS m/z: 561 (M^+).

4.1.15. 5(S)-(Aminomethyl)-3-(3,5-difluoro-4-(2-(tert-butoxycarbonyl) [1,2,5]oxadiazepan-5-yl)phenyl)oxazolidin-2-one (**6c**)

Compound **6c** (1.6435 g, 100%) was prepared from **5c** (1.7502 g, 3.851 mmol) in the same manner as described for **6a**. Colourless prisms (benzene/*n*-hexane); mp: 73–74 °C; ^{1}H NMR ($CDCl_3$) $\delta = 1.52$ (9H, s, *t*-C_4H_9), 2.96 (1H, dd, $J = 5.5, 13.5$ Hz, $-CHH-NH_2$), 3.14 (1H, dd, $J = 4.0, 13.5$ Hz, $-CHH-NH_2$), 3.39 (4H, br t, $J = 5$ Hz, $-CH_2-$), 3.78 (2H, br t, $J = 5$ Hz, $-CH_2-$), 3.82 (1H, dd, $J = 6.5, 9.0$ Hz, oxazolidinone-H4), 3.98 (1H, t, $J = 9.0$ Hz, oxazolidinone-H4), 4.08 (2H, br t, $J = 5$ Hz, $-CH_2-$), 4.69 (1H, dddd, $J = 4.0, 5.5, 6.5, 9.0$ Hz, oxazolidinone-H5), and 7.13 (2H, d, $J = 10.8$ Hz, Ar–H2 and H6); EI-LRMS m/z: 428 (M^+).

4.1.16. 5(S)-(Acetylaminomethyl)-3-(3-fluoro-4-(1-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**7a**)

To a solution of **6a** (1.2371 g, 2.276 mmol) and pyridine (0.3669 g, 4.638 mmol) in CH_2Cl_2 (8 mL) was added acetic anhydride (462.2 mg, 4.527 mmol), and the mixture was stirred for 30 min at ambient temperature. The reaction mixture was then concentrated in vacuo to afford a residue, which was used without further purification. A suspension of the above residue and 10% Pd/C (254.3 mg) in 95% MeOH (12 mL) was hydrogenated at 1 atm at ambient temperature for 21 h, and then filtered through a Celite pad. Evaporation of the solvent followed by silica gel (25 g) column chromatography of the residue using $CHCl_3$/MeOH (98:2 to 90:10) as the eluent afforded **7a** (0.9824 g, 96%). Amorphous solid; ^{1}H NMR ($CDCl_3$) $\delta = 1.38$ (9H, s, *t*-C_4H_9), 2.02 (3H, s, $CH_3-C=O$), 3.11 (2H, t, $J = 5.3$ Hz, $-CH_2-$), 3.43 (2H, t, $J = 5.5$ Hz, $-CH_2-$), 3.53–3.74 (7H, m, $-CH_2-$), 3.72 (1H, dd, $J = 6.6, 9.1$ Hz, oxazolidinone-H4), 3.99 (1H, t, $J = 9.1$ Hz, oxazolidinone-H4), 4.70–4.81 (1H, m, oxazolidinone-H5), 6.37 (1H, br t, $J = 6$ Hz, $-NH-C=O$), 6.86 (1H, t, $J = 9.1$ Hz, Ar–H5), 6.99 (1H, dd, $J = 2.3, 9.1$ Hz, Ar–H6), and 7.35 (1H, dd, $J = 2.3, 15.1$ Hz, Ar–H2); EI-LRMS m/z: 451 (M^+).

4.1.17. 5(S)-(Acetylaminomethyl)-3-(3,5-difluoro-4-(1-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**7b**)

Compound **7b** (1.2867 g, 97%) was prepared from **6b** (1.5912 g, 2.833 mmol) in the same manner as described for **7a**. Colourless needles (EtOH); mp: 131–132 °C; ^{1}H NMR ($CDCl_3$) $\delta = 1.49$ (9H, s, *t*-C_4H_9), 2.03 (3H, s, $CH_3-C=O$), 3.04 (2H, t, $J = 5.2$ Hz, $-CH_2-$), 3.27 (2H, t, $J = 5.2$ Hz, $-CH_2-$), 3.40 (2H, t, $J = 5.8$ Hz, $-CH_2-$), 3.60 (2H, t, $J = 5.8$ Hz, $-CH_2-$), 3.62–3.68 (2H, m, $-CH_2-$), 3.73 (1H, dd, $J = 6.8, 9.1$ Hz, oxazolidinone-H4), 3.99 (1H, t, $J = 9.1$ Hz, oxazolidinone-H4), 4.72–4.82 (1H, m, oxazolidinone-H5), 6.33 (1H, br t, $J = 6$ Hz, $-NH-C=O$), and 7.07 (2H, d, $J = 10.7$ Hz, Ar–H2 and H6); EI-LRMS m/z: 469 (M^+).

4.1.18. 5(S)-(Acetylaminomethyl)-3-(3,5-difluoro-4-([1,2,5] oxadiazepan-5-yl)phenyl)oxazolidin-2-one (**7c**)

Compound **6c** was converted to its acetamide intermediate in the same manner as described for **7a**. The obtained residue was dissolved in $CHCl_3$ (10 mL) and to this solution was added trifluoroacetic acid (0.5 mL). Stirring was continued for 15 h. The reaction mixture was neutralized with 10% sodium carbonate, and extracted with 10% MeOH/$CHCl_3$. The organic layer was dried and evaporated, followed by preparative TLC of the residue using $CHCl_3$/MeOH (9 : 1) as the eluent to afford **7c** (41.0 mg, 71%). Colourless needles (EtOH); mp: 104–105 °C; ^{1}H NMR ($CDCl_3$) $\delta = 2.03$ (3H, s, $CH_3-C=O$), 3.22 (2H, br t, $J = 6$ Hz, $-CH_2-$), 3.40 (2H, br t, $J = 6$ Hz, $-CH_2-$), 3.49 (2H, br t, $J = 6$ Hz, $-CH_2-$), 3.66 (2H, dd, $J = 4.5, 6.3$ Hz, $-CH_2-$), 3.75 (1H, dd, $J = 6.3, 9.0$ Hz, oxazolidinone-H4), 3.90 (2H, br t, $J = 6$ Hz, $-CH_2-$), 4.00 (1H, t, $J = 9.0$ Hz, oxazolidinone-H4), 4.79 (1H, ddt, $J = 6.3, 9.0, 4.5$ Hz, oxazolidinone-H5), 6.68 (1H, br t, $J = 6$ Hz, $-NH-C=O$), and 7.06 (2H, d, $J = 10.8$ Hz, Ar–H2 and H6); ^{13}C NMR ($CDCl_3$) $\delta = 23.0, 41.8, 47.4, 53.6, 55.1, 55.7, 72.0, 72.3, 102.4$ (2C, d, $J = 30$ Hz), 125.6 (t, $J = 14$ Hz), 132.3 (t, $J = 13$ Hz), 154.0, 157.5 (2C, dd, $J = 9, 244$ Hz), and 171.2.; EI-LRMS m/z: 370 (M^+). EI-HRMS m/z: calcd. for $C_{16}H_{20}F_2N_4O_4$ (M^+): 370.1451; found 370.1436.

4.1.19. 5(S)-(Aminomethyl)-3-(3-fluoro-4-(1-(tert-butoxy carbonyl)[1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**8a**)

A suspension of **5a** (0.6064 g, 1.065 mmol) and 10% Pd/C (121.5 mg) in 95% MeOH (10 mL) was hydrogenated at 1 atm at ambient temperature for 42 h, and then filtered through a Celite pad. Evaporation of the solvent followed by silica gel (15 g) column chromatography of the residue using $CHCl_3$/MeOH (97:3 to 70:30) as the eluent afforded **8a** (0.3792 g, 87%). Amorphous solid; ^{1}H NMR ($CD_3OD + CDCl_3$) $\delta = 1.39$ (9H, s, *t*-C_4H_9), 3.08–3.74 (10H, m, $-CH_2-$), 3.78 (1H, dd, $J = 6.6, 9.1$ Hz, oxazolidinone-H4), 4.14 (1H, t, $J = 9.1$ Hz, oxazolidinone-H4), 4.92–5.03 (1H, m, oxazolidinone-H5), 6.89 (1H, t, $J = 9.1$ Hz, Ar–H5), 7.04 (1H, dd, $J = 2.2, 9.1$ Hz, Ar–H6), and 7.35 (1H, dd, $J = 2.2, 15.3$ Hz, Ar–H2); EI-LRMS m/z: 410 (M^+).

4.1.20. 5(S)-(Aminomethyl)-3-(3,5-difluoro-4-(1-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**8b**)

Compound **8b** (0.4265 g, 87%) was prepared from **5b** (0.6721 g, 1.144 mmol) in the same manner as described for **8a**. Amorphous solid; ^{1}H NMR ($CD_3OD + CDCl_3$) $\delta = 1.49$ (9H, s, *t*-C_4H_9), 3.05 (2H, t, $J = 5.5$ Hz, $-CH_2-$), 3.14–3.48 (6H, m, $-CH_2-$), 3.61 (2H, t, $J = 5.5$ Hz, $-CH_2-$), 3.80 (1H, dd, $J = 6.6, 9.1$ Hz, oxazolidinone-H4), 4.18 (1H, t, $J = 9.1$ Hz, oxazolidinone-H4), 5.02–5.13 (1H, m, oxazolidinone-H5), and 7.11 (2H, d, $J = 10.7$ Hz, Ar–H2 and H6); EI-LRMS m/z: 328 (M^+-Boc).

*4.1.21. 5(S)-(Thioacetylaminomethyl)-3-(3-fluoro-4-(1-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**9a**)*

To a solution of **8a** (0.2720 g, 0.664 mmol) and triethylamine (0.1090 g, 1.077 mmol) in THF (6 mL) was added ethyl dithioacetate (0.1351 g, 1.124 mmol), and the mixture was stirred for 20 h at ambient temperature. Evaporation of the solvent followed by silica gel (10 g) column chromatography of the residue using $CHCl_3$/MeOH (99:1 to 95:5) as the eluent afforded **9a** (0.2466 g, 80%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.38 (9H, s, *t*-$C_4\underline{H}_9$), 2.60 (3H, s, $C\underline{H}_3$–C═S), 3.11 (2H, t, J = 5.2 Hz, –CH_2–), 3.44 (2H, t, J = 5.2 Hz, –CH_2–), 3.54–3.69 (4H, m, –CH_2–), 3.79 (1H, dd, J = 6.9, 9.1 Hz, oxazolidinone-H4), 3.99–4.10 (2H, m, –CH_2–), 4.24 (1H, ddd, J = 2.7, 6.1, 14.3 Hz, oxazolidinone-H4), 4.92–5.01 (1H, m, oxazolidinone-H5), 6.86 (1H, t, J = 9.1 Hz, Ar–H6), 6.98 (1H, dd, J = 2.5, 9.1 Hz, Ar–H5), 7.32 (1H, dd, J = 2.5, 15.4 Hz, Ar–H2), and 8.33 (1H, br t, J = 6 Hz, –N$\underline{H}$–C═S); EI-LRMS m/z: 467 (M^+).

*4.1.22. 5(S)-(Thioacetylaminomethyl)-3-(3,5-difluoro-4-(1-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**9b**)*

Compound **9b** (0.4074 g, 95%) was prepared from **8b** (0.3782 g, 0.885 mmol) in the same manner as described for **9a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.49 (9H, s, *t*-$C_4\underline{H}_9$), 2.60 (3H, s, $C\underline{H}_3$–C═S), 3.04 (2H, t, J = 5.5 Hz, –CH_2–), 3.27 (2H, t, J = 5.8 Hz, –CH_2–), 3.41 (2H, t, J = 5.8 Hz, –CH_2–), 3.60 (2H, t, J = 5.8 Hz, –CH_2–), 3.79 (1H, dd, J = 6.9, 9.1 Hz, oxazolidinone-H4), 4.00–4.13 (2H, m, –CH_2–), 4.24 (1H, ddd, J = 2.7, 6.1, 14.3 Hz, oxazolidinone-H4), 4.93–5.03 (1H, m, oxazolidinone-H5), 7.05 (2H, d, J = 10.7 Hz, Ar–H2 and H6), and 8.18 (1H, br t, J = 6 Hz, –N$\underline{H}$–C═S); EI-LRMS m/z: 485 (M^+).

*4.1.23. 5(S)-(Thioacetylaminomethyl)-3-(3,5-difluoro-4-([1,2,5] oxadiazepan-5-yl)phenyl)oxazolidin-2-one (**9c**)*

Compound **9c** (0.3269 g, 71%) was prepared from **6c** (0.5098 g, 1.190 mmol) in the same manner as described for **9a**. Colourless needles (EtOH); mp: 170–171 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ = 2.57 (3H, s, $C\underline{H}_3$C═S), 3.23 (2H, br t, J = 5 Hz, –CH_2–), 3.41 (2H, br t, J = 6 Hz, –$C\underline{H}_2$–), 3.49 (2H, br t, J = 5 Hz, –CH_2–), 3.82 (1H, dd, J = 6.9, 9.0 Hz, oxazolidinone-H4), 3.92 (2H, br t, J = 6 Hz, –CH_2–), 4.00 (1H, dd, J = 6.9, 14.5 Hz, –C$\underline{H}$H–NH–C═S), 4.08 (1H, t, J = 9.0 Hz, oxazolidinone-H4), 4.17 (1H, dd, J = 2.5, 14.5 Hz, –CH$\underline{H}$–NH–C═S), 5.00 (1H, ddt, J = 2.5, 9.0, 6.9 Hz, oxazolidinone-H5), and 7.10 (2H, d, J = 10.8 Hz, Ar–H2 and H6); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 32.9, 47.6, 47.8, 53.2, 55.0, 55.4, 71.1, 72.3, 102.4 (2C, d, J = 30 Hz), 125.5 (t, J = 14 Hz), 132.3 (t, J = 13 Hz), 154.3, 157.4 (2C, dd, J = 9, 244 Hz), and 203.1; EI-LRMS m/z: 386 (M^+). EI-HRMS m/z: calcd. for $C_{16}H_{20}F_2N_4O_3S$ (M^+): 386.1223; found 386.1217.

*4.1.24. 5(R)-(Hydroxymethyl)-3-(3-fluoro-4-(1-(tert-butoxycarbonyl)-2-(2,2,2-trichloroacetyl) [1,2,5]triazepan-5-yl)-phenyl)oxazolidin-2-one (**10a**)*

A suspension of **4a** (1.8671 g, 3.429 mmol) and 10% Pd/C (95.6 mg) in 95% MeOH (20 mL) was hydrogenated at 1 atm at ambient temperature for 20 h, and then filtered through a Celite pad. Evaporation of the solvent afforded a residue, which was used without further purification. To a solution of the above residue and triethylamine (1.10 mL, 7.827 mmol) in THF (15 mL) was added trifluoroacetic anhydride (1.10 mL, 7.924 mmol) at 0 °C, and the mixture was stirred for 30 min at ambient temperature. The reaction mixture was quenched with 1.4% NH_3 aqueous solution. The resulting mixture was extracted with AcOEt, washed with brine, and dried. Evaporation of the solvent followed by silica gel (20 g) column chromatography of the residue using *n*-hexane/AcOEt (50:50 to 0:100) as the eluent afforded **10a** (1.6569 g, 95%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.43–1.52 (9H, m, *t*-$C_4\underline{H}_9$), 3.06–3.68 (6H, m, –CH_2–), 3.77 (1H, dd, J = 3.9, 12.4 Hz, –CH$\underline{H}$-OH), 3.90–4.35 (5H, m, –CH_2–), 4.69–4.79 (1H, m, oxazolidinone-H5), 6.92 (1H, t, J = 9.1 Hz, Ar–H6), 7.10 (1H, br d, J = 9 Hz, Ar–H5), and 7.43 (1H, br d, J = 15 Hz, Ar–H2); EI-LRMS m/z: 506 (M^+).

*4.1.25. 5(R)-(Hydroxymethyl)-3-(3,4-difluoro-4-(1-(tert-butoxycarbonyl)-2-(2,2,2-trichloroacetyl) [1,2,5]triazepan-5-yl) phenyl)oxazolidin-2-one (**10b**)*

Compound **10b** (1.7092 g, 85%) was prepared from **4b** (2.1532 g, 3.828 mmol) in the same manner as described for **10a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.46–1.54 (9H, m, *t*-$C_4\underline{H}_9$), 3.04–3.66 (6H, m, –CH_2–), 3.76 (1H, dd, J = 3.8, 12.6 Hz, –CH$\underline{H}$-OH), 3.90–4.27 (5H, m, –CH_2–), 4.70–4.80 (1H, m, oxazolidinone-H5), and 7.15 (2H, d, J = 10.7 Hz, Ar–H2 and H6); EI-LRMS m/z: 524 (M^+).

*4.1.26. 5(R)-(Azidomethyl)-3-(3-fluoro-4-(1-(tert-butoxycarbonyl)-2-(2,2,2-trichloroacetyl) [1,2,5]triazepan-5-yl)phenyl) oxazolidin-2-one (**11a**)*

To a solution of **10a** (1.5342 g, 3.049 mmol) and triethylamine (0.60 mL, 4.269 mmol) in CH_2Cl_2 (15 mL) was added dropwise methanesulfonyl chloride (0.30 mL, 3.876 mmol) at 0 °C, and the resulting mixture was stirred for 20 min at ambient temperature. The reaction mixture was quenched with H_2O (20 mL), and extracted with $CHCl_3$. The organic layer was washed with brine, dried, and evaporated to afford a residue, which was used without further purification. To a solution of the above residue in *N*,*N*-dimethylformamide (15 mL) was added sodium azide (301.5 mg, 4.638 mmol), and the mixture was stirred for 16 h within the temperature range of 50–60 °C. The reaction mixture was then cooled and poured into water (30 mL). The aqueous layer was extracted with AcOEt and the combined organic layer was washed with H_2O and brine, and dried. Evaporation of the solvent followed by silica gel (20 g) column chromatography of the residue using *n*-hexane/AcOEt (75:25 to 40:60) as the eluent afforded **11a** (1.5859 g, 99%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.44–1.52 (9H, m, *t*-$C_4\underline{H}_9$), 3.06–3.66 (6H, m, –CH_2–), 3.60 (1H, dd, J = 4.4, 13.2 Hz, –C$\underline{H}$H–N_3), 3.70 (1H, dd, J = 4.7, 13.2 Hz, –CH$\underline{H}$–N_3), 3.82 (1H, dd, J = 6.1, 9.1 Hz, oxazolidinone-H4), 4.04 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.10–4.36 (2H, m, –CH_2–), 4.78 (1H, dddd, J = 4.4, 4.7, 6.1, 9.1 Hz, oxazolidinone-H5), 6.93 (1H, t, J = 9.1 Hz, Ar–H6), 7.11 (1H, br d, J = 9 Hz, Ar–H5), and 7.43 (1H, br d, J = 15 Hz, Ar–H2); EI-LRMS m/z: 531 (M^+).

*4.1.27. 5(R)-(Azidomethyl)-3-(3,4-difluoro-4-(1-(tert-butoxycarbonyl)-2-(2,2,2-trichloroacetyl) [1,2,5]triazepan-5-yl) phenyl)oxazolidin-2-one (**11b**)*

Compound **11b** (1.5026 g, 91%) was prepared from **10b** (1.5736 g, 3.001 mmol) in the same manner as described for **11a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.41–1.54 (9H, m, *t*-$C_4\underline{H}_9$), 3.05–3.66 (6H, m, –CH_2–), 3.59 (1H, dd, J = 4.1, 13.2 Hz, –C$\underline{H}$H–N_3), 3.72 (1H, dd, J = 4.4, 13.2 Hz, –CH$\underline{H}$–N_3), 3.80 (1H, dd, J = 6.2, 9.1 Hz, oxazolidinone-H4), 4.02 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.04–4.27 (2H, m, –CH_2–), 4.79 (1H, dddd, J = 4.1, 4.4, 6.2, 9.1 Hz, oxazolidinone-H5), and 7.15 (2H, d, J = 10.7 Hz, Ar–H2 and H6); EI-LRMS m/z: 549 (M^+).

*4.1.28. 5(S)-(Aminomethyl)-3-(3-fluoro-4-(1-(tert-butoxycarbonyl)-2-(2,2,2-trichloroacetyl) [1,2,5]triazepan-5-yl) phenyl) oxazolidin-2-one (**12a**)*

To a solution of **11a** (1.4647 g, 2.756 mmol) and triphenylphosphine (1.0730 g, 4.091 mmol) in tetrahydrofuran (14 mL) was added H_2O (0.5 mL, 27.78 mmol) at ambient temperature and the resulting mixture was refluxed for 2 h. After cooling, the reaction mixture was concentrated in vacuo followed by silica gel (20 g) column chromatography of the residue using $CHCl_3$/MeOH (97:3 to

80:20) as the eluent to afford **12a** (1.2871 g, 92%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.35–1.52 (9H, m, *t*-$C_4\underline{H}_9$), 2.91 (2H, br s, $N\underline{H}_2$), 3.00–4.34 (12H, m, $-CH_2-$), 4.71–4.82 (1H, m, oxazolidinone-H5), 6.90 (1H, t, J = 9.1 Hz, Ar–H6), 7.09 (1H, br d, J = 8 Hz, Ar–H5), and 7.40 (1H, br d, J = 15 Hz, Ar–H2); EI-LRMS m/z: 505 (M^+).

4.1.29. 5(S)-(Aminomethyl)-3-(3,5-difluoro-4-(1-(tert-butoxycarbonyl)-2-(2,2,2-trichloroacetyl) [1,2,5]triazepan-5-yl)-phenyl)oxazolidin-2-one (**12b**)

Compound **12b** (1.1454 g, 92%) was prepared from **11b** (1.3080 g, 2.381 mmol) in the same manner as described for **12a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.45–1.54 (9H, m, *t*-$C_4\underline{H}_9$), 2.10 (2H, br s, $N\underline{H}_2$), 3.00–4.27 (12H, m, $-CH_2-$), 4.67–4.78 (1H, m, oxazolidinone-H5), and 7.14 (2H, d, J = 10.7 Hz, Ar–H2 and H6); EI-LRMS m/z: 523 (M^+).

4.1.30. O-Methyl (S)-N-(3-(4-(1-(tert-butoxycarbonyl)-2-(2,2,2-trichloroacetyl) [1,2,5]triazepan-5-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methylthiocarbamate (**13a**)

A mixture of compound **12a** (1.2069 g, 2.388 mmol), carbon disulfide (0.28 mL, 4.634 mmol) and triethylamine (0.34 mL, 2.419 mmol) in tetrahydrofuran (12 mL) was stirred for 30 min at ambient temperature. Then ethyl chloroformate (0.26 mL, 2.729 mmol) was added dropwise to the reaction mixture at the same temperature. Stirring was continued for 10 min, then the reaction mixture was washed with water and extracted with AcOEt. The extract was washed with brine, dried, and evaporated to afford a residue, which was used without further purification. To a solution of NaH (55% in mineral oil, 143.9 mg, 3.298 mmol) in MeOH (12 mL) was added a solution of the above residue in MeOH (10 mL) at 0 °C, followed by stirring for 30 min at the same temperature. The reaction mixture was then poured into saturated ammonium chloride aqueous solution (15 mL). The aqueous layer was extracted with AcOEt and the combined organic layer was washed with brine, and dried. Evaporation of the solvent followed by silica gel (20 g) column chromatography of the residue using *n*-hexane/AcOEt (90:10 to 50:50) as the eluent afforded **13a** (1.2809 g, 93%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.45–1.51 (9H, m, *t*-$C_4\underline{H}_9$), 3.07–4.35 (12H, m, $-CH_2-$), 4.01 (3H, s, $OC\underline{H}_3$), 4.86–4.97 (1H, m, oxazolidinone-H5), 6.74 (1H, t, J = 6.3 Hz, $-N\underline{H}-C{=}S$), 6.92 (1H, t, J = 9.1 Hz, Ar–H6), 7.07 (1H, br d, J = 9 Hz, Ar–H5), and 7.42 (1H, br d, J = 14 Hz, Ar–H2); EI-LRMS m/z: 579 (M^+).

4.1.31. O-Methyl (S)-N-(3-(4-(1-(tert-butoxycarbonyl)-2-(2,2,2-trichloroacetyl) [1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl)methylthiocarbamate (**13b**)

Compound **13b** (1.1156 g, 90%) was prepared from **12b** (1.0816 g, 2.066 mmol) in the same manner as described for **13a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.46–1.55 (9H, m, *t*-$C_4\underline{H}_9$), 3.05–4.27 (12H, m, $-CH_2-$), 4.01 (3H, s, $OC\underline{H}_3$), 4.87–4.98 (1H, m, oxazolidinone-H5), 6.69 (1H, t, J = 6.3 Hz, $-N\underline{H}-C{=}S$), and 7.12 (2H, d, J = 10.7 Hz, Ar–H2 and H6); EI-LRMS m/z: 597 (M^+).

4.1.32. O-Methyl (S)-N-(3-(4-(1-(tert-butoxycarbonyl) [1,2,5] oxadiazepan-5-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl)-methylthiocarbamate (**13c**)

Compound **13c** (0.9323 g, 89%) was prepared from **6c** (0.8893 g, 2.076 mmol) in the same manner as described for **13a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.51 (9H, s, *t*-$C_4\underline{H}_9$), 3.35–3.44 (4H, m, $-CH_2-$), 3.78 (2H, br t, J = 6 Hz, $-CH_2-$), 3.83 (1H, dd, J = 7.2, 9.0 Hz, oxazolidinone-H4), 3.96–4.12 (5H, m, $-CH_2-$), 4.00 (3H, s, $OC\underline{H}_3$), 4.89–4.99 (1H, m, oxazolidinone-H5), 7.04–7.21 (1H, br, $-N\underline{H}-C{=}S$), and 7.09 (2H, d, J = 10.8 Hz, Ar–H2 and H6); EI-LRMS m/z: 502 (M^+). EI-HRMS m/z: calcd. for $C_{21}H_{28}F_2N_4O_6S$ (M^+): 502.1696; found 502.1685.

4.1.33. O-Methyl (S)-N-(3-(4-(1-(tert-butoxycarbonyl) [1,2,5] triazepan-5-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)-methylthiocarbamate (**14a**)

To a stirred solution of **13a** (1.0483 g, 1.809 mmol) in tetrahydrofuran (4 mL) and MeOH (4 mL) and H_2O (2 mL) was added lithium hydroxide monohydrate (116.6 mg, 2.779 mmol) at 0 °C. Stirring was continued for 1 h at the same temperature, then the reaction mixture was poured into saturated ammonium chloride aqueous solution (15 mL), and extracted with AcOEt. The combined organic layer was washed with brine, dried, and evaporated, followed by silica gel (20 g) column chromatography of the residue using *n*-hexane/AcOEt (70:30 to 20:80) as the eluent to afford **14a** (0.8433 g, 96%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.38 (9H, m, *t*-$C_4\underline{H}_9$), 3.11 (2H, t, J = 5.2 Hz, $-CH_2-$), 3.44 (2H, t, J = 5.2 Hz, $-CH_2-$), 3.54–3.68 (4H, m, $-CH_2-$), 3.80 (1H, dd, J = 6.8, 9.1 Hz, oxazolidinone-H4), 3.89–4.14 (3H, m, $-CH_2-$), 4.00 (3H, s, $OC\underline{H}_3$), 4.84–4.95 (1H, m, oxazolidinone-H5), 6.80 (1H, t, J = 6.3 Hz, $-N\underline{H}-C{=}S$), 6.87 (1H, t, J = 9.1 Hz, Ar–H6), 7.00 (1H, dd, J = 2.5, 9.1 Hz, Ar–H5), and 7.35 (1H, dd, J = 2.5, 15.2 Hz, Ar–H2); EI-LRMS m/z: 483 (M^+).

4.1.34. O-Methyl (S)-N-(3-(4-(1-(tert-butoxycarbonyl) [1,2,5] triazepan-5-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl)-methylthiocarbamate (**14b**)

Compound **14b** (1.5184 g, 98%) was prepared from **13b** (1.8471 g, 3.091 mmol) in the same manner as described for **14a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.49 (9H, m, *t*-$C_4\underline{H}_9$), 3.05 (2H, br t, J = 5 Hz, $-CH_2-$), 3.27 (2H, br t, J = 5 Hz, $-CH_2-$), 3.41 (2H, t, J = 5.8 Hz, $-CH_2-$), 3.60 (2H, t, J = 5.8 Hz, $-CH_2-$), 3.80 (1H, dd, J = 7.1, 9.1 Hz, oxazolidinone-H4), 3.93–4.13 (3H, m, $-CH_2-$), 4.01 (3H, s, $OC\underline{H}_3$), 4.87–4.97 (1H, m, oxazolidinone-H5), 6.77 (1H, t, J = 6.3 Hz, $-N\underline{H}-C{=}S$), and 7.08 (2H, d, J = 10.8 Hz, Ar–H2 and H6); EI-LRMS m/z: 501 (M^+).

4.1.35. O-Methyl (S)-N-(3-(4-[1,2,5]oxadiazepan-5-yl)-3,5-difluorophenyl)-2-oxooxazolidin-5-yl)methylthiocarbamate (**14c**)

To a solution of **13c** (36.0 mg, 0.072 mmol) in $CHCl_3$ (5 mL) was added trifluoroacetic acid (0.3 mL). The mixture was stirred for 15 h at ambient temperature, then neutralized with 10% sodium carbonate aqueous solution, and extracted with 10% MeOH/$CHCl_3$. The organic solution was dried, and evaporated, followed by preparative TLC of the residue using $CHCl_3$/MeOH (90:10) as the eluent to afford **14c** (22.0 mg, 76%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 3.22 (2H, br t, J = 5 Hz, $-CH_2-$), 3.40 (2H, br t, J = 5 Hz, $-CH_2-$), 3.44–3.52 (2H, m, $-CH_2-$), 3.81 (1H, dd, J = 6.9, 9.0 Hz, oxazolidinone-H4), 3.90 (2H, br t, J = 5 Hz, $-CH_2-$), 3.97–4.10 (3H, m, $-CH_2-$), 4.00 (3H, s, $OC\underline{H}_3$), 4.89–4.99 (1H, m, oxazolidinone-H5), 7.06 (2H, d, J = 10.8 Hz, Ar–H2 and H6), and 7.30 (1H, br t, J = 6 Hz, $-N\underline{H}-C{=}S$); ^{13}C NMR ($CDCl_3$) δ = 47.2, 47.4, 53.5, 55.1, 55.6, 57.6, 71.3, 72.3, 102.4 (2C, d, J = 31 Hz), 125.7 (t, J = 14 Hz), 132.4 (t, J = 14 Hz), 153.9, 157.6 (2C, dd, J = 9, 244 Hz), and 192.8; EI-LRMS m/z: 402 (M^+). EI-HRMS m/z: calcd. for $C_{16}H_{20}F_2N_4O_4S$ (M^+): 402.1171; found 402.1157.

4.1.36. 5(R)-3-(4-(1-(Benzyloxycarbonyl)-2-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)-3-fluorophenyl)-5-(1,2,3-triazol-1-ylmethyl) oxazolidin-2-one (**15a**)

To a solution of **5a** (0.8759 g, 1.538 mmol) in 1,4-dioxane (15 mL) was added 2,5-norbornadiene (0.7088 g, 7.693 mmol) and the mixture was refluxed for 40 h. Evaporation of the solvent followed by silica gel (20 g) column chromatography of the residue using *n*-hexane/AcOEt (50:50 to 0:100) as the eluent afforded **15a** (0.8754 g, 96%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.32–1.49 (9H, m, *t*-$C_4\underline{H}_9$), 3.16–3.59 (6H, m, $-CH_2-$), 3.87 (1H, br dd, J = 6, 9 Hz, oxazolidinone-H4), 3.96–4.26 (3H, m, $-CH_2-$), 4.70–4.84 (2H, m,

−CH$_2$−, [1,2,3]triazole), 4.98−5.09 (1H, m, oxazolidinone-H5), 5.04−5.29 (2H, m, Ar−CH$_2$O), 6.83 (1H, t, J = 9.1 Hz, Ar−H5), 6.86−6.97 (1H, m, Ar−H6), 7.18−7.38 (6H, m, Ar−H), 7.74 (1H, s, [1,2,3]triazole-H), and 7.79 (1H, s, [1,2,3]triazole-H); EI-LRMS m/z: 595 (M^+).

4.1.37. 5(R)-3-(4-(1-(Benzyloxycarbonyl)-2-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**15b**)

Compound **15b** (2.5053 g, 89%) was prepared from **5b** (2.6920 g, 4.582 mmol) in the same manner as described for **15a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.34−1.52 (9H, m, t-C$_4$H$_9$), 3.03−3.50 (6H, m, −CH$_2$−), 3.84−4.17 (3H, m, −CH$_2$−), 4.10(1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.78 (2H, J = 4.1 Hz, −CH$_2$−, [1,2,3]triazole), 5.01−5.11 (1H, m, oxazolidinone-H5), 5.07−5.32 (2H, m, Ar−CH$_2$O), 6.97 (2H, d, J = 10.7 Hz, Ar−H2 and H6), 7.27−7.39 (5H, m, Ar−H), 7.75 (1H, s, [1,2,3]triazole-H), and 7.77 (1H, s, [1,2,3]triazole-H); EI-LRMS m/z: 613 (M^+).

4.1.38. 5(R)-3-(4-(2-(tert-Butoxycarbonyl) [1,2,5]oxadiazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**15c**)

Compound **15c** (1.3578 g, 69%) was prepared from **5c** (1.8597 g, 4.096 mmol) in the same manner as described for **15a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.51 (9H, s, t-C$_4$H$_9$), 3.35−3.42 (4H, m, −CH$_2$−), 3.77 (2H, br t, J = 6 Hz, −CH$_2$−), 3.90 (1H, dd, J = 6.0, 9.3 Hz, oxazolidinone-H4), 4.06 (2H, br t, J = 5 Hz, −CH$_2$−), 4.14 (1H, t, J = 9.3 Hz, oxazolidinone-H4), 4.81 (2H, d, J = 4.0 Hz, −CH$_2$−, [1,2,3]triazole), 5.09 (1H, ddt, J = 6.0, 9.3, 4.0 Hz, oxazolidinone-H5), 6.99 (2H, d, J = 10.8 Hz, Ar−H2 and H6), 7.74 (1H, d, J = 0.5 Hz, [1,2,3]triazole-H), and 7.81 (1H, d, J = 0.5 Hz, [1,2,3]triazole-H); EI-LRMS m/z: 480 (M^+).

4.1.39. 5(R)-3-(4-(1-(tert-Butoxycarbonyl) [1,2,5]triazepan-5-yl)-3-fluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazoli din-2-one (**16a**)

A suspension of **15a** (0.6789 g, 1.140 mmol) and 10% Pd/C (136.2 mg) in 95% MeOH (10 mL) was hydrogenated at 1 atm at ambient temperature for 24 h, and then filtered through a Celite pad. Evaporation of the solvent followed by silica gel (15 g) column chromatography of the residue using $CHCl_3$/MeOH (98:2 to 90:10) as the eluent afforded **16a** (0.4838 g, 92%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.37 (9H, s, t-C$_4$H$_9$), 3.10 (2H, t, J = 5.5 Hz, −CH$_2$−), 3.43 (2H, t, J = 5.5 Hz, −CH$_2$−), 3.52−3.59 (2H, m, −CH$_2$−), 3.60−3.68 (2H, m, −CH$_2$−), 3.86 (1H, dd, J = 6.1, 9.1 Hz, oxazolidinone-H4), 4.10 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.76 (1H, dd, J = 4.7, 14.9 Hz, −CHH−, [1,2,3]triazole), 4.80 (1H, dd, J = 3.9, 14.9 Hz, −CHH−, [1,2,3]triazole), 5.03 (1H, dddd, J = 3.9, 4.7, 6.1, 9.1 Hz, oxazolidinone-H5), 6.83 (1H, t, J = 9.1 Hz, Ar−H5), 6.88 (1H, dd, J = 2.5, 9.1 Hz, Ar−H6), 7.21 (1H, dd, J = 2.5, 15.2 Hz, Ar−H2), 7.75 (1H, br s, [1,2,3]triazole-H), and 7.79 (1H, br s, [1,2,3]triazole-H); EI-LRMS m/z: 461 (M^+).

4.1.40. 5(R)-3-(4-(1-(tert-Butoxycarbonyl) [1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**16b**)

Compound **16b** (0.4778 g, 96%) was prepared from **15b** (0.6342 g, 1.034 mmol) in the same manner as described for **15a**. Colourless prisms (EtOH); mp 158−159 °C; ^{1}H NMR ($CDCl_3$) δ = 1.49 (9H, s, t-C$_4$H$_9$), 3.03 (2H, t, J = 5.2 Hz, −CH$_2$−), 3.25 (2H, t, J = 5.2 Hz, −CH$_2$−), 3.39 (2H, t, J = 5.7 Hz, −CH$_2$−), 3.59 (2H, t, J = 5.7 Hz, −CH$_2$−), 3.88 (1H, dd, J = 6.1, 9.1 Hz, oxazolidinone-H4), 4.10 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.78 (2H, d, J = 4.1 Hz, −CH$_2$−, [1,2,3]triazole), 5.05 (1H, ddt, J = 6.1, 9.1, 4.1 Hz, oxazolidinone-H5), 6.88 (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); EI-LRMS m/z: 479 (M^+).

4.1.41. 5(R)-3-(4-(2-[1,2,5]Oxadiazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**16c**)

Compound **16c** (0.8097 g, 94%) was prepared from **15c** (1.0895 g, 2.268 mmol) in the same manner as described for **14c**. Colourless needles (EtOH); mp: 152−153 °C; ^{1}H NMR ($CDCl_3$) δ = 3.21 (2H, br t, J = 6 Hz, −CH$_2$−), 3.38 (2H, br t, J = 5 Hz, −CH$_2$−), 3.47 (2H, br t, J = 6 Hz, −CH$_2$−), 3.84−3.93 (3H, m, −CH$_2$−), 4.13 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.77 (1H, dd, J = 5.0, 15.0 Hz, −CHH−, [1,2,3]triazole), 4.82 (1H, dd, J = 4.0, 15.0 Hz, −CHH−, [1,2,3]triazole), 5.03−5.12 (1H, m, oxazolidinone-H5), 6.91−7.03 (2H, m, Ar−H2 and H6), 7.74 (1H, br s, [1,2,3]triazole-H), and 7.80 (1H, br s, [1,2,3]triazole-H); ^{13}C NMR ($CDCl_3$) δ = 47.1, 51.9, 53.6, 55.1, 55.6, 70.3, 72.3, 102.6 (2C, d, J = 30 Hz), 125.0, 125.9 (t, J = 14 Hz), 131.6 (t, J = 13 Hz), 134.4, 152.9, and 157.2 (2C, dd, J = 9, 244 Hz); EI-LRMS m/z: 380 (M^+). EI-HRMS m/z: calcd. for $C_{16}H_{18}F_2N_6O_3$ (M^+): 380.1407; found 380.1399.

4.1.42. 5(R)-(Isoxazol-3-yl-N-(tert-butoxycarbonyl)aminomethyl)-3-(3-fluoro-4-(1-(benzyloxycarbonyl)-2-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**17a**)

To a solution of compound **4a** (383.1 mg, 0.703 mmol) in THF (3 mL) was added tri-n-butylphosphine (590.1 mg, 2.917 mmol), ADDP (709.6 mg, 2.812 mmol) and isoxazol-3-yl-carbamic acid $tert$-butyl ester (454.3 mg, 2.466 mmol). The mixture was stirred for 21 h at ambient temperature. Evaporation of the solvent followed by silica gel (20 g) column chromatography of the residue using n-hexane/AcOEt (80:20 to 40:60) as the eluent afforded **17a** (465.1 mg, 93%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.33−1.60 (18H, m, t-C$_4$H$_9$ ×2), 3.17−3.60 (6H, m, −CH$_2$−), 3.75 (1H, br dd, J = 6, 9 Hz, oxazolidinone-H4), 3.97−4.28 (3H, m, −CH$_2$−), 4.11 (1H, dd, J = 4.9, 14.6 Hz, −CHH−NBoc-isozazole), 4.36 (1H, dd, J = 7.7, 14.6 Hz, −CHH−NBoc-isoxazole), 5.00−5.10 (1H, m, oxazolidinone-H5), 5.05−5.29 (2H, m, Ar−CH$_2$O), 6.88 (1H, t, J = 9.1 Hz, Ar−H5), 6.91 (1H, br s, isoxazole-H), 7.01−7.11 (1H, m, Ar−H6), 7.28−7.44 (6H, m, Ar−H), and 8.25 (1H, d, J = 1.9 Hz, isoxazole-H); EI-LRMS m/z: 610 (M^+-Boc).

4.1.43. 5(R)-(Isoxazol-3-yl-N-(tert-butoxycarbonyl)aminomethyl)-3-(3,5-difluoro-4-(1-(benzyloxycarbonyl)-2-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**17b**)

Compound **17b** (463.3 mg, 93%) was prepared from **4b** (385.4 mg, 0.685 mmol) in the same manner as described for **17a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.35−1.61 (18H, m, t-C$_4$H$_9$ ×2), 3.05−3.55 (6H, m, −CH$_2$−), 3.76 (1H, br dd, J = 6, 9 Hz, oxazolidinone-H4), 3.97−4.19 (3H, m, −CH$_2$−), 4.12 (1H, dd, J = 4.9, 14.6 Hz, −CHH−NBoc-isoxazole), 4.35 (1H, dd, J = 7.5, 14.6 Hz, −CHH−NBoc-isoxazole), 5.01−5.12 (1H, m, oxazolidinone-H5), 5.05−5.32 (2H, m, Ar−CH$_2$O), 6.90 (1H, br s, isoxazole-H), 7.11 (2H, d, J = 10.7 Hz, Ar−H2 and H6), 7.28−7.40 (5H, m, Ar−H), and 8.26 (1H, d, J = 1.9 Hz, isoxazole-H); EI-LRMS m/z: 728 (M^+).

4.1.44. 5(R)-(Isoxazol-3-yl-N-(tert-butoxycarbonyl)aminomethyl)-3-(3,5-difluoro-4-(2-(tert-butoxycarbonyl) [1,2,5]oxadiazepan-5-yl) phenyl)oxazolidin-2-one (**17c**)

Compound **17c** (839.8 mg, 89%) was prepared from **4c** (650.1 mg, 1.093 mmol) in the same manner as described for **17a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.51 (9H, s, t-C$_4$H$_9$), 1.59 (9H, s, t-C$_4$H$_9$), 3.33−3.44 (4H, m, −CH$_2$−), 3.74−3.82 (3H, m, −CH$_2$−), 4.06 (1H, t, J = 9.0 Hz, oxazolidinone-H4), 4.08 (2H, br t, J = 5 Hz, −CH$_2$−), 4.12 (1H, dd, J = 4.5, 14.7 Hz, −CHH−NBoc-isoxazole), 4.36 (1H, dd t, J = 7.5, 14.7 Hz, −CHH−NBoc-isoxazole), 5.02−5.12 (1H, m, oxazolidinone-H5), 6.90 (1H, br s, isoxazole-H), 7.12 (2H, d, J = 11.1 Hz, Ar−H2 and H6), and 8.27 (1H, d, J = 1.8 Hz, isoxazole-H); EI-LRMS m/z: 595 (M^+).

*4.1.45. 5(R)-(Isoxazol-3-yl-N-(tert-butoxycarbonyl)aminomethyl)-3-(3-fluoro-4-(1-(tert-butoxycarbonyl) [1,2,5]triazepan-5-yl) phenyl)oxazolidin-2-one (**18a**)*

A suspension of **17a** (465.1 mg, 0.654 mmol) and 10% Pd/C (93.1 mg) in 95% MeOH (7 mL) was hydrogenated at 1 atm at ambient temperature for 4 h, and then filtered through a Celite pad. Evaporation of the solvent followed by silica gel (15 g) column chromatography of the residue using *n*-hexane/AcOEt (70:30 to 20:80) as the eluent afforded **18a** (301.0 mg, 80%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.38 (9H, s, *t*-$C_4\underline{H}_9$), 1.56 (9H, s, *t*-$C_4\underline{H}_9$), 3.12 (2H, t, J = 5.5 Hz, $-CH_2-$), 3.44 (2H, t, J = 5.5 Hz, $-CH_2-$), 3.57 (2H, t, J = 5.2 Hz, $-CH_2-$), 3.65 (2H, t, J = 5.2 Hz, $-CH_2-$), 3.75 (1H, dd, J = 5.2, 9.1 Hz, oxazolidinone-H4), 4.05 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.11 (1H, dd, J = 4.9, 14.6 Hz, $-C\underline{H}H-$NBoc-isoxazole), 4.36 (1H, dd, J = 7.7, 14.6 Hz, $-CH\underline{H}-$NBoc-isoxazole), 5.04 (1H, dddd, J = 4.9, 5.2, 7.7, 9.1 Hz, oxazolidinone-H5), 6.88 (1H, t, J = 9.1 Hz, Ar−H5), 6.91 (1H, br s, isoxazole-H), 7.03 (1H, dd, J = 2.7, 9.1 Hz, Ar−H6), 7.37 (1H, dd, J = 2.7, 15.4 Hz, Ar−H2), and 8.26 (1H, d, J = 1.7 Hz, isoxazole-H); EI-LRMS m/z: 576 (M^+).

*4.1.46. 5(R)-(Isoxazol-3-yl-N-(tert-butoxycarbonyl)aminomethyl)-3-(3,5-difluoro-4-(1-(tert-butoxycarbonyl) [1,2,5]triaze-pan-5-yl) phenyl)oxazolidin-2-one (**18b**)*

Compound **18b** (305.6 mg, 81%) was prepared from **17b** (463.3 mg, 0.636 mmol) in the same manner as described for **18a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 1.49 (9H, s, *t*-$C_4\underline{H}_9$), 1.56 (9H, s, *t*-$C_4\underline{H}_9$), 3.05 (2H, t, J = 5.2 Hz, $-CH_2-$), 3.27 (2H, t, J = 5.2 Hz, $-CH_2-$), 3.41 (2H, t, J = 5.7 Hz, $-CH_2-$), 3.60 (2H, t, J = 5.7 Hz, $-CH_2-$), 3.76 (1H, dd, J = 5.5, 9.1 Hz, oxazolidinone-H4), 4.04 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.12 (1H, dd, J = 4.9, 14.7 Hz, $-C\underline{H}H-$NBoc-isoxazole), 4.36 (1H, dd, J = 7.5, 14.7 Hz, $-CH\underline{H}-$NBoc-isoxazole), 5.04 (1H, dddd, J = 4.9, 5.5, 7.3, 9.1 Hz, oxazolidinone-H5), 6.90 (1H, br s, isoxazole-H), 7.10 (2H, d, J = 10.7 Hz, Ar−H2 and H6), and 8.26 (1H, d, J = 1.9 Hz, isoxazole-H); EI-LRMS m/z: 594 (M^+).

*4.1.47. 5(S)-(Isoxazol-3-yl-aminomethyl)-3-(3,5-difluoro-4-([1,2,5] oxadiazepan-5-yl)phenyl)oxazolidin-2-one (**18c**)*

Compound **18c** (180.6 mg, 73%) was prepared from **17c** (372.0 mg, 0.625 mmol) in the same manner as described for **14c**. Colourless prisms (EtOH); mp: 139–140 °C; ^{1}H NMR ($CDCl_3$) δ = 3.21 (2H, br t, J = 6 Hz, $-CH_2-$), 3.38 (2H, br t, J = 6 Hz, $-CH_2-$), 3.48 (2H, br t, J = 6 Hz, $-CH_2-$), 3.61 (1H, dt, J = 14.7, 6.0 Hz, $-C\underline{H}H-$NH-isoxazole), 3.71 (1H, ddd, J = 3.6, 6.0, 14.7 Hz, $-CH\underline{H}-$NH-isoxazole), 3.81 (1H, dd, J = 6.6, 9.0 Hz, oxazolidinone-H4), 3.89 (2H, br t, J = 6 Hz, $-CH_2-$), 4.03 (1H, t, J = 9.0 Hz, oxazolidinone-H4), 4.92 (1H, br t, J = 6 Hz, $-CH_2-$), 4.93 (1H, dddd, J = 3.6, 6.0, 6.6, 9.0 Hz, oxazolidinone-H5), 5.82 (1H, br s, N$\underline{H}$), 5.90 (1H, d, J = 2.1 Hz, isoxazole-H), 7.06 (2H, d, J = 11.1 Hz, Ar−H2 and H6), and 8.05 (1H, d, J = 2.1 Hz, isoxazole-H); ^{13}C NMR ($CDCl_3$) δ = 46.4, 47.5, 53.6, 55.1, 55.7, 71.4, 72.3, 96.4, 102.3 (2C, d, J = 30 Hz), 125.5 (t, J = 14 Hz), 132.5 (t, J = 13 Hz), 154.0, 157.5 (2C, dd, J = 9, 244 Hz), 158.1, and 163.4; EI-LRMS m/z: 395 (M^+). EI-HRMS m/z: calcd. for $C_{17}H_{19}F_2N_5O_4$ (M^+): 395.1404; found 395.1399.

*4.1.48. (S)-N-((3-(3-Fluoro-4-(1-(hydroxyacetyl) [1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**19a**)*

To a solution of compound **7a** (229.7 mg, 0.509 mmol) and pyridine (61.0 mg, 0.771 mmol) in CH_2Cl_2 (3 mL) was added acetoxyacetyl chloride (84.1 mg, 0.616 mmol). The mixture was stirred for 10 min, and then 10% citric acid aqueous solution (10 mL) was added. The mixture was extracted with $CHCl_3$ and dried. Evaporation of the solvent afforded a residue, which was used without further purification. To a solution of the residue in MeOH (3 mL) was added potassium carbonate (138.1 mg, 0.999 mmol), and the mixture was stirred for 10 min at ambient temperature. The reaction mixture was diluted by the addition of H_2O (10 mL), and extracted with 5% MeOH/$CHCl_3$. The organic solution was dried and evaporated to afford a residue, which was used without further purification. To a stirred solution of the residue in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (0.5 mL) and stirring was continued for 3 h at ambient temperature. The reaction mixture was neutralized by the addition of 10% sodium carbonate aqueous solution, and the mixture was extracted with 10% MeOH/$CHCl_3$. The organic solution was dried and evaporated, followed by silica gel (8 g) column chromatography of the residue using $CHCl_3$/MeOH (97:3 to 90:10) as the eluent to afford **19a** (192.5 mg, 92%). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 2.02 (3H, s, $C\underline{H}_3C{=}O$), 3.12–3.78 (9H, m, $-CH_2-$), 3.91–4.05 (3H, m, $-CH_2-$), 4.37 (2H, br s, $-C\underline{H}_2-$OH), 4.72–4.81 (1H, m, oxazolidinone-H5), 6.27 (1H, br t, J = 6 Hz, $-N\underline{H}-C{=}O$), 6.89 (1H, t, J = 9.1 Hz, Ar−H5), 6.98–7.06 (1H, m, Ar−H6), and 7.37–7.46 (1H, m, Ar−H2); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 22.3, 41.8, 47.7, 49.9, 50.7 (2C), 53.8, 60.2, 71.9, 107.6 (d, J = 27 Hz), 114.0, 118.8, 131.4 (d, J = 10 Hz), 136.0 (d, J = 9 Hz), 154.0 (d, J = 242 Hz), 154.7, 172.0, and 174.0.; EI-LRMS m/z: 409 (M^+). EI-HRMS m/z: calcd. for $C_{18}H_{24}FN_5O_5$ (M^+): 409.1761; found 409.1769.

*4.1.49. (S)-N-((3-(3,5-Difluoro-4-(1-(hydroxyacetyl) [1,2,5] triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**19b**)*

Compound **19b** (193.7 mg, 90%) was prepared from **7b** (236.5 mg, 0.504 mmol) in the same manner as described for **19a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 2.03 (3H, s, $C\underline{H}_3-C{=}O$), 3.10–3.22 (2H, m, $-CH_2-$), 3.25–3.31 (2H, m, $-CH_2-$), 3.34–3.42 (2H, m, $-CH_2-$), 3.63–3.70 (2H, m, $-CH_2-$), 3.75 (1H, dd, J = 6.6, 9.1 Hz, oxazolidinone-H4), 3.88–3.93 (2H, m, $-CH_2-$), 4.01 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.39 (2H, s, $-C\underline{H}_2-$OH), 4.75–4.85 (1H, m, oxazolidinone-H5), 6.77 (1H, t, J = 6.1 Hz, $-N\underline{H}-C{=}O$), and 7.09 (2H, d, J = 10.7 Hz, Ar−H2 and H6); ^{13}C NMR ($CDCl_3$) δ = 23.0, 41.8, 51.2, 51.9, 52.4, 55.5, 60.6, 72.0, 102.2 (2C, d, J = 29 Hz), 124.7 (t, J = 14 Hz), 134.1 (t, J = 13 Hz), 153.9, 158.3 (2C, dd, J = 9, 244 Hz), 171.3, and 174.2.; ESI-LRMS m/z: 428 (M^+ + H). ESI-HRMS m/z: calcd. for $C_{18}H_{24}F_2N_5O_5$ (M^+ + H): 428.1740; found 428.1739.

*4.1.50. (S)-N-((3-(3,5-Difluoro-4-(2-(hydroxyacetyl) [1,2,5] oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide (**19c**)*

To a solution of compound **7c** (129.8 mg, 0.433 mmol) and Et_3N (0.80 mL, 5.692 mmol) in CH_2Cl_2 (10 mL) was added acetoxyacetyl chloride (0.20 mL, 1.860 mmol) at 0 °C. The mixture was stirred for 1 h at the same temperature, and then extracted with $CHCl_3$. The organic solution was dried and evaporated to afford a residue, which was used without further purification. To a solution of the residue in MeOH (10 mL) was added potassium carbonate (112.9 mg, 0.817 mmol). The mixture was stirred for 30 min at ambient temperature, diluted by the addition of H_2O (5 mL), extracted with 5% MeOH/$CHCl_3$, and dried. Evaporation of the solvent followed by preparative TLC of the residue using $CHCl_3$/MeOH (9:1) as the eluent afforded **19c** (111.2 mg, 74%). Colourless needles (EtOH); mp: 145–146 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ = 2.03 (3H, s, $C\underline{H}_3-C{=}O$), 3.42 (2H, br t, J = 5 Hz, $-CH_2-$), 3.47 (2H, br t, J = 5 Hz, $-CH_2-$), 3.51–3.67 (2H, m, $-CH_2-$), 3.74 (1H, dd, J = 6.6, 9.0 Hz, oxazolidinone-H4), 3.94 (2H, br t, J = 5 Hz, $-CH_2-$), 4.04 (1H, t, J = 9.0 Hz, oxazolidinone-H4), 4.14 (2H, br t, J = 5 Hz, $-CH_2-$), 4.38 (2H, s, $-C\underline{H}_2-$OH), 4.74–4.84 (1H, m, oxazolidinone-H5), 7.14 (2H, d, J = 10.8 Hz, Ar−H2 and H6), and 7.91 (1H, br t, J = 6 Hz, $-N\underline{H}-C{=}O$); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 22.3, 41.7, 47.4, 50.2, 51.9, 54.4, 59.5, 71.9, 77.7, 102.2 (2C, d, J = 30 Hz), 124.1 (t, J = 14 Hz), 133.9 (t, J = 14 Hz), 154.2, 157.9 (2C, dd, J = 8, 244 Hz), 172.0, and 172.1.; EI-

LRMS *m/z*: 380 (M^+). HRMS-EI (*m/z*): calcd. for $C_{18}H_{22}F_2N_4O_6$ (M^+): 428.1506; found 428.1520.

4.1.51. (S)-N-((3-(3-Fluoro-4-(1-(hydroxyacetyl) [1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)thioacetamide (**20a**)

Compound **20a** (120.1 mg, 87%) was prepared from **9a** (151.0 mg, 0.323 mmol) in the same manner as described for **19a**. Colourless prisms (EtOH); mp 158–159 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ = 2.57 (3H, s, C<u>H</u>$_3$–C=S), 3.12–3.21 (2H, m, –C<u>H</u>$_2$–), 3.32–3.39 (2H, m, –C<u>H</u>$_2$–), 3.41–3.47 (2H, m, –C<u>H</u>$_2$–), 3.84 (1H, dd, *J* = 6.9, 9.1 Hz, oxazolidinone-H4), 3.88–4.20 (5H, m, –C<u>H</u>$_2$–), 4.38 (2H, s, –C<u>H</u>$_2$–OH), 4.94–5.04 (1H, m, oxazolidinone-H5), 6.93 (1H, t, *J* = 9.1 Hz, Ar–H5), 7.05 (1H, dd, *J* = 2.5, 9.1 Hz, Ar–H6), and 7.40 (1H, dd, *J* = 2.5, 14.5 Hz, Ar–H2); ESI-LRMS *m/z*: 426 (M^+ + H). ESI-HRMS *m/z*: calcd. for $C_{18}H_{25}FN_5O_4S$ (M^+ + H): 426.1606; found 426.1602.

4.1.52. (S)-N-((3-(3,5-Difluoro-4-(1-(hydroxyacetyl) [1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)thioacetamide (**20b**)

Compound **20b** (102.7 mg, 70%) was prepared from **9b** (160.3 mg, 0.330 mmol) in the same manner as described for **19a**. White powder (EtOH); mp 136–137 °C; ^{1}H NMR (CD_3OD + $CDCl_3$), δ = 2.56 (3H, s, C<u>H</u>$_3$–C=S), 3.09–3.16 (2H, m, –C<u>H</u>$_2$–), 3.25–3.33 (2H, m, –C<u>H</u>$_2$–), 3.34–3.43 (2H, m, –C<u>H</u>$_2$–), 3.80–3.88 (3H, m, –C<u>H</u>$_2$–), 3.96–4.21 (3H, m, –C<u>H</u>$_2$–), 4.41 (2H, s, –C<u>H</u>$_2$–OH), 4.95–5.05 (1H, m, oxazolidinone-H5), and 7.13 (2H, d, *J* = 10.7 Hz, Ar–H2 and H6); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 31.9, 46.3, 46.8, 49.6, 50.8 (2C), 54.3, 59.2, 69.4, 101.0 (2C, dd, *J* = 9, 30 Hz), 123.4 (t, *J* = 14 Hz), 133.0 (t, *J* = 11 Hz), 152.5, 156.9 (2C, dd, *J* = 9, 244 Hz), 172.7, and 201.1; ESI-LRMS *m/z*: 444 (M^+ + H). ESI-HRMS *m/z*: calcd. for $C_{18}H_{24}F_2N_5O_4S$ (M^+ + H): 444.1512; found 444.1511.

4.1.53. (S)-N-((3-(3,5-Difluoro-4-(2-(hydroxyacetyl) [1,2,5]oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl) thioacetamide (**20c**)

Compound **20c** (57.1 mg, 80%) was prepared from **9c** (61.9 mg, 0.160 mmol) in the same manner as described for **19c**. Colourless needles (EtOH); mp: 137–138 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ = 2.57 (3H, s, C<u>H</u>$_3$–C=S), 3.42 (2H, br t, *J* = 5 Hz, –C<u>H</u>$_2$–), 3.48 (2H, br t, *J* = 6 Hz, –C<u>H</u>$_2$–), 3.83 (1H, dd, *J* = 6.9, 9.0 Hz, oxazolidinone-H4), 3.94 (2H, br t, *J* = 6 Hz, –C<u>H</u>$_2$–), 4.02 (1H, dd, *J* = 6.6, 14.4 Hz, –C<u>H</u>H–NH–C=S), 4.07 (1H, t, *J* = 9.0 Hz, oxazolidinone-H4), 4.13 (2H, br t, *J* = 5 Hz, –C<u>H</u>$_2$–), 4.18 (1H, dd, *J* = 3.0, 14.4 Hz, –CH<u>H</u>–NH–C=S), 4.38 (2H, s, –C<u>H</u>$_2$–OH), 4.99 (1H, dddd, *J* = 3.0, 6.6, 6.9, 9.0 Hz, oxazolidinone-H5), and 7.14 (2H, d, *J* = 10.8 Hz, Ar–H2 and H6); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 33.1, 47.6, 47.8, 50.3, 52.0, 54.5, 59.6, 71.3, 77.8, 102.4 (2C, d, *J* = 30 Hz), 124.4 (t, *J* = 14 Hz), 133.7 (t, *J* = 13 Hz), 154.3, 157.9 (2C, dd, *J* = 8, 244 Hz), 172.2, and 203.3; EI-LRMS *m/z*: 444 (M^+). EI-HRMS *m/z*: calcd. for $C_{18}H_{22}F_2N_4O_5S$ (M^+): 444.1279; found 444.1272.

4.1.54. (S)-N-((3-[3-Fluoro-4-(1-(hydroxyacetyl) [1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate) (**21a**)

Compound **21a** (221.1 mg, 87%) was prepared from **14a** (279.1 mg, 0.577 mmol) in the same manner as described for **19a**. White powder (EtOH); mp: 116–119 °C; ^{1}H NMR ($CDCl_3$) δ = 3.12–3.48 (6H, m, –C<u>H</u>$_2$–), 3.62–3.76 (2H, m, –C<u>H</u>$_2$–), 3.82 (1H, dd, *J* = 6.9, 9.1 Hz, oxazolidinone-H4), 3.90–4.14 (3H, m, –C<u>H</u>$_2$–), 4.00 (3H, s, OC<u>H</u>$_3$), 4.37 (2H, br s, –C<u>H</u>$_2$–OH), 4.85–4.96 (1H, m, oxazolidinone-H5), 6.87 (1H, br t, *J* = 6 Hz, –N<u>H</u>–C=S), 6.89 (1H, t, *J* = 9.1 Hz, Ar–H5), 7.05 (1H, dd, *J* = 2.5, 9.1 Hz, Ar–H6), and 7.41 (1H, dd, *J* = 2.5, 14.6 Hz, Ar–H2); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 47.3, 47.7, 49.9, 50.7, 51.3, 53.9, 57.2, 60.2, 71.5, 107.7 (d, *J* = 26 Hz), 114.1, 118.8 (d, *J* = 4 Hz), 131.4 (d, *J* = 11 Hz), 136.1 (d, *J* = 9 Hz), 154.0 (d, *J* = 242 Hz), 154.7, 174.0, and 192.5; ESI-LRMS *m/z*: 442 (M^+ + H). ESI-HRMS *m/z*: calcd. for $C_{18}H_{25}FN_5O_5S$ (M^+ + H): 442.1555; found 442.1561.

4.1.55. (S)-N-((3-(3,5-Difluoro-4-(1-(hydroxyacetyl) [1,2,5]triazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**21b**) [43]

Compound **21b** (201.7 mg, 86%) was prepared from **14b** (257.5 mg, 0.513 mmol) in the same manner as described for **19a**.

4.1.56. (S)-N-((3-(3,5-Difluoro-4-(2-(hydroxyacetyl) [1,2,5]oxadiazepan-5-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)-O-methylthiocarbamate (**21c**) [43]

Compound **21c** (87.2 mg, 66%) was prepared from **14c** (115.8 mg, 0.288 mmol) in the same manner as described for **19c**.

4.1.57. 5(R)-3-(4-(1-(Hydroxyacetyl) [1,2,5]triazepan-5-yl)-3-fluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**22a**)

Compound **22a** (212.0 mg, 88%) was prepared from **16a** (266.3 mg, 0.577 mmol) in the same manner as described for **19a**. White powder (EtOH); mp 138.5–139.5 °C; ^{1}H NMR ($CDCl_3$) δ = 3.11–4.00 (9H, m, –C<u>H</u>$_2$–), 4.12 (1H, t, *J* = 9.1 Hz, oxazolidinone-H4), 4.36 (2H, d, *J* = 4.3 Hz, –C<u>H</u>$_2$–OH), 4.78 (2H, d, *J* = 4.1 Hz, –C<u>H</u>$_2$–, [1,2,3]triazole), 5.00–5.10 (1H, m, oxazolidinone-H5), 6.85 (1H, t, *J* = 9.1 Hz, Ar–H5), 6.92 (1H, dd, *J* = 2.5, 9.1 Hz, Ar–H6), 7.26 (1H, dd, *J* = 2.5, 14.3 Hz, Ar–H2), 7.75 (1H, s, [1,2,3]triazole-H), and 7.79 (1H, s, [1,2,3]triazole-H); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 47.3, 49.9, 50.6 (2C), 51.9, 53.7, 60.2, 70.4, 107.9 (d, *J* = 26 Hz), 114.3, 118.6, 125.2, 130.6 (d, *J* = 10 Hz), 133.8, 136.2 (d, *J* = 9 Hz), 153.5, 153.8 (d, *J* = 242 Hz), and 174.0; ESI-LRMS *m/z*: 420 (M^+ + H). ESI-HRMS *m/z*: calcd. for $C_{18}H_{23}FN_7O_4$ (M^+ + H): 420.1790; found 420.1795.

4.1.58. 5(R)-3-(4-(1-(Hydroxyacetyl) [1,2,5]triazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**22b**)

Compound **22b** (147.3 mg, 97%) was prepared from **16b** (167.4 mg, 0.349 mmol) in the same manner as described for **19a**. White powder (EtOH); mp 155–156 °C; ^{1}H NMR ($CDCl_3$) δ = 3.01–4.18 (10H, m, –C<u>H</u>$_2$–), 4.38 (2H, d, *J* = 4.5 Hz, –C<u>H</u>$_2$–OH), 4.79 (2H, d, *J* = 4.1 Hz, –C<u>H</u>$_2$–, [1,2,3]triazole), 5.02–5.12 (1H, m, oxazolidinone-H5), 6.98 (2H, d, *J* = 10.7 Hz, Ar–H2 and H6), 7.75 (1H, s, [1,2,3]triazole-H), and 7.78 (1H, s, [1,2,3]triazole-H).; ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 47.0, 51.0, 51.6, 51.8, 52.1, 55.3, 60.3, 70.4, 102.4 (2C, dd, *J* = 6, 30 Hz), 125.0 (t, *J* = 14 Hz), 125.2, 133.3 (t, *J* = 13 Hz), 133.9, 153.1, 158.1 (2C, dd, *J* = 9, 244 Hz), and 174.0; ESI-LRMS *m/z*: 438 (M^+ + H). ESI-HRMS *m/z*: calcd. for $C_{18}H_{22}F_2N_7O_4$ (M^+ + H): 438.1696; found 438.1700.

4.1.59. 5(R)-3-(4-(2-(Hydroxyacetyl) [1,2,5]oxadiazepan-5-yl)-3,5-difluorophenyl)-5-(1,2,3-triazol-1-ylmethyl)oxazolidin-2-one (**22c**)

Compound **22c** (53.2 mg, 92%) was prepared from **16c** (50.1 mg, 0.131 mmol) in the same manner as described for **19c**. Colourless prisms (EtOH); mp: 136–137 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ = 3.40 (2H, br t, *J* = 5 Hz, –C<u>H</u>$_2$–), 3.46 (2H, br t, *J* = 6 Hz, –C<u>H</u>$_2$–), 3.85–3.96 (3H, m, –C<u>H</u>$_2$–), 4.13 (2H, br t, *J* = 5 Hz, –C<u>H</u>$_2$–), 4.17 (1H, t, *J* = 9.3 Hz, oxazolidinone-H4), 4.37 (2H, s, –C<u>H</u>$_2$–OH), 4.81 (1H, dd, *J* = 4.5, 14.7 Hz, –C<u>H</u>H–, [1,2,3]triazole), 4.85 (1H, dd, *J* = 3.9, 14.7 Hz, –CH<u>H</u>–, [1,2,3]triazole), 5.07–5.17 (1H, m, oxazolidinone-H5), 7.04 (2H, d, *J* = 10.5 Hz, Ar–H2 and H6), 7.74 (1H, d, *J* = 0.9 Hz, [1,2,3]triazole-H), and 7.89 (1H, d, *J* = 0.9 Hz, [1,2,3]triazole-H); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 46.9, 50.2, 51.7 (2C), 54.4, 59.5, 70.5, 77.7, 102.4 (2C, d, *J* = 29 Hz), 124.4 (t, *J* = 14 Hz), 125.2, 133.2 (t, *J* = 13 Hz), 133.8, 153.1, 157.8 (2C, dd, *J* = 9, 244 Hz), and 172.1; EI-LRMS *m/z*: 438 (M^+). EI-HRMS *m/z*: calcd. for $C_{18}H_{20}F_2N_6O_5$ (M^+): 438.1462; found 438.1469.

*4.1.60. 5(S)-(Isoxazol-3-yl-aminomethyl)-3-(3-fluoro-4-(1-(hydroxyacetyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**23a**)*

Compound **23a** (123.2 mg, 84%) was prepared from **18a** (194.3 mg, 0.337 mmol) in the same manner as described for **19a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 3.11–3.76 (9H, m, $-CH_2-$), 3.81 (1H, dd, J = 6.9, 9.1 Hz, oxazolidinone-H4), 3.89–3.95 (1H, m, $-CH_2-$), 4.04 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.36 (2H, s, $-C\underline{H}_2$-OH), 4.73 (1H, br s, J = 6 Hz, N$\underline{H}$), 4.87–4.98 (1H, m, oxazolidinone-H5), 5.89 (1H, d, J = 1.9 Hz, isoxazole-H), 6.87 (1H, t, J = 9.1 Hz, Ar–H5), 7.03 (1H, br d, J = 9 Hz, Ar–H6), 7.39 (1H, dd, J = 2.5, 14.6 Hz, Ar–H2), and 8.05 (1H, d, J = 1.9 Hz, isoxazole-H); ^{13}C NMR ($CDCl_3$) δ = 46.6, 47.8, 50.3, 51.0, 51.1, 54.1, 60.6, 71.3, 96.4, 107.7 (d, J = 26 Hz), 114.0, 119.0, 131.9 (d, J = 10 Hz), 136.0 (d, J = 9 Hz), 154.3 (d, J = 242 Hz), 154.3, 158.1, 163.4, and 174.3; ESI-LRMS m/z: 435 (M^+ + H). ESI-HRMS m/z: calcd. for $C_{19}H_{24}FN_6O_5$ (M^+ + H): 435.1787; found 435.1794.

*4.1.61. 5(S)-(Isoxazol-3-yl-aminomethyl)-3-(3,5-difluoro-4-(1-(hydroxyacetyl) [1,2,5]triazepan-5-yl)phenyl)oxazolidin-2-one (**23b**)*

Compound **23b** (379.2 mg, 90%) was prepared from **18b** (555.5 mg, 0.934 mmol) in the same manner as described for **19a**. Amorphous solid; ^{1}H NMR ($CDCl_3$) δ = 3.01–3.89 (11H, m, $-CH_2-$), 4.04 (1H, t, J = 9.1 Hz, oxazolidinone-H4), 4.38 (2H, br s, $-C\underline{H}_2-$OH), 4.67 (1H, br t, J = 6 Hz, N$\underline{H}$), 4.90–5.00 (1H, m, oxazolidinone-H5), 5.89 (1H, d, J = 1.9 Hz, isoxazole-H), 7.11 (2H, d, J = 10.7 Hz, Ar–H2 and H6), and 8.05 (1H, d, J = 1.9 Hz, isoxazole-H); ^{13}C NMR ($CDCl_3$) δ = 46.5, 47.5, 51.3, 51.9, 52.4, 55.5, 60.6, 71.4, 96.4, 102.2 (2C, d, J = 30 Hz), 124.8 (t, J = 15 Hz), 134.2 (t, J = 13 Hz), 153.9, 158.4 (2C, dd, J = 9, 244 Hz), 158.5, 163.4, and 174.2; ESI-LRMS m/z: 453 (M^+ + H). ESI-HRMS m/z: calcd. for $C_{19}H_{22}F_2N_6O_5$ (M^+ + H): 453.1693; found 453.1693.

*4.1.62. 5(S)-(Isoxazol-3-yl-aminomethyl)-3-(3,5-difluoro-4-(2-(hydroxyacetyl) [1,2,5]oxadiazepan-5-yl)phenyl)oxazolidin-2-one (**23c**)*

Compound **23c** (38.1 mg, 74%) was prepared from **18c** (55.9 mg, 0.141 mmol) in the same manner as described for **19c**. Colourless needles (EtOH); mp: 154.5–155.5 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ = 3.41 (2H, br t, J = 5 Hz, $-CH_2-$), 3.47 (2H, br t, J = 5 Hz, $-CH_2-$), 3.57 (1H, dd, J = 5.7, 14.4 Hz, $-C\underline{H}H-$NH-isoxazole), 3.64 (1H, dd, J = 3.9, 14.4 Hz, $-CH\underline{H}-$NH-isoxazole), 3.83 (1H, dd, J = 6.6, 9.0 Hz, oxazolidinone-H4), 3.93 (2H, br t, J = 5 Hz, $-CH_2-$), 4.07 (1H, t, J = 9.0 Hz, oxazolidinone-H4), 4.14 (2H, br t, J = 5 Hz, $-CH_2-$), 4.38 (2H, s, $-C\underline{H}_2-$OH), 4.94 (1H, dddd, J = 3.9, 5.7, 6.6, 9.0 Hz, oxazolidinone-H5), 5.93 (1H, d, J = 1.5 Hz, isoxazole-H), 7.14 (2H, d, J = 10.8 Hz, Ar–H2 and H6), and 8.07 (1H, d, J = 1.5 Hz, isoxazole-H); ^{13}C NMR (CD_3OD + $CDCl_3$) δ = 46.0, 47.4, 50.2, 51.9, 54.5, 59.5, 71.6, 77.7, 96.2, 102.2 (2C, d, J = 29 Hz), 124.0 (t, J = 14 Hz), 134.0 (t, J = 13 Hz), 154.3, 157.9, 157.9 (2C, dd, J = 9, 244 Hz), 163.4, and 172.1; EI-LRMS m/z: 453 (M^+). EI-HRMS m/z: calcd. for $C_{19}H_{21}F_2N_5O_6$ (M^+): 453.1458; found 453.1459.

4.2. In vitro antibacterial activity

The *in vitro* antibacterial activities of the compounds shown in Table 1 were determined by the broth microdilution method recommended by the Clinical Laboratory Standards Institute (CLSI). Cation-adjusted Mueller-Hinton broth (CAMHB) (Difco) was used except for *S. pneumoniae* and *H. influenzae*. For *S. pneumoniae*, CAMHB supplemented with 5% lysed horse blood was used. For *H. influenzae*, Haemophilus test medium (Nissui Pharmaceutical Co., Ltd., Japan) was used. The tested Gram-positive organisms included clinical isolate of *S. aureus* SR20549, *S. pneumoniae* SR26207, *E. faecalis* SR1004 and *E. faecium* SR7940. *S. aureus* Smith and *S. aureus* resistant to linezolid NRS271 (NARSA) were also used. Gram-negative bacteria used in the study were clinical isolates of *M. catarrhalis* SR26840 and *H. influenzae* SR27914.

4.3. In vivo antibacterial efficacy

The data on *in vivo* efficacy of the compounds are summarized in Table 2. Five-week-old male JCL/ICR mice (body weight 20–25 g) from Clea Japan, Inc. (Tokyo) were used in systemic infection models (five mice per group). All studies with animals were approved by the Animal Care and Use Committee of Shionogi Co., Ltd. The test strain was methicillin-resistant *S. aureus* SR3637 [51]. Mice were injected intraperitoneally with 0.5 or 1.0 mL of bacterial suspension (approximately 100 times the 50% lethal dose). Test and reference compounds were administered intravenously or orally 1 h after infection. Mortality was recorded over 7 days to estimate the 50% effective dose (ED_{50}), and 95% confidence limits, which were determined by the logit method.

4.4. In vitro inhibition assay for CYP450 isoforms

The inhibitory effects of the compounds on selected CYP450 isoforms are summarized in Table 3. Human CYP450 activities were measured using the following reactions: ethoxyresorufin *O*-deethylation for CYP1A2, tolbutamide hydroxylation for CYP2C9, dextromethorphan *O*-demethylation for CYP2D6, and terfenadine hydroxylation for CYP3A4. The incubation mixture consisted of 1 mM NADPH, 50 mM HEPES buffer (pH 7.4) including 10 mM $MgCl_2$ and 0.1 mM EDTA, human liver microsomes (0.2 mg protein/mL) and a cocktail of the 4 substrates (0.375 μM ethoxyresorufin, 100 μM tolbutamide, 5 μM dextromethorphan and 1 μM terfenadine) in the presence or absence of test compound in a final volume of 500 μl. A solution of test compound in DMSO (final 0.5%) was added to give a final concentration of 0, 1, 5, 10 and 20 μM. Reactions were initiated by adding NADPH. After incubation for 20 min at 37 °C, reactions were terminated by the addition of an equivalent volume of acetonitrile/methanol (1/1, v/v). A standard curve was prepared by adding authentic metabolite cocktail to the same reaction components without incubation. After centrifugation, the supernatants were evaluated with a fluorescence plate reader (for CYP1A2) or an LC/MS/MS system (for CYP2C9, 2D6 and 3A4).

4.5. In vitro inhibition assay for MAO-A and MAO-B

The inhibitory effects of test compounds on MAO-A and MAO-B activities are summarized in Table 3. MAO-A and MAO-B activities were measured by a slight modification of the method of Curet et al. [52]. Rat forebrains were homogenized in 20 volumes of buffer (0.25 M sucrose, 10 mM sodium phosphate buffer, pH 7.4) at 4 °C (final concentration: 500 μg of tissue/assay). Briefly, 100 μl of homogenate was preincubated for 20 min at 37 °C with or without test compound (final concentration of 30 μM) in a total volume of 400 μl. After this preincubation, the reaction was started by the addition of [^{14}C]5-HT as a specific MAO-A substrate (final concentration 500 μM, specific activity 1 μCi/μmol) or [^{14}C]PEA as a specific MAO-B substrate (final concentration 125 μM, specific activity 0.1 μCi/μmol). The final volume of incubation buffer (0.25 M sucrose, 10 mM sodium phosphate buffer, pH 7.4) was 500 μl and the incubation times were 5 min for MAO-A and 10 min for MAO-B. The reaction was stopped by adding 200 μl of 4 M HCl and 5 mL of extraction solvent (toluene/ethyl acetate vol/vol). After vigorous shaking and centrifugation (1000 rpm, 5 min) of the mixture, the radioactivity of the organic layer was measured with a liquid scintillation counter.

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