Synthesis and Antibacterial Activity of 3-(Substituted arylmethyl)-4-acylaminomethyloxazolidin-2-ones and Derivatization to Symmetrical Twin-Drug Type Molecules

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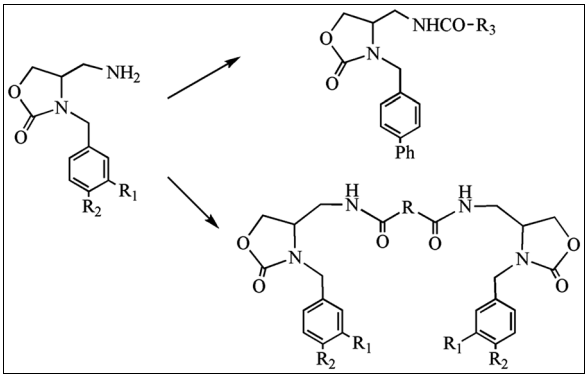

In connection with our studies on antibacterial active compounds in the class of new oxazolidinones against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) strains, some molecular modifications were attempted. In this study, molecular modifications of 4-aminomethyloxazolidin-2-ones (**3a**) to the corresponding 4-acylaminomethyloxazolidin-2-one derivatives (**3c–d**) and preparations of the represented twin-drug type molecules (**10–14**) were investigated. Some additional 4-dialkylaminomethyloxazolidin-2-ones (**2**) were also synthesized. The synthesized compounds were evaluated for antibacterial activity with Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) strains.

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INTRODUCTION

In the course of work on new antibacterial compounds, extensive efforts have been made to find new promising candidates. Many reports on synthetic molecular modifications have appeared [1].

Infection by bacteria is initiated by specific recognition of host epithelial surfaces, and subsequent adhesion is essential for invasion. In this process for recognition or binding to glycoconjugates (glycans), microorganisms usually use sugar-binding proteins such as lectins [2]. For such molecular recognition of glycans, the major recognition patterns between the host and target guest molecules are through suprafacial interactions. This suprafacial interaction process is a logical path and is thought to direct a controlled biological response [3]. We have been interested in target compounds that interfere with such a suprafacial recognition process in order to find new leads for antibacterial agents [4]. In this article, synthesis of target designed molecules (**2**, **3c–d**, and **14–18**) and results of biological evaluation of the 4-acylaminomethyloxazolidin-2-one derivatives for antibacterial activity are described.

RESULTS AND DISCUSSION

In connection with our synthetic studies in the search for new bioactive lead compounds, some molecular modifications of β-aminoalanines (**4**) to a new class of linezolid (**1**) mimetic oxazolidin-2-ones [such as (**2**) or (**3**)] (Fig. 1) have been reported [5–9].

Compounds **2** were synthesized by the same method as that used for the preparation of 4-dialkylaminomethyloxazolidn-2-ones reported previously [6]. Compounds **2a–c** were obtained from 3,4-methylendioxycinnamic acid and corresponding β-aminoalanines (**4a** and **4b**) as starting materials. In the reduction stage (**5** → **6**) prior to cyclization with $NaAlH_2(OCH_2CH_2OMe)_2$, the double bond in cinnamoyl groups is easily hydrogenated, and we obtained 3-(3,4-methylenedioxyphenyl)propyl derivatives **2a** and **2b** as final products (Scheme 1). Compounds **2d** and **2e** having a urea moiety in the molecules were prepared from the addition of 3-aminophenylmethyl-4-pyrrolidinomethyloxazolidin-2-one (**2c**) obtained from the transformation of β-aminoalanines (**4a**) to phenyl isothiocyanate or phenyl isocyanate (Scheme 2).

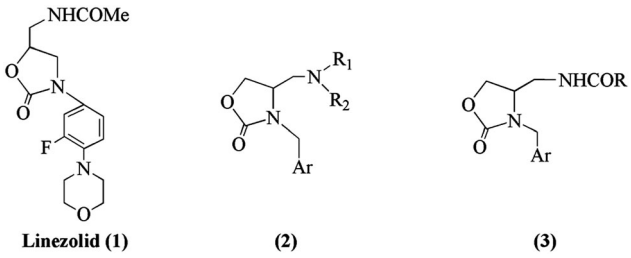
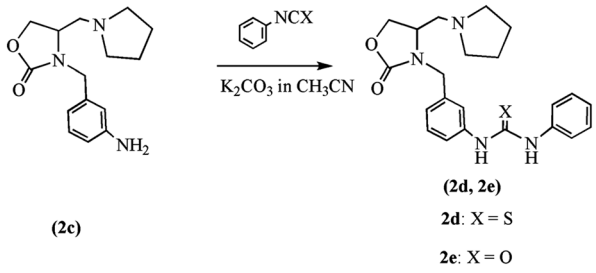


Figure 1. Structures of linezolid and compounds **2** and **3**.

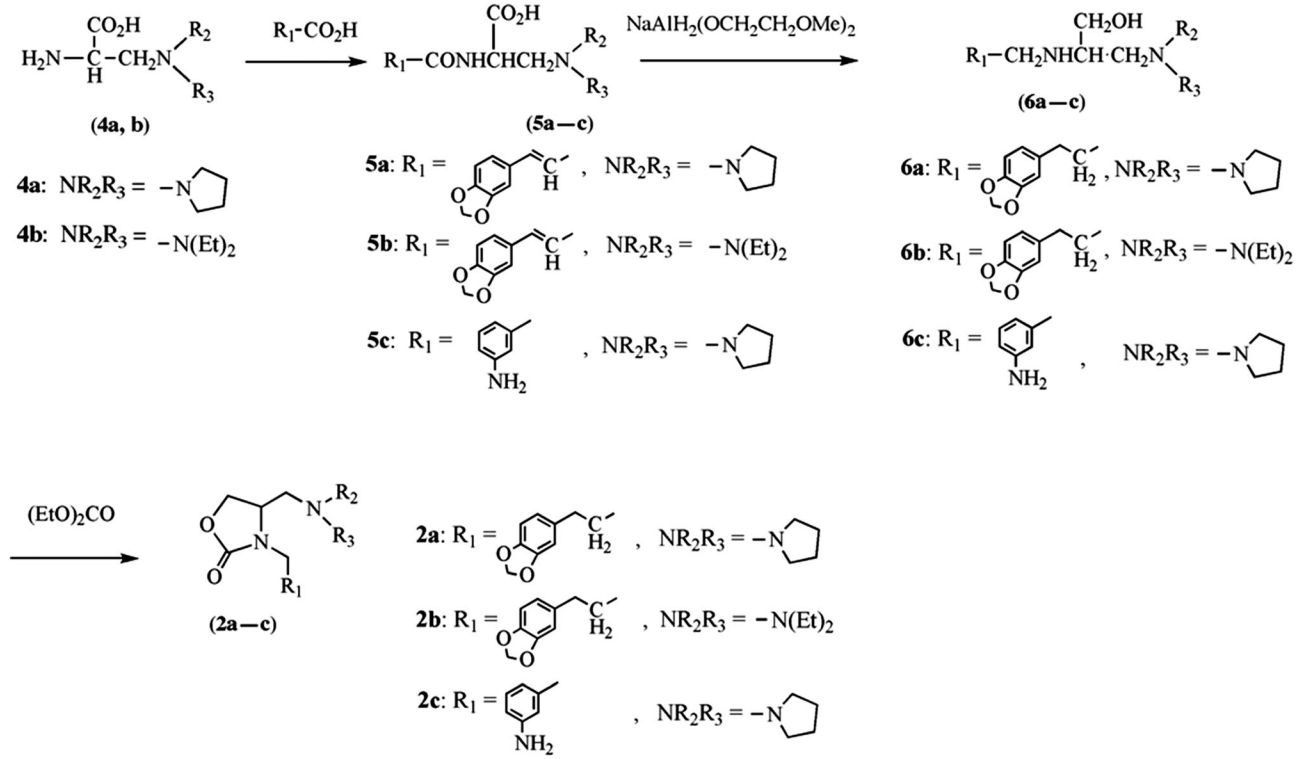
We have already attempted molecular modification to the compounds (**3a** and **3b**) from serine methyl ester (**7**) as a starting material [7]. These compounds were prepared with 4-aminomethyloxazolidin-2-ones (**9a** and **9b**) generated *in situ* from the corresponding phthalimide derivative (**8a** and **8b**). New acyl derivatives **3c** and **3d** were prepared from direct *N*-acylation reaction of isolated intermediary 4-aminomethyloxazolidin-2-one (**9a**) with corresponding acid derivatives (R_3CO_2H) (Scheme 3). Among these target compounds (**2–3**) [10,11], compounds (**3a** and **3b**) showed bacteriostatic activity against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) strains and **3a** showed higher activity than that of **3b**, which apparently mimics linezolid (**1**) because of the presence of two substituents (morpholine and fluorine) on the phenyl ring in the molecule (**3b**) [7,11].

Scheme 2. Synthesis of compounds **2d** and **2e**.

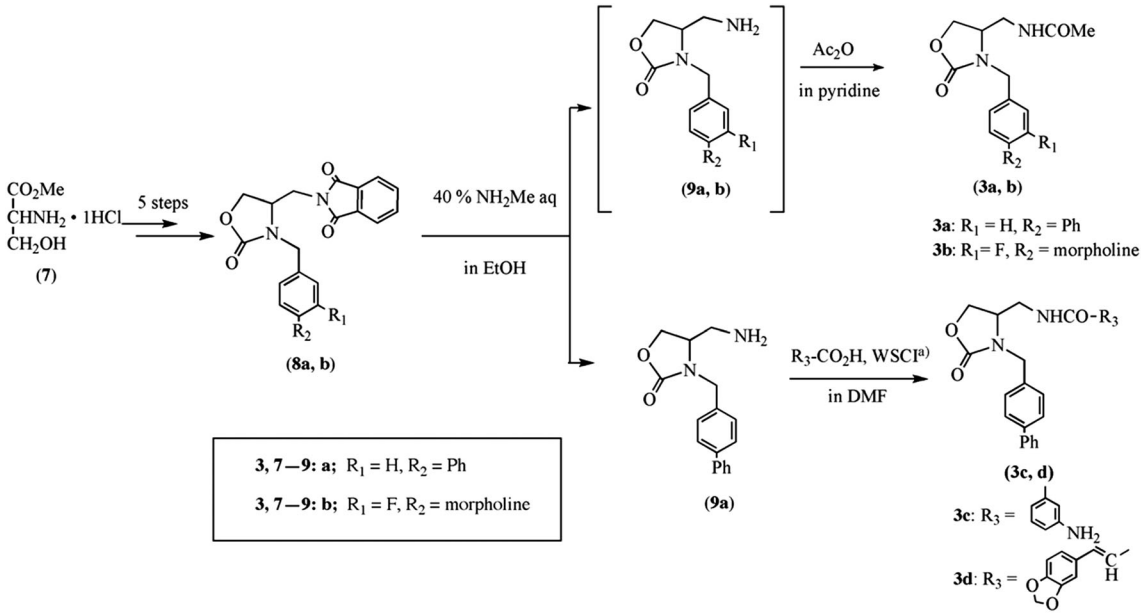


For a suprafacial three-dimensional interaction for its binding site, the substituent on the phenyl ring at *N*-3 of oxazolidinone in linezolid is dictated largely by its van der Waals interactions with the sugar residue in the bacterial ribosome (rRNA residue in the peptide transferase center) [12]. Because a compound with a phenyl azide substituent instead of a morpholine on the phenyl ring was successfully developed as one of the photoprobes [12], the biphenyl group at *N*-3 of the oxazolidinone ring may have a good shape for the binding site. In fact, a new molecular modification of *N*-3 biphenyl derivatives on oxazolidin-2-one ring of linezolid has been investigated to find new antibacterial candidates [13,14]. Because many endogenous macromolecules regulating cell functions are known to be dimeric forms

Scheme 1. Synthesis of compounds **2a–c**.



Scheme 3. Synthesis of compounds **3c** and **3d**.



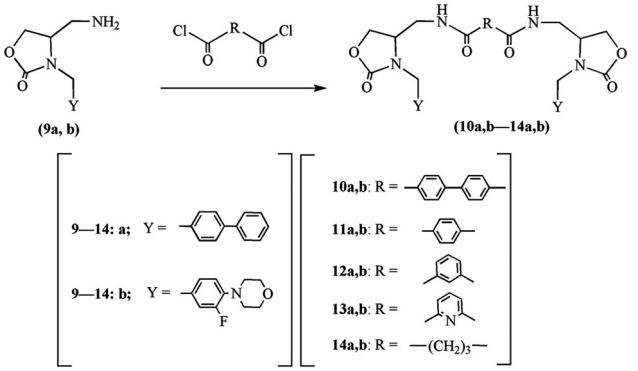
a) WSCI =1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

of subunits and some of these molecules frequently have twofold symmetrical features [15,16], we designed symmetrical molecules in the search for antibacterial leads. In terms of molecular symmetry, small symmetrical molecules frequently appear in various synthetic twin-drug type molecules and biologically active compounds. Biologically active symmetrical molecules are usually constructed on a symmetrical template. For linker mode twin-drug molecules, the nature of a linker plays an important role in binding to the receptor (or recognition) site for biological activity [17,18]. Inspired by the antibacterial profiles of compounds, it was thought worthwhile to undertake a synthetic molecular modification study with the aim of obtaining new candidates with antibacterial activity. From this point of view, we therefore carried out further synthetic investigation of new symmetrical molecules (**10a**,**b–14a**,**b**) (Scheme 4).

Molecular modification to the represented new symmetrical molecules (**10a**,**b–13a**,**b**) can be considered to be an identical twin-drug approach based on 4-aminomethyloxazolidin-2-ones as a single drug moiety [18]. Furthermore, we synthesized symmetrical target molecules (**14a** and **14b**) having a simple flexible methylene group [-$(CH_2)_3$-] as a linker for another identical twin-drug approach.

The structures of the synthesized compounds were easily confirmed by NMR spectroscopic analysis. All of the twin-drug type compounds except for compound **13** showed magnetically equivalent spectroscopic signal patterns, indicating a symmetrical molecular feature in DMSO-d_6 [19] (see Experimental section).

Scheme 4. Synthesis of twin-drug type compounds **10–14**.



Among the twin-drug type compounds described in this paper, compound **10–14**, except for **10b** and **14a**, showed antibacterial activities (minimum inhibitory concentration (MIC) = 0.171~0.184 μ*M*/mL) against *E. coli* and antibacterial activities (MIC = 0.171–>0.184 μ*M*/mL) against *S. aureus*. We found that compounds **10b** and **14a** are more active than the original prototype compound **3a** (MIC = >0.395 μ*M*/mL against both strains) in the compounds that have been tested. The determined MIC (μ*M*/mL) values for compounds **10b** and **14a** against Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) strains were in the range of 0.078~0.097 and 0.155~0.194 μ*M*/mL, respectively [20]. These experimental results indicate the importance of the nature of the linker used for *N*-acylation

and also the substituent at C-3 of the oxazolidin-2-one ring for antibacterial activity. Because two selected substituents at C-3 of the oxazolidin-2-one ring (see compounds **9a** and **9b**) were found to be effective for the derivatization to twin-drug type compounds, we are now investigating further synthetic applications of 4-aminomethyloxazolidin-2-one derivatives (**9**) and performing biological evaluation of the antibacterial (biological) properties of these single drug *N*-acyl derivatives and related twin-drug type symmetrical derivatives to find a new candidate (or lead) for antibacterial agents.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured by a Shimadzu FT/IR-8100 spectrometer (Japan). The ^{1}H- and ^{13}C-NMR spectra were obtained by a JEOL JNM A-500 (Japan) at 35°C. The chemical shifts were expressed in δ ppm downfield from an internal TMS signal. The signal assignments were confirmed by ^{1}H–^{1}H 2D COSY and by ^{1}H–^{13}C HMQC and ^{1}H–^{13}C HMBC spectra. High FABMS spectra were obtained by a JEOL JMS-HX110 mass spectrometer. The following abbreviations were used: Mor, morpholine ring; FAr, 3-fluorobenzene ring; and Oxaz, oxazolidinones-2-one ring.

Assays for antibacterial activity. We used *S. aureus* ATCC6538P and *E. coli* NBRC14237 (NIHJ) (Gram-positive and Gram-negative bacteria, respectively) as target organisms. Synthesized compounds were dissolved in DMSO to a concentration of 1.280 μg/mL. The MIC of a standard strain was measured by the authentic microdilution method to monitor the bacterial growth turbidity in Mueller–Hinton broth according to the Japanese Society of Chemotherapy [21,22].

Preparation of 3-alkyl-(4-*N*,*N*-disubstituted aminomethyl) oxazolidin-2-ones (2a–c). 3-Alkyl-(4-*N*,*N*-disubstituted aminomethyl)oxazolidin-2-ones (**2a–c**) were prepared by the same method as that described previously [6]. Physical and spectroscopic data are shown below.

3-(3-(Benzo[d][1,3]dioxol-5-yl)propyl)-4-(pyrrolidine-1-ylmethyl) oxazolidin-2-one (2a). This compound was obtained in 47.8% yield from compound **5a** as a hygroscopic oil. IR (KBr) cm^{-1}: 1745. FABMS (positive) *m/z*: 333 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.64–1.66 (4H, m, Pyr H-3, H-4), 1.80–1.82 (2H, m, Ph-$CH_2\underline{CH_2}CH_2$), 2.42–2.50 (7H, m, Pyr H-2, H-5, Ph-$\underline{CH}HCH_2CH_2$ and $\underline{CH_2}$-Pyr), 2.62–2.66 (1H, m, Ph-CH$\underline{H}$CH$_2$CH$_2$), 3.09–3.15 (1H, m, Ph-CH$_2$CH$_2$C$\underline{H}$H), 3.27–3.28 (1H, m, Ph-CH$_2$CH$_2$C$\underline{H}$H), 3.88–3.92 (1H, m, Oxaz H-4), 3.92–3.98 (1H, m, Oxaz H-5), 4.28–4.30 (1H, m, Oxaz H-5), 5.95 (2H, s, O-$\underline{CH_2}$-O), 6.65–6.67 (1H, m, Ar H-6), 6.79–6.82 (2H, m, Ar H-2, H-5). ^{13}C-NMR (DMSO-d_6) δ: 23.1 (Pyr C-3, C-4), 28.9 (Ph-$CH_2\underline{CH_2}CH_2$), 32.0 ($\underline{CH_2}$-Pyr), 41.6 (Ph-$CH_2CH_2\underline{CH_2}$), 53.1 (Oxaz C-4), 54.0 (Pyr C-2, C-5), 57.6 (Ph-$\underline{CH_2}CH_2CH_2$), 66.0 (Oxaz C-5), 100.5 (O-$\underline{CH_2}$-O), 107.9 (Ar C-5), 108.6 (Ar C-2), 120.9 (Ar C-6), 135.1 (Ar C-1), 145.2 (Ar C-3), 147.1 (Ar C-4), 157.5 (Oxaz C-2). *Anal*. Calcd for $C_{18}H_{24}N_2O_4 \cdot 0.2H_2O$: C, 64.34; H, 7.32; N, 8.34. Found: C, 64.40; H, 7.16; N, 8.05.

3-(3-(Benzo[d][1,3]dioxol-5-yl)propyl)-4-(diethylaminomethyl) oxazolidin-2-one (2b). This compound was obtained in 65.2% yield from compound **5b** as an oil. IR (KBr) cm^{-1}: 1749. FABMS (positive) *m/z*: 335 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 0.89–0.93 (6H, m, N($CH_2\underline{CH_3}$)$_2$), 1.67–1.82 (2H, m, Ph-$CH_2\underline{CH_2}CH_2$), 2.33–2.60 (8H, m, N($\underline{CH_2}CH_3$)$_2$, Ph-$\underline{CH_2}CH_2CH_2$ and $\underline{CH_2}$-N(CH_2CH_3)$_2$), 3.11–3.17 (1H, m, Ph-CH$_2$CH$_2$CH$\underline{H}$), 3.24–3.26 (1H, m, Ph-CH$_2$CH$_2$CH$\underline{H}$), 3.85–3.90 (1H, m, Oxaz H-4), 3.91–3.94 (1H, m, Oxaz H-5), 4.27 (1H, t, J = 8.0 Hz, Oxaz H-5), 5.95 (2H, s, O-$\underline{CH_2}$-O), 6.65–6.67 (1H, m, Ar H-6), 6.67–6.80 (2H, m, Ar H-2, H-5). ^{13}C-NMR (DMSO-d_6) δ: 11.5 (N($CH_2\underline{CH_3}$)$_2$), 28.8 (Ph-$CH_2\underline{CH_2}CH_2$), 31.9 ($\underline{CH_2}$N(CH_2CH_3)$_2$), 41.6 (Ph-$CH_2CH_2\underline{CH_2}$), 46.8 (N($\underline{CH_2}CH_3$)$_2$), 52.4 (Oxaz C-4), 55.3 (Ph-$\underline{CH_2}CH_2CH_2$), 66.1 (Oxaz C-5), 100.5 (O-$\underline{CH_2}$-O), 107.9 (Ar C-5), 108.6 (Ar C-2), 120.9 (Ar C-6), 135.1 (Ar C-1), 145.2 (Ar C-3), 147.1 (Ar C-4), 157.5 (Oxaz C-2). *Anal*. Calcd for $C_{18}H_{26}N_2O_4 \cdot 0.1H_2O$: C, 64.30; H, 7.85; N, 8.33. Found: C, 64.27; H, 7.79; N, 8.24.

3-(3-Aminobenzyl)-4-(pyrrolidin-1-ylmethyl)oxazolidin-2-one (2c). This compound was obtained in 51.4% yield from compound **5c** as an oil. IR (KBr) cm^{-1}: 1741. FABMS (positive) *m/z*: 276 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.63–1.65 (4H, m, Pyr H-3, H-4), 2.38–2.40 (4H, m, Pyr H-2, H-5), 2.46–2.49 (1H, m, Pyr-C$\underline{H}$H), 2.50–2.69 (1H, m, Pyr-CH$\underline{H}$), 3.69–3.72 (1H, m, Oxaz H-4), 4.01 (1H, dd, J = 8.5, 4.0 Hz, Oxaz H-5), 4.10 (1H, d, J = 15.0 Hz, Ph-C$\underline{H}$H), 4.34 (1H, t, J = 8.5 Hz, Oxaz H-5), 4.44 (1H, d, J = 15.0 Hz, Ph-CH$\underline{H}$), 5.04 (2H, br s, $\underline{NH_2}$), 6.39 (1H, d, J = 7.5 Hz, Ar H), 6.46–6.47 (2H, d, J = 7.5 Hz, Ar H), 6.96–6.99 (1H, m, Ar H). ^{13}C-NMR (DMSO-d_6) δ: 23.1 (Pyr C-3, C-4), 45.9 ($\underline{CH_2}$-Ph), 52.7 (Oxaz C-4), 53.9 (Pyr C-2, C-5), 57.3 ($\underline{CH_2}$-Pyr), 66.2 (Oxaz C-5), 112.7 (Ar C-4), 113.0 (Ar C-2), 114.9 (Ar C-6), 128.9 (Ar C-5), 137.1 (Ar C-1), 148.2 (Ar C-3), 157.7 (Oxaz C-2). *Anal*. Calcd for $C_{15}H_{21}N_3O_2 \cdot 0.15H_2O$: C, 64.79; H, 7.72; N, 15.11. Found: C, 64.87; H, 7.70; N, 14.90.

1-(3-((2-Oxo-4-(pyrrolidin-1-ylmethyl)oxazolidin-3-yl)methyl) phenyl)-3-phenylthiourea (2d). Phenyl isothiocyanate (58 mg, 0.43 mmol) was added to a solution of **2c** (100 mg, 0.36 mmol) and 1 mL of aqueous K_2CO_3 (200 mg, 1.44 mmol) in MeCN (10 mL) and stirred for 10 min at room temperature. The mixture was stirred for another 10 min at 50°C, and the solvent was removed under reduced pressure. Water was added to the resulting residue, and the separated material was extracted with AcOEt. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration of the solvent, the residue was purified by silica gel column chromatography (successively with MeCN and EtOH) to give **2c** (93 mg, 62.4%) as amorphous white powder. IR (KBr) cm^{-1}: 1732. FABMS (positive) *m/z*: 411 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.63 (4H, br, Pyr H-3, H-4), 2.38 (4H, br, Pyr H-2, H-5), 2.50–2.52 (1H, m, Pyr-C$\underline{H}$H), 2.71 (1H, dd, J = 12.5, 5.5 Hz, Pyr-CH$\underline{H}$), 3.79–3.83 (1H, m, Oxaz H-4), 4.00–4.03 (1H, m, Oxaz H-5), 4.31 (1H, d, J = 15.5 Hz, Ph-C$\underline{H}$H-Oxaz), 4.35 (1H, t, J = 8.5 Hz, Oxaz H-5), 4.55 (1H, d, J = 15.5 Hz, Ph-CH$\underline{H}$-Oxaz), 7.03 (1H, d, J = 7.5 Hz, Ar H), 7.12 (1H, t, J = 7.5 Hz, Ar H), 7.30 (1H, d, J = 7.5 Hz, Ar H), 7.31–7.34 (3H, m, Ar H), 7.41–7.49 (3H, m, Ar H), 9.76, 9.79 (each 1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 23.1 (Pyr C-3, C-4), 45.6 (Ph-$\underline{CH_2}$-Oxaz), 52.9 (Oxaz C-4), 53.9 (Pyr C-2, C-5), 57.5 ($\underline{CH_2}$-Pyr), 66.2 (Oxaz C-5), 122.3, 122.5, 123.5, 123.5, 124.3, 128.3, 128.5 (Ar C), 137.1 (1,3-disubstituted phenyl Ar C-3), 139.3 (monosubstituted phenyl Ar C-1), 139.6 (1,3-disubstituted phenyl Ar C-1), 157.8 (Oxaz C-2), 179.6 (NH$\underline{C}$SNH). *Anal*. Calcd for $C_{22}H_{26}N_4O_2S \cdot 0.2H_2O$: C, 63.80; H, 6.43; N, 13.53. Found: C, 63.75; H, 6.36; N, 13.32.

1-(3-((2-Oxo-4-(pyrrolidin-1-ylmethyl)oxazolidin-3-yl)methyl) phenyl)-3-phenylurea (2e). This compound was prepared by the same procedure as that described above. Compound **2e** was obtained in 89.0% yield as amorphous white powder. IR (KBr) cm^{-1}: 1733. FABMS (positive) *m/z*: 395 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.64 (4H, t, *J* = 4.5 Hz, Pyr H-3, H-4), 2.38 (4H, br, Pyr H-2, H-5), 2.47–2.51 (1H, m, Pyr-CHH), 2.71 (1H, dd, *J* = 12.5, 5.5 Hz, Pyr-CHH), 3.73–3.79 (1H, m, Oxaz H-4), 4.00–4.03 (1H, m, Oxaz H-5), 4.29 (1H, d, *J* = 15.5 Hz, Ph-CHH-Oxaz), 4.37 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.54 (1H, d, *J* = 15.5 Hz, Ph-CHH-Oxaz), 6.88 (1H, d, *J* = 7.5 Hz, 1,3-disubstituted phenyl Ar H-4), 6.97 (1H, d, *J* = 7.5 Hz, monosubstituted phenyl Ar H-4), 7.24–7.29 (3H, m, 1,3-disubstituted phenyl Ar H-5, monosubstituted phenyl Ar H-3, H-5), 7.35 (1H, s, 1,3-disubstituted phenyl Ar H-2), 7.35–7.45 (3H, s, 1,3-disubstituted phenyl Ar H-6, and monosubstituted phenyl Ar H-2, H-6), 8.58 (1H, s, monosubstituted phenyl-NH), 8.68 (1H, s, NH-1,3-disubstituted phenyl). ^{13}C-NMR (DMSO-d_6) δ: 23.1 (Pyr C-3, C-4), 45.8 (Ph-CH_2-Oxaz), 52.9 (Oxaz C-4), 53.9 (Pyr C-2, C-5), 57.5 (CH_2-Pyr), 66.2 (Oxaz C-5), 117.1, 117.2, 118.1, 121.0, 121.8, 128.7, 128.9 (Ar C), 137.5 (1,3-disubstituted phenyl Ar C-3), 139.5 (monosubstituted phenyl Ar C-1), 139.6 (1,3-disubstituted phenyl Ar C-1), 152.4 (NHCONH), 157.8 (Oxaz C-2). *Anal*. Calcd for $C_{22}H_{26}N_4O_3 \cdot 0.2H_2O$: C, 66.38; H, 6.68; N, 14.07. Found: C, 66.38; H, 6.70; N, 13.96.

3-Amino-N-((3-(biphenyl-4-ylmethyl)-2-oxooxazolidin-4-yl) methyl)benzamide (3c). To a solution of compound (**9a**) (180 mg, 0.64 mmol) and *m*-aminobenzoic acid (88 mg, 0.64 mmol) in DMF (4 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCI) (122 mg, 0.64 mmol) at room temperature, and the mixture was stirred for 3 h. After addition of water, precipitated material was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography with AcOEt as a solvent to give **3c** (180 mg, 70.3%) as a colorless oil. IR (KBr) cm^{-1}: 3352, 1736, 1644. FABMS (positive) *m/z*: 402 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.43–3.54 (2H, m, Oxaz-CH_2NH), 3.80–3.84 (1H, m, Oxaz H-4), 4.23 (1H, dd, *J* = 9.0, 5.0 Hz. Oxaz H-5), 4.33 (1H, d, *J* = 9.0 Hz, Oxaz H-5), 4.37, 4.64 (each 1H, d, *J* = 16.0 Hz, Oxaz CH_2-Ph), 5.20 (2H, s, NH_2), 6.69–6.71 (1H, m, aminobenzene H-4), 6.90–6.92 (1H, m, aminobenzene H-6), 7.00–7.01 (1H, m, aminobenzene H-2), 7.08 (1H, t, *J* = 8.0 Hz, aminobenzene H-5), 7.35–7.40 (3H, m, biphenyl Ar H), 7.46 (2H, t, *J* = 8.0 Hz, biphenyl Ar H), 7.65–7.67 (4H, m, biphenyl Ar H), 8.35 (1H, t, *J* = 6.0 Hz, NH). ^{13}C-NMR (DMSO-d_6) δ: 39.2 (Oxaz-CH_2NH), 44.8 (CH_2-Ph), 53.7 (Oxaz C-4), 65.2 (Oxaz C-5), 112.7 (aminobenzene C-2), 114.3 (aminobenzene C-6), 116.5 (aminobenzene C-4), 128.5 (aminobenzene C-5), 135.1 (aminobenzene C-1), 126.5, 126.9, 127.4, 128.3, 128.8 (biphenyl Ar C), 135.7 (biphenyl Ar C-1), 139.4 (biphenyl Ar C-1′ or C-4), 139.7 (biphenyl Ar C-4 or C-1′), 148.6 (aminobenzene C-3), 157.7 (Oxaz C-2), 167.9 (NHCO). *Anal*. Calcd for $C_{24}H_{23}N_3O_3 \cdot 0.6H_2O$: C, 69.92; H, 5.92; N, 10.19. Found: C, 69.87; H, 6.02; N, 9.91.

3-(Benzo[d][1,3]dioxol-4-yl)-N-((3-(biphenyl-4-ylmethyl)-2-oxooxazolidin-4-yl)methyl)prop-2-enamide (3d). To a solution of compound (**9a**) (680 mg, 2.41 mmol) and 3,4-(methylenedioxy) cinnamic acid (460 mg, 2.40 mmol) in DMF (20 mL) was added WSCI (510 mg, 2.66 mmol) at room temperature, and the mixture was stirred for 1 h. After removal of the solvent under reduced pressure, water was added to the residue, and the precipitated material was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography with AcOEt/*n*-hexane as a solvent to give **3d** (620 mg, 56.4%). Mp 133–134°C (with dec). IR (KBr) cm^{-1}: 3309, 1725, 1669, 1623. FABMS (positive) *m/z*: 457 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.45–3.47 (2H, m, CH_2NHCO), 3.78–3.79 (1H, m, Oxaz H-4), 4.11 (1H, dd, *J* = 9.0, 6.0 Hz. Oxaz H-5), 4.30–4.37 (2H, m, Oxaz H-5 and CHH-Ph), 4.66 (1H, d, *J* = 15.0 Hz, CHH-Ph), 6.06 (2H, s, O-CH_2-O), 6.48 (1H, d, *J* = 16.0 Hz, CH=CH-CO), 6.95 (1H, d, *J* = 8.0 Hz, cinnamic acid Ar H-5), 7.07–7.09 (1H, m, cinnamic acid Ar H-6), 7.16 (1H, d, *J* = 1.0 Hz, cinnamic acid Ar H-2), 7.37 (1H, d, *J* = 16.0 Hz, CH=CH-CO), 7.35–7.47 (6H, m, biphenyl Ar H), 7.64–7.67 (3H, m, biphenyl Ar H), 8.16 (1H, t, *J* = 6.0 Hz, NH). ^{13}C-NMR (DMSO-d_6) δ: 38.4 (Oxaz-CH_2NH), 44.7 (CH_2-Ph), 53.7 (Oxaz C-4), 64.9 (Oxaz C-5), 101.3 (O-CH_2-O), 106.2 (cinnamic acid Ar C-2), 108.4 (cinnamic acid Ar C-5), 120.1 (CH=CH-CO), 123.3 (cinnamic acid Ar C-6), 126.5, 126.9, 127.4, 128.3, 128.8 (biphenyl Ar C), 129.1 (cinnamic acid Ar C-1), 135.6 (biphenyl Ar C), 139.0 (CH=CH-CO), 139.4, 139.7 (biphenyl Ar C), 147.9 (cinnamic acid Ar C-3), 148.5 (cinnamic acid Ar C-4), 157.7 (Oxaz C-2), 165.9 (NHCOCH=). *Anal*. Calcd for $C_{27}H_{24}N_2O_5 \cdot 0.3H_2O$: C, 70.21; H, 5.37; N, 6.06. Found: C, 70.29; H, 5.51; N, 5.92.

4-(Aminomethyl)-3-(biphenyl-4-ylmethyl)oxazolidin-2-one (9a). A mixture of 2-((3-(biphenyl-4-ylmethyl)-2-oxooxazolidin-4-yl)methyl)isoindoline-1,3-dione (**8a**) [23] (1.0 g, 2.43 mmol) and aqueous 40% methylamine (7 mL) in EtOH (100 mL) was refluxed for 1 h. The resulting mixture was concentrated under a reduced pressure. The residue was purified by column chromatography (SiO_2/EtOH) to afford compound **9a** (440 mg, 64.3%). Mp 90–92°C. IR (KBr) cm^{-1}: 3370, 1743. FABMS (positive) *m/z*: 283 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.49–2.50 (2H, br, NH_2), 2.64–2.73 (2H, m, CH_2NH_2), 3.60–3.65 (1H, m, Oxaz H-4), 4.17 (1H, dd, *J* = 8.5, 6.5 Hz, Oxaz H-5), 4.27 (1H, d, *J* = 15.5 Hz, CHH-Ph), 4.30 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.56 (1H, d, *J* = 15.5 Hz, CHH-Ph), 7.34–7.40 (3H, m, Ar H), 7.44–7.48 (2H, m, Ar H), 7.64–7.67 (4H, m, Ar H). ^{13}C-NMR (DMSO-d_6) δ: 41.3 (NH_2CH_2-Oxaz), 44.8 ($PhCH_2$), 55.9 (Oxaz C-4), 65.0 (Oxaz C-5), 126.5, 126.8, 127.3, 128.2, 128.9 (Ar C), 136.1 (biphenyl Ar C-1), 139.3 (biphenyl Ar C-4 or C-1′), 139.7 (biphenyl Ar C-1′ or C-4), 158.2 (Oxaz C-2). *Anal*. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.28; H, 6.68; N, 9.93.

4-(Aminomethyl)-3-(3-fluoro-4-morpholinobenzyl)oxazolidin-2-one (9b). A mixture of 2-((3-(3-fluoro-4-morpholinobenzyl)-2-oxooxazolidin-4-yl)methyl)isoindoline-1,3-dione (**8b**) [24] (0.5 g, 1.14 mmol) and aqueous 40% methylamine (4 mL) in EtOH (50 mL) was refluxed for 1 h. The resulting mixture was concentrated under a reduced pressure. The residue was purified by column chromatography (SiO_2/MeCN) to afford compound **9b** (163 mg, 46.3%) as an oil. IR (KBr) cm^{-1}: 3378, 1740. FABMS (positive) *m/z*: 310 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.64–2.68 (2H, br, NH_2), 2.99 (4H, t, *J* = 4.5 Hz, Mor H-2, H-6), 3.02–3.17 (2H, m, CH_2NH_2), 3.58–3.61 (1H, m, Oxaz H-4), 3.73 (4H, t, *J* = 4.5 Hz, Mor H-3, H-5), 4.14 (1H, dd, *J* = 8.5, 6.0 Hz, Oxaz H-5), 4.15 (1H, d, *J* = 15.5 Hz, CHH-Ph), 4.28 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.44 (1H, d, *J* = 15.5 Hz, CHH-Ph), 7.01–7.09 (3H, m, Ar H). ^{13}C-NMR (DMSO-d_6) δ: 41.1 ($CONHCH_2$), 44.2 ($PhCH_2$), 50.4 (Mor C-2, C-6), 55.6 (Oxaz C-4), 64.9 (Oxaz C-5), 66.1 (Mor C-3, C-5), 115.4 (d, *J* = 20.7 Hz, FAr C-2), 119.0 (d, *J* = 4.1 Hz, FAr C-5), 124.0 (d, *J* = 3.1 Hz, FAr C-6), 131.4 (d, *J* = 7.2 Hz, FAr C-1), 138.8 (d, *J* = 8.3 Hz, FAr C-4), 154.6 (d, *J* = 245.2 Hz,

FAr C-3), 158.1 (Oxaz C-2). *Anal.* Calcd for $C_{15}H_{20}N_3O_3F \cdot 0.6H_2O$: C, 56.27; H, 6.67; N, 13.13. Found: C, 56.33; H, 6.58; N, 12.92.

N⁴,N⁴′-Bis((3-(biphenyl-4-ylmethyl)-2-oxooxazolidin-4-yl) methyl)biphenyl-4,4′-dicarbamide (10a). To a solution of compound (**9a**) (400 mg, 1.42 mmol) and NEt_3 (143 mg, 1.42 mmol) in CH_2Cl_2 (10 mL) was added biphenyl-4,4′-dicarbonyl dichloride (150 mg, 0.54 mmol), and the mixture was refluxed for 2 h. After cooling, the insoluble product **10a** (330 mg, 79.7%) was obtained by filtration. Mp >240°C. IR (KBr) cm^{-1}: 3356, 1728, 1657. FABMS (positive) *m/z*: 771 $(M+H)^+$. ^{1}H-NMR (DMF-d_7) δ: 3.61–3.77 (4H, m, CONHC$\underline{H}_2$), 4.02–4.05 (2H, m, Oxaz H-4), 4.43 (2H, dd, *J* = 9.0, 5.0 Hz, Oxaz H-5), 4.48 (2H, m, Oxaz H-5), 453, 4.78 (each 2H, d, *J* = 15.5 Hz, C$\underline{H}_2$-Ph), 7.37–7.40 (2H, m, CH_2-biphenyl Ar H-4′), 7.47–7.51 (8H, m, CH_2-biphenyl Ar H), 7.71–7.73 (8H, m, CH_2-biphenyl Ar H), 7.86 (4H, d, *J* = 8.5 Hz, biphenyldicarbamide Ar H-3, H-5, H-3′, H-5′), 8.04 (4H, d, *J* = 8.5 Hz, biphenyldicarbamide Ar H-2, H-6, H-2′, H-6′), 8.75 (2H, t, *J* = 6.0 Hz, NH). ^{13}C-NMR (DMF-d_7) δ: 40.4 (CONHC$\underline{H}_2$), 46.0 (PhC$\underline{H}_2$), 55.1 (Oxaz C-4), 66.3 (Oxaz C-5), 127.4, 127.6, 127.8, 128.2, 128.7, 129.3, 129.6 (Ar C), 134.7 (biphenyldicarbamide Ar C-1, C-1′), 137.0 (CH_2-biphenyl Ar C-1), 140.7 (CH_2-biphenyl Ar C-4 or C-1′), 140.9 (CH_2-biphenyl Ar C-1′ or C-4), 143.2 (biphenyldicarbamide Ar C-4, C-4′), 158.9 (Oxaz C═O), 167.8 (biphenyldicarbamide C═O). *Anal.* Calcd for $C_{48}H_{42}N_4O_6 \cdot 0.8H_2O$: C, 73.41; H, 5.60; N, 7.13. Found: C, 73.46; H, 5.60; N, 7.15.

N⁴,N⁴′-Bis((3-(3-fluoro-4-morpholinobenzyl)-2-oxooxazolidin-4-yl)methyl)biphenyl-4,4′-dicarbamide (10b). To a solution of compound (**9b**) (120 mg, 0.39 mmol) and NEt_3 (30 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) was added biphenyl-4,4′-dicarbonyl dichloride (42 mg, 0.15 mmol) at room temperature, and the mixture was stirred for 20 min. Precipitated material was collected by filtration to give compound **10b** (120 mg, 96.8%) in a high state of purity. Mp 158–160°C (dec). IR (KBr) cm^{-1}: 3315, 1729, 1649 cm^{-1}. FABMS (positive) *m/z*: 825 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.99 (8H, t, *J* = 4.5 Hz, Mor H-2, H-6), 3.47–3.58 (4H, m, CONHC$\underline{H}_2$), 3.73 (8H, t, *J* = 4.5 Hz, Mor H-3, H-5), 3.82–3.85 (2H, m, Oxaz H-4), 4.23–4.25 (2H, m, Oxaz H-5), 4.28 (2H, d, *J* = 15.5 Hz, C$\underline{H}$H-Ph), 4.35 (2H, t, *J* = 8.5 Hz, Oxaz H-5), 4.54 (2H, d, *J* = 15.5 Hz, CH$\underline{H}$-Ph), 6.99–7.10 (6H, m, FAr H), 7.84 (4H, d, *J* = 8.5 Hz, biphenyldicarbamide Ar H-3, H-5, H-3′, H-5′), 7.92 (4H, d, *J* = 8.5 Hz, biphenyldicarbamide Ar H-2, H-6, H-2′, H-6′), 8.65 (2H, t, *J* = 6.0 Hz, NH). ^{13}C-NMR (DMSO-d_6) δ: 39.3 (CONHC$\underline{H}_2$), 44.3 (PhC$\underline{H}_2$), 50.4 (d, *J* = 3.1 Hz, Mor C-2, C-6), 53.7 (Oxaz C-4), 65.2 (Oxaz C-5), 66.1 (Mor C-3, C-5), 115.4 (d, *J* = 20.7 Hz, FAr C-2), 119.1 (d, *J* = 3.1 Hz, FAr C-5), 124.1 (d, *J* = 3.1 Hz, FAr C-6), 126.7 (biphenyldicarbamide Ar C-3, C-5, C-3′, C-5′), 127.9 (biphenyldicarbamide Ar C-2, C-6, C-2′, C-6′), 131.0 (d, *J* = 6.2 Hz, FAr C-1), 133.4 (biphenyldicarbamide Ar C-1, C-1′), 138.9 (d, *J* = 8.3 Hz, FAr C-4), 141.3 (biphenyldicarbamide Ar C-4, C-4′), 154.7 (d, *J* = 245.2 Hz, FAr C-3), 157.6 (Oxaz C-2), 166.6 (biphenyldicarbamide C═O). *Anal.* Calcd for $C_{44}H_{46}N_6O_8\ F_2 \cdot H_2O$: C, 62.70; H, 5.74; N, 9.97. Found: C, 62.68; H, 5.73; N, 9.75.

General procedure for the preparation of compounds 11–14. The corresponding dicarbonyl dichloride (0.22 mmol) was added to a solution of compound **9** (0.50 mmol) and NEt_3 (0.50 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred for 20 min at room temperature. The product was purified by column chromatography to give compounds **11–14**, respectively. Physical and spectroscopic data are shown below.

N¹,N⁴-Bis((3-(biphenyl-4-ylmethyl)-2-oxooxazolidin-4-yl) methyl)benzene-1,4-dicarbamide (11a). This compound was obtained in 76.6% yield. Mp >230°C (hygroscopic). IR (KBr) cm^{-1}: 3330, 1723, 1658 cm^{-1}. FABMS (positive) *m/z*: 695 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.52–3.60 (4H, m, CONHC$\underline{H}_2$), 3.85–3.88 (2H, m, Oxaz H-4), 4.25 (2H, dd, *J* = 8.5, 5.0 Hz, Oxaz H-5), 4.37 (2H, t, *J* = 8.5 Hz, Oxaz H-5), 4.38 (2H, d, *J* = 15.5 Hz, C$\underline{H}$H-Ph), 4.66 (2H, d, *J* = 15.5 Hz, CH$\underline{H}$-Ph), 7.35–7.41 (6H, m, biphenyl Ar H), 7.45–7.48 (4H, m, Biphenyl br H), 7.64–7.66 (8H, m, biphenyl Ar H), 7.89 (4H, benzenedicarbamide Ar H), 8.70 (2H, t-like, NH). ^{13}C-NMR (DMSO-d_6) δ: 39.6 (CONHC$\underline{H}_2$), 44.9 (PhC$\underline{H}_2$), 53.7 (Oxaz C-4), 65.3 (Oxaz C-5), 126.5, 126.9 (biphenyl Ar C), 127.2 (benzenedicarbamide Ar C-2, C-3, C-5, C-6), 127.4 (biphenyl Ar C), 128.3, 128.9 (biphenyl Ar C), 135.7 (biphenyl Ar C-1), 136.5 (benzenedicarbamide Ar C-1, C-4), 139.4 (biphenyl Ar C-4 or C-1′), 139.7 (biphenyl Ar C-1′ or C-4), 157.7 (Oxaz C-2), 166.4 (benzenedicarbamide C═O). *Anal.* Calcd for $C_{42}H_{38}N_4O_6 \cdot 0.2H_2O$: C, 72.23; H, 5.54; N, 8.02. Found: C, 72.14; H, 5.59; N, 8.17.

N¹,N⁴-Bis((3-(3-fluoro-4-morpholinobenzyl)-2-oxooxazolidin-4-yl)methyl)benzene-1,4-dicarbamide (11b). This compound was obtained in 91.0% yield. Mp 132–138°C. IR (KBr) cm^{-1}: 3431, 1738, 1649 cm^{-1}. FABMS (positive) *m/z*: 749 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.98 (8H, t, *J* = 4.5 Hz, Mor H-2, H-6), 3.28–3.54 (4H, m, CONHC$\underline{H}_2$), 3.72–3.73 (8H, m, Mor H-3, H-5), 3.82–3.83 (2H, m, Oxaz H-4), 4.21 (2H, dd, *J* = 9.0, 5.0 Hz, Oxaz H-5), 4.27 (2H, d, *J* = 16.0 Hz, C$\underline{H}$H-Ph), 4.34 (2H, t, *J* = 8.5 Hz, Oxaz H-5), 4.44 (2H, d, *J* = 16.0 Hz, CH$\underline{H}$-Ph), 6.98–7.09 (6H, m, FAr H), 7.87 (4H, s, benzenedicarbamide Ar H), 8.69 (2H, t-like, NH). ^{13}C-NMR (DMSO-d_6) δ: 40.0 (CONHC$\underline{H}_2$), 44.3 (PhC$\underline{H}_2$), 50.4 (Mor C-2, C-6), 53.6 (Oxaz C-4), 65.3 (Oxaz C-5), 66.1 (Mor C-3, C-5), 115.4 (d, *J* = 20.7 Hz, FAr C-2), 119.0 (d, *J* = 4.1 Hz, FAr C-5), 124.1 (d, *J* = 3.1 Hz, FAr C-6), 127.1 (benzenedicarbamide Ar C), 131.0 (d, *J* = 6.2 Hz, FAr C-1), 136.5 (benzenedicarbamide Ar C-1, C-4), 138.9 (d, *J* = 8.3 Hz, FAr C-4), 154.7 (d, *J* = 245.1 Hz, FAr C-3), 157.6 (Oxaz C-2), 166.5 (benzenedicarbamide C═O). *Anal.* Calcd for $C_{38}H_{42}N_6O_8\ F_2 \cdot H_2O$: C, 59.52; H, 5.78; N, 10.96. Found: C, 59.61; H, 5.71; N, 10.85.

N¹,N³-Bis((3-(biphenyl-4-ylmethyl)-2-oxooxazolidin-4-yl) methyl)benzene-1,3-dicarbamide (12a). This compound was obtained in 56.9% yield. Mp 107–122°C. IR (KBr) cm^{-1}: 3390, 1733, 1662 cm^{-1}. FABMS (positive) *m/z*: 695 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.53–3.58 (4H, m, CONHC$\underline{H}_2$), 3.84–3.88 (2H, m, Oxaz H-4), 4.24–4.27 (2H, m, Oxaz H-5), 4.32–4.38 (2H, m, Oxaz H-5), 4.39 (2H, d, *J* = 16.0 Hz, C$\underline{H}$H-Ph), 4.66 (2H, d, *J* = 16.0 Hz, CH$\underline{H}$-Ph), 7.35–7.40 (6H, m, biphenyl Ar H), 7.44–7.47 (4H, m, biphenyl Ar H), 7.58–7.61 (1H, benzenedicarbamide Ar H-5), 7.64–7.66 (8H, m, biphenyl Ar H), 7.96–7.97 (2H, benzenedicarbamide Ar H-4, H-6), 8.30 (1H, benzenedicarbamide Ar H-2), 8.75 (2H, t, *J* = 5.5 Hz, NH). ^{13}C-NMR (DMSO-d_6) δ: 39.7 (CONHC$\underline{H}_2$), 44.8 (PhC$\underline{H}_2$), 53.7 (Oxaz C-4), 65.2 (Oxaz C-5), 126.4 (benzenedicarbamide Ar C-2), 126.5, 126.9, 127.4 (biphenyl Ar C), 128.3 (biphenyl Ar C + benzenedicarbamide Ar C-5), 128.8 (biphenyl Ar C), 129.8 (benzenedicarbamide Ar C-4, C-6), 134.3 (benzenedicarbamide Ar C-1), 135.7 (biphenyl Ar C-1), 139.4 (biphenyl Ar C-4 or C-1′), 139.7 (biphenyl Ar C-1′ or C-4), 155.7 (Oxaz C-2), 166.6 (benzenedicarbamide C═O). *Anal.* Calcd for $C_{42}H_{38}N_4O_6 \cdot H_2O$: C, 70.77; H, 5.66; N, 7.86. Found: C, 70.78; H, 5.67; N, 7.59.

N^1,N^3-Bis((3-(3-fluoro-4-morpholinobenzyl)-2-oxooxazolidin-4-yl)methyl)benzene-1,3-dicarbamide (12b). This compound was obtained in 40.1% yield as amorphous powder. IR (KBr) cm^{-1}: 3431, 1739, 1660 cm^{-1}. FABMS (positive) *m/z*: 749 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.98 (8H, t, J = 4.5 Hz, Mor H-2, H-6), 3.50–3.54 (4H, m, CONHC$\underline{H}_2$), 3.71–3.74 (8H, m, Mor H-3, H-5), 3.80–3.83 (2H, m, Oxaz H-4), 4.20–4.23 (2H, m, Oxaz H-5), 4.27 (2H, d, J = 15.5 Hz, C$\underline{H}$H-Ph), 4.34 (2H, t, J = 9.0 Hz, Oxaz H-5), 4.54 (2H, d, J = 15.5 Hz, CH$\underline{H}$-Ph), 6.98–7.09 (6H, m, FAr H), 7.58–7.61 (1H, benzenedicarbamide Ar H-5), 7.94–7.96 (2H, m, benzenedicarbamide Ar H-4, H-6), 8.27 (1H, br s, benzenedicarbamide Ar H-2), 8.70–8.73 (2H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 39.8 (CONH$\underline{C}H_2$), 44.3 (Ph$\underline{C}H_2$), 50.4 (Mor C-2, C-6), 53.6 (Oxaz C-4), 65.2 (Oxaz C-5), 66.1 (Mor C-3, C-5), 115.4 (d, J = 20.7 Hz, FAr C-2), 119.0 (d, J = 3.1 Hz, FAr C-5), 124.1 (d, J = 3.1 Hz, FAr C-6), 126.4 (benzenedicarbamide Ar C-2), 128.3 (benzenedicarbamide Ar C-5), 129.8 (benzenedicarbamide Ar C-4, C-6), 131.0 (d, J = 7.2 Hz, FAr C-1), 134.3 (benzenedicarbamide Ar C-1, C-3), 138.9 (d, J = 8.3 Hz, FAr C-4), 154.7 (d, J = 245.2 Hz, FAr C-3), 157.6 (Oxaz C-2), 166.5 (benzenedicarbamide C═O). *Anal*. Calcd for $C_{38}H_{42}N_6O_8$ $F_2 \cdot 0.6H_2O$: C, 60.09; H, 5.73; N, 11.06. Found: C, 60.03; H, 5.67; N, 10.98.

N^2,N^6-Bis((3-(biphenyl-4-ylmethyl)-2-oxooxazolidin-4-yl)methyl)pyridine-2,6-dicarboxamide (13a). This compound was obtained in 87.6% yield. Mp 115–119°C. IR (KBr) cm^{-1}: 3345, 1747, 1676 cm^{-1}. FABMS (positive) *m/z*: 696 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.55–3.72 (4H, m, CONHC$\underline{H}_2$), 3.92–3.96 (2H, m, Oxaz H-4), 4.26–4.29 (2H, m, Oxaz H-5), 4.39 (2H, d, J = 9.0 Hz, Oxaz H-5), 4.42–4.45 (2H, m, C$\underline{H}$H-Ph), 4.69 (2H, dd, J = 16.0, 3.0 Hz, CH$\underline{H}$-Ph), 7.33–7.37 (6H, m, biphenyl Ar H), 7.43–7.46 (4H, m, biphenyl Ar H), 7.58–7.62 (8H, m, biphenyl Ar H), 8.16–8.22 (3H, m, pyridine H), 9.38 (2H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 39.8, 39.9 (CONH$\underline{C}H_2$), 45.11, 45.13 (Ph$\underline{C}H_2$), 53.54, 53.62 (Oxaz C-4), 65.23, 65.28 (Oxaz C-5), 124.5 (pyridine C-3, C-5), 126.6, 126.9, 127.4, 128.20, 128.22, 128.9 (biphenyl Ar C), 135.57, 135.63 (biphenyl Ar C-1), 139.4 (biphenyl Ar C-4 or C-1′), 139.7 (pyridine C-4 and biphenyl Ar C-1′ or C-4), 148.2 (pyridine C-2, C-6), 157.8 (Oxaz C-2), 163.79, 163.82 (pyridinedicarbamide C═O). *Anal*. Calcd for $C_{41}H_{37}N_5O_6 \cdot 0.5H_2O$: C, 69.87; H, 5.43; N, 9.94. Found: C, 69.84; H, 5.43; N, 9.94.

N^1,N^5-Bis((3-(3-fluoro-4-morpholinobenzyl)-2-oxooxazolidin-4-yl)methyl)pyridine-2,6-dicarboxamide (13b). This compound was obtained in 64.5% yield. Mp 128–133°C. IR (KBr) cm^{-1}: 3353, 1747, 1677 cm^{-1}. FABMS (positive) *m/z*: 749 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.94–2.96 (8H, m, Mor H-2, H-6), 3.56–3.72 (12H, m, Mor H-3, H-5 and CONHC$\underline{H}_2$), 3.88–3.92 (2H, m, Oxaz H-4), 4.21–4.25 (2H, m, Oxaz H-5), 4.31 (2H, d, J = 15.5 Hz, C$\underline{H}$H-Ph), 4.36–4.39 (2H, m, Oxaz H-5), 4.56 (2H, dd, J = 15.5, 2.5 Hz, CH$\underline{H}$-Ph), 6.91–7.03 (6H, m, FAr H), 8.18–8.19 (3H, m, pyridine H), 9.32–9.37 (2H, m, NH). ^{13}C-NMR (DMSO-d_6) δ: 39.93, 40.00 (CONH$\underline{C}H_2$), 44.6 (Ph-$\underline{C}H_2$), 50.32, 50.34 (Mor C-2, C-6), 53.42, 53.48 (Oxaz C-4), 65.15, 65.18 (Oxaz C-5), 66.0 (Mor C-3, C-5), 115.3 (d, J = 20.7 Hz, FAr C-2), 118.9 (d, J = 3.1 Hz, FAr C-5), 123.9 (d, J = 3.1 Hz, FAr C-6), 124.4 (pyridine C-3, C-5), 130.8 (d, J = 7.2 Hz, FAr C-1), 138.8 (d, J = 8.3 Hz, FAr C-4), 139.6 (pyridine C-4), 148.4 (pyridine C-2, C-6), 154.6 (d, J = 245.2 Hz, FAr C-3), 157.6 (Oxaz C-2), 163.69, 163.71 (pyridinedicarbamide C═O). *Anal*. Calcd for $C_{37}H_{41}N_7O_8$ $F_2 \cdot 0.5H_2O$: C, 58.57; H, 5.58; N, 12.92. Found: C, 58.48; H, 5.76; N, 12.78.

N^1,N^5-Bis((3-(biphenyl-4-ylmethyl)-2-oxooxazolidin-4-yl)methyl)pentanediamide (14a). This compound was obtained in 67.6% yield. Mp 81–92°C (with dec). IR (KBr) cm^{-1}: 3317, 1739, 1658 cm^{-1}. FABMS (positive) *m/z*: 661 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.73 (2H, dd, J = 15.0, 7.5 Hz, pentanediamide H-3), 2.08–2.12 (4H, t-like, pentanediamide H-2, H-4), 3.30–3.39 (4H, m, CONHC$\underline{H}_2$), 3.69–3.73 (2H, m, Oxaz H-4), 4.06–4.09 (2H, m, Oxaz H-5), 4.28 (2H, d, J = 15.5 Hz, C$\underline{H}$H-Ph), 4.31–4.33 (2H, m, Oxaz H-5), 4.62 (2H, d, J = 15.5 Hz, CH$\underline{H}$-Ph), 7.34–7.39 (6H, m, biphenyl Ar H), 7.44–7.47 (4H, m, biphenyl Ar H), 7.64–7.67 (8H, m, biphenyl Ar H), 7.98 (2H, t-like, NH). ^{13}C-NMR (DMSO-d_6) δ: 21.3 (pentanediamide C-3), 34.6 (pentanediamide C-2), 38.3 (CONH$\underline{C}H_2$), 44.6 (Ph$\underline{C}H_2$), 53.6 (Oxaz C-4), 65.0 (Oxaz C-5), 126.5, 126.9, 127.4, 128.3, 128.8 (biphenyl Ar C), 135.6 (biphenyl Ar C-1), 139.4 (biphenyl Ar C-4 or C-1′), 139.7 (biphenyl Ar C-1′or C-4), 157.7 (Oxaz C-2), 172.5 (pentanediamide C═O). *Anal*. Calcd for $C_{39}H_{40}N_4O_6 \cdot 1.5H_2O$: C, 68.11; H, 6.30; N, 8.15. Found: C, 68.04; H, 6.14; N, 8.16.

We confirmed that the diastereomeric mixture of compound **14a** exhibited significant differences in the ^{1}H and ^{13}C-NMR spectra in $CDCl_3$. The data are shown below.

^{1}H-NMR ($CDCl_3$) δ: 2.09–2.12 (2H, *m*, Pentanediamide H-3), 2.16–2.30 (4H, m, Pentanediamide H-2, H-4), 3.39–3.50 (2H, m, CONHC$\underline{H}_2$), 3.61–3.75 (4H, m, CONHC$\underline{H}_2$ + Oxaz H-4), 4.29–4.33 (2H, m, Oxaz H-5), 4.35 (1H, d, J = 15.5 Hz, C$\underline{H}$H-Ph), 4.44 (1H, d, J = 15.5 Hz, C$\underline{H}$H-Ph), 4.53 (1H, d, J = 9.0 Hz, Oxaz H-5), 4.64 (1H, dd, J = 9.0, 2.5 Hz, Oxaz H-5), 4.92 (1H, d, J = 15.5 Hz, CH$\underline{H}$-Ph), 4.95 (1H, d, J = 15.5 Hz, CH$\underline{H}$-Ph), 6.82–6.86 (2H, m, NH), 7.34–7.46 (10H, m, biphenyl Ar H), 7.56–7.61 (8H, m, biphenyl Ar H). ^{13}C-NMR ($CDCl_3$) δ: 21.86, 21.99 (pentanediamide C-3), 34.37, 34.52 (pentanediamide C-2), 38.64, 38.68 (CONH$\underline{C}H_2$), 45.64, 45.70 (Ph$\underline{C}H_2$), 54.72, 54.77 (Oxaz C-4), 66.12, 66.17 (Oxaz C-5), 127.04, 127.04, 127.53, 127.69, 127.69, 128.58, 128.58, 128.62, 128.84, 128.84 (biphenyl Ar C), 134.67, 134.74 (biphenyl Ar C-1), 140.40, 140.40 (biphenyl Ar C-4 or C-1′), 141.13, 141.13 (biphenyl Ar C-1′or C-4), 159.27, 159.27 (Oxaz C-2), 174.42, 174.44 (pentanediamide C═O).

N^1,N^5-Bis((3-(3-fluoro-4-morpholinobenzyl)-2-oxooxazolidin-4yl)methyl)pentanediamide (14b). This compound was obtained in 91.0% yield as amorphous powder. IR (KBr) cm^{-1}: 3418, 3328, 1741, 1656 cm^{-1}. FABMS (positive) *m/z*: 715 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.68–1.71 (2H, m, pentanediamide H-3), 2.06–3.00 (4H, t-like, pentanediamide H-2), 2.98–3.00 (8H, m, Mor H-2, H-6), 3.24–3.34 (4H, m, CONHC$\underline{H}_2$), 3.65–3.68 (2H, m, Oxaz H-4), 3.72–3.74 (8H, m, Mor H-3, H-5), 4.03 (2H, dd, J = 9.0, 5.5 Hz, Oxaz H-5), 4.15 (2H, d, J = 15.5 Hz, C$\underline{H}$H-Ph), 4.28 (2H, t, J = 9.0 Hz, Oxaz H-5), 4.49 (2H, d, J = 15.5 Hz, CH$\underline{H}$-Ph), 6.99–7.07 (6H, m, FAr H), 7.92 (2H, t-like, NH). ^{13}C-NMR (DMSO-d_6) δ: 21.3 (pentanediamide C-3), 34.6 (pentanediamide C-2), 39.3 (CONH$\underline{C}H_2$), 44.1 (Ph$\underline{C}H_2$), 50.4 (Mor C-2, C-6), 53.5 (Oxaz C-4), 65.0 (Oxaz C-5), 66.1 (Mor C-3, C-5), 115.4 (d, J = 20.7 Hz, FAr C-2), 119.0 (d, J = 3.1 Hz, FAr C-5), 124.1 (d, J = 3.1 Hz, FAr C-6), 130.9 (d, J = 7.2 Hz, FAr C-1), 138.9 (d, J = 8.3 Hz, FAr C-4), 154.7 (d, J = 245.2 Hz, FAr C-3), 157.7 (Oxaz C-2), 172.5 (pentanediamide C═O). *Anal*. Calcd for $C_{35}H_{44}N_6O_8$ $F_2 \cdot H_2O$: C, 57.37; H, 6.33; N, 11.47. Found: C, 57.50; H, 6.29; N, 11.48.

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REFERENCES AND NOTES

[1] Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. Angew Chem Int Ed 2007, 46, 2366.

[2] Imberty, A.; Varrot A. Curr Opin Struct Biol 2008, 18, 567.

[3] Varki, A. Essentials of Glycobiology, 2nd ed.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, N. Y., 2009; pp 719–732.

[4] Fujisaki, F.; Shoji, K.; Shimodouzono, M.; Kashige, N.; Miake, F.; Sumoto, K. Chem Pharm Bull 2010, 58, 1123.

[5] Abe, N.; Fujisaki, F.; Sumoto, K. Chem Pharm Bull 1998, 46, 142.

[6] Fujisaki, F.; Abe, N.; Sumoto, K. Chem Pharm Bull 2004, 52, 1238.

[7] Fujisaki, F.; Abe, N.; Sumoto, K. Heterocycles 2008, 75, 1681.

[8] Fujisaki, F.; Shoji, K.; Sumoto, K. Chem Pharm Bull 2009, 57, 1415.

[9] Fujisaki, F.; Shoji, K.; Sumoto, K. Heterocycles 2009, 78, 213.

[10] These compounds (**2**) synthesized in this study showed weak antibacterial activities (MIC = 0.286–0.465 μ*M*/mL) against *E. coli* but had no antibacterial activities against *S. aureus* (at the concentration of >0.286–0.465 μ*M*/mL).

[11] Compounds (**3c** and **3d**) showed antibacterial activities (MIC = 0.293 and 0.280 μ*M*/mL, respectively) against *E. coli* and antibacterial activities (MIC > 0.293 and >0.280 μ*M*/mL, respectively) against *S. aureus*. Regarding compounds **3a** and **3b**, we could not determine the precise MIC values against both strains (>0.395 and > 0.365 μ*M*/mL, respectively). However, we confirmed antibacterial activity against both strains by calculating the number of readily observable colonies for compounds in agar culture medium. Compound **3a** showed a higher level of bacterial static activity at the concentration of 5 μ*M* than that of **3b** at the concentration of 10 μ*M*. Therefore, we used the derivative (**3a** and **3b**) as a template for the scaffold of twin-drug type molecules.

[12] Leach, K. L.; Swaney, S. M.; Colca, J. R.; McDonald, W. G.; Blinn, J. R.; Thomasco, L. M.; Gadwood, R. C.; Shinabarger, D.; Xiong, L.; Mankin, A. S. Mol Cell 2007, 26, 393.

[13] Locke, J. B.; Finn, J.; Hilgers, M.; Morales, G.; Rahawi, S.; Kedar, G. C.; Picazo, J. J.; Im, W.; Shaw, K. J.; Stein, J. L. Antimicrob Agents Chemother 2010, 54, 5337 and related references cited therein.

[14] Lemaire, S.; Tulkens, P. M.; Bambeke, F. V. Antimicrob Agents Chemother 2010, 54, 2540 and related references cited therein.

[15] Balzarini, J. Antiviral Res 2006, 71, 237 and related references cited therein.

[16] Bax, B. D.; Chan, P. F.; Eggleston, D. S.; Fosberry, A.; Gentry, D. R.; Gorrec, F.; Giordano, I.; Hann, M. M.; Hennessy, A.; Hibbs, M.; Huang, J.; Jones, E.; Jones, J.; Brown, K. K.; Lewis, C. J.; May, E. W.; Saunders, M. R.; Singh, O.; Spitzfaden, C. E.; Shen, C.; Shillings, A.; Theobald, A. J.; Wohlkonig, A.; Pearson, N. D.; Gwynn, M. N. Nature 2010, 466, 935.

[17] Camille, G. W. The Practice of Medicinal Chemistry, 3rd ed.; Academic Press: San Diego, 2008.

[18] Krishnamurthy, V. M.; Estroff, L. A.; Whitesides, G. M. Multivalency in ligand design. In Methods and Principles in Medicinal Chemistry: Fragment-based Approaches in Drug Discovery, Mannhold, R.; Kubinyi, H.; Folkers, G., Eds. WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006, Vol 34, pp 11–53.

[19] We used a racemic 4-aminomethyloxazolidin-2-one (**9**) as a starting material in the synthesis of twin-drug type compounds. The obtained twin-drug type products (**10–14**) can be considered to be a mixture of three twin-drug type molecules, that is, a Cs-symmetrical meso compound and two enantiomeric C_2-symmetrical molecules that have the same absolute configuration regarding two C-4-substituted oxazolidin-2-one rings in each molecule. For instance, three components in product **14a** were detected by HPLC enantioseparation with the use of CHIRALPAK IA® as a chiral stationary phase. The obtained diastereomeric mixture exhibited very simple symmetrical ^{13}C-NMR in DMSO-d_6, showing little difference with respect to all of the signals assignable to substituted oxazolidin-2-one rings and a linker group. However, we found that the diastereomeric mixture of compound **14a** exhibited significant differences in the ^{1}H and ^{13}C-NMR spectra in $CDCl_3$ (see Experimental section). In the case of compounds **13a** and **13b**, ^{13}C-NMR spectra indicated unsymmetrical molecular features. It is likely that intramolecular hydrogen bonding between pyridine ring nitrogen and one of the amide functionalities [25] gave rise to a slightly different non-equivalent magnetic resonance patterns.

[20] This result has considerable significance in comparison with antibacterial activity of cephalothin. Thus, when the experiments with *E. coli* NIHJ or *S. aureus* Terajima were carried out under similar conditions, antibacterial activity of cephalothin (MIC = 12.5 μg/mL (0.032 μ*M*/mL) or 0.20 μg/mL (0.001 μ*M*/mL), respectively) had been reported [26].

[21] Japanese Society of Chemotherapy (1989). Chemotherapy 1990, 38, 102.

[22] Japanese Society of Chemotherapy (1992). Chemotherapy 1993, 41, 184.

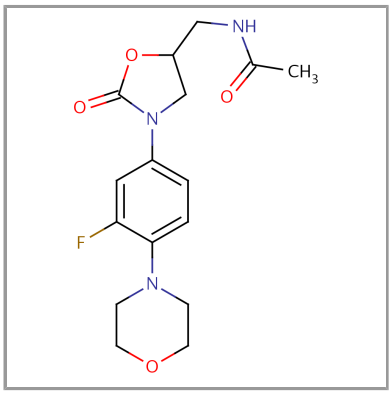
[23] This compound (**8a**) was easily obtained by the procedure described in our previous paper [7]. Yield was 85.0%, mp 208–210°C. IR (KBr) cm^{-1}: 1773, 1736, 1717. FABMS (positive) *m/z*: 413 $(M+H)^+$. *Anal*. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 72.87; H, 4.94; N, 6.83.

[24] This compound (**8b**) was prepared by the procedure reported previously [7]. Yield was 61.4%, mp 196–199°C. IR (KBr) cm^{-1}: 1772, 1736, 1713. FABMS (positive) *m/z*: 439 (M^+). *Anal*. Calcd for $C_{23}H_{22}N_3O_5F$: C, 62.86; H, 5.05; N, 9.56. Found: C, 62.66; H, 5.26; N, 9.57.

[25] Affeld, A.; Hübner, G. M.; Seel, C.; Schalley, C. A. Eur J Org Chem 2001, 2877.

[26] Noto, T.; Nehashi, T.; Endo, H.; Saito, S.; Matsubara, S.; Harada, S.; Ogawa, H.; Koyama, K. J Antibiot 1976, 19, 1058.

1



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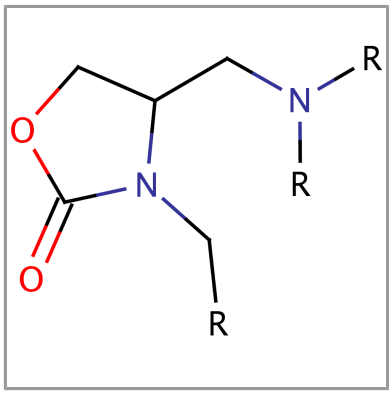

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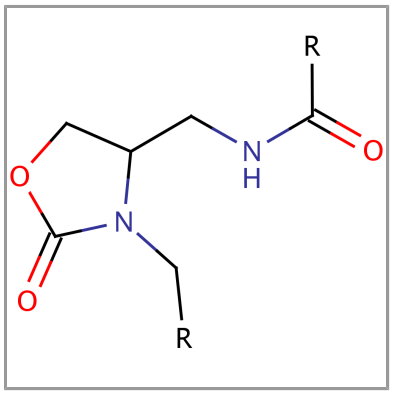

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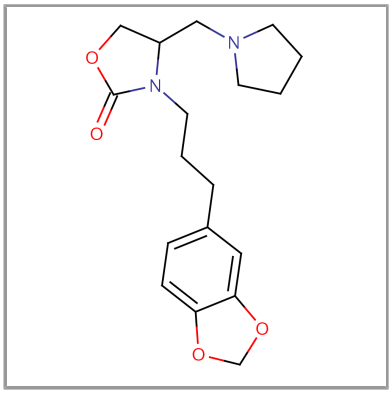
2a



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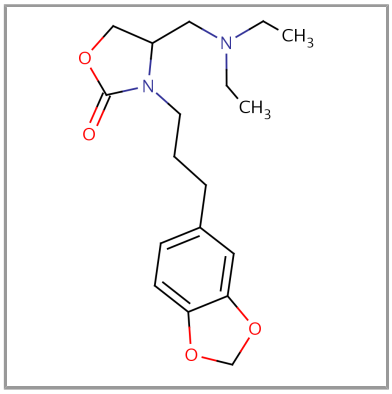
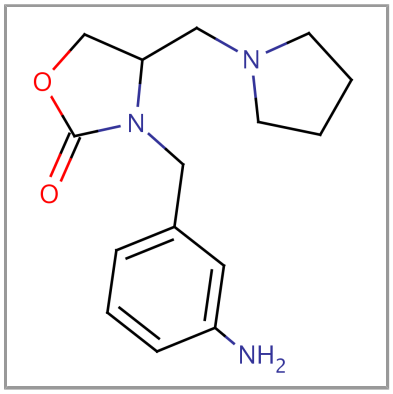


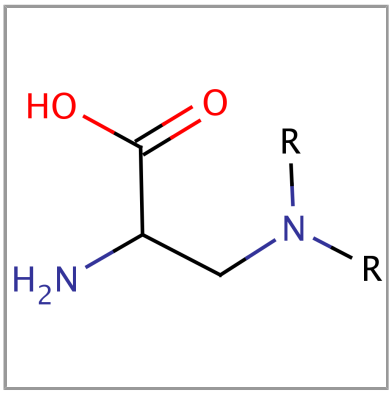
Compound Details Structure Search

2c



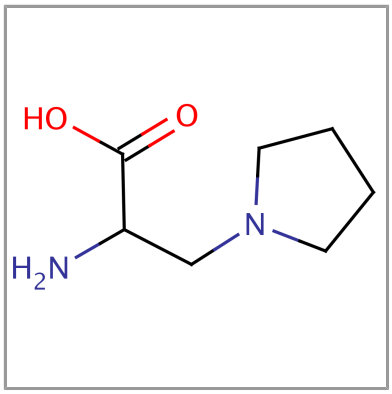
Compound Details Structure Search

4



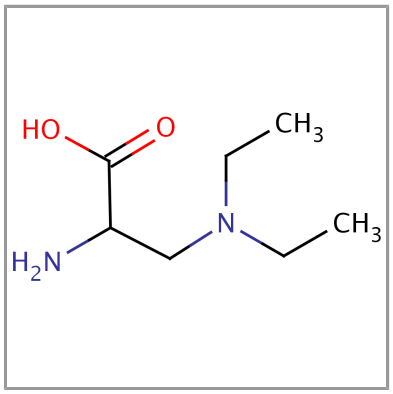
Compound Details Structure Search

4a



Compound Details Structure Search

4b



Compound Details Structure Search

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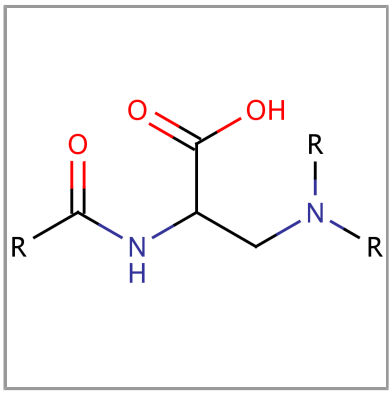

Compound Details Structure Search

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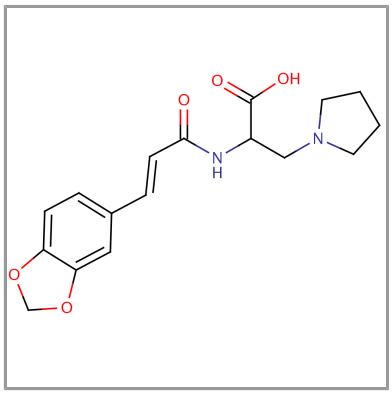

Compound Details Structure Search

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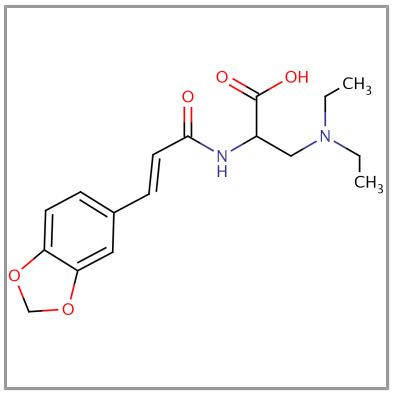

Compound Details Structure Search

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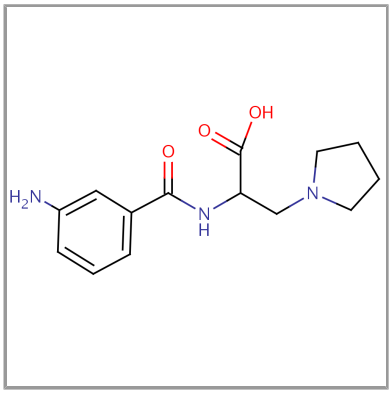

Compound Details Structure Search

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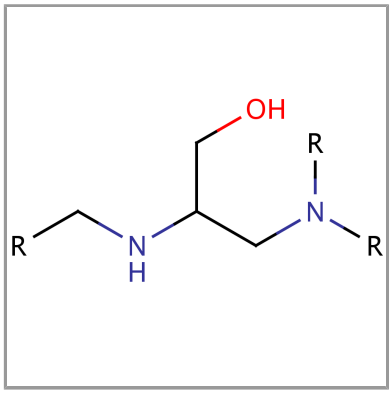
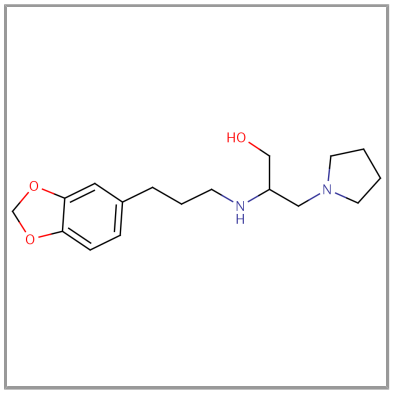


Compound Details Structure Search

6a



Compound Details Structure Search

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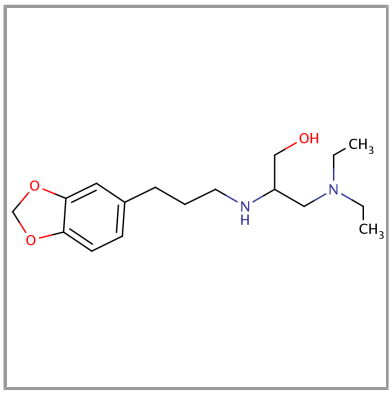

Compound Details Structure Search

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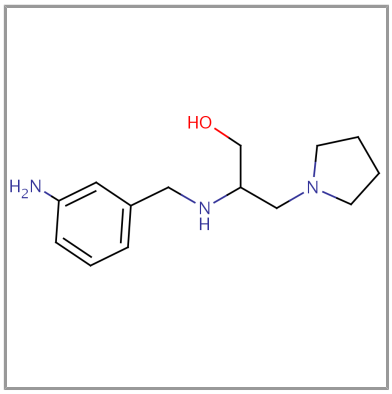

Compound Details Structure Search

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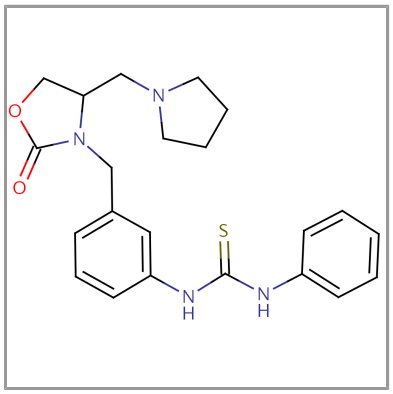

Compound Details Structure Search

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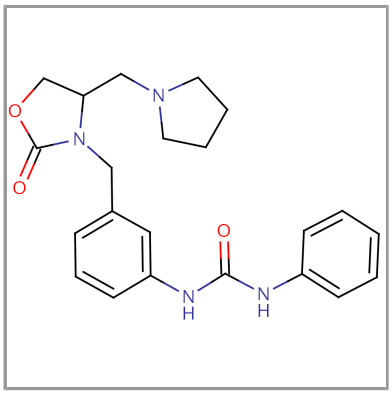

Compound Details Structure Search

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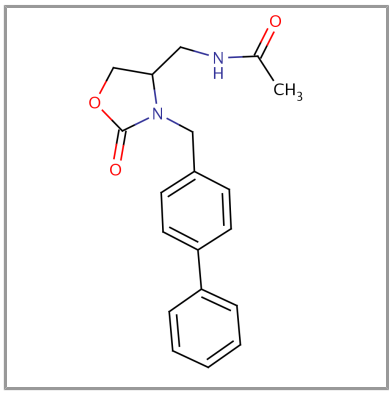

Compound Details Structure Search

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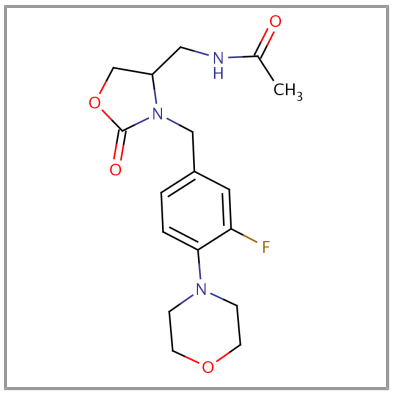

Compound Details Structure Search

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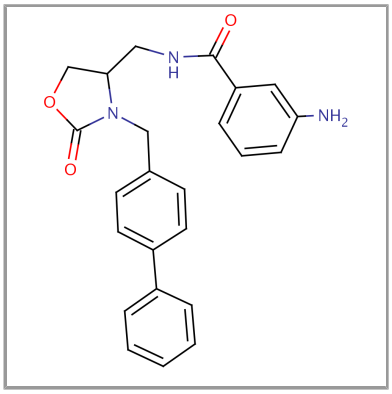

Compound Details Structure Search

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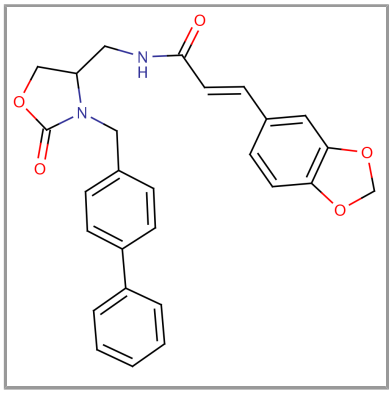

Compound Details Structure Search

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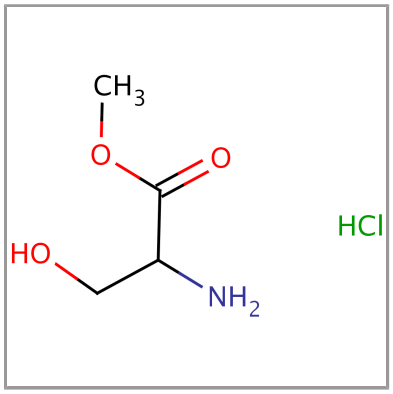
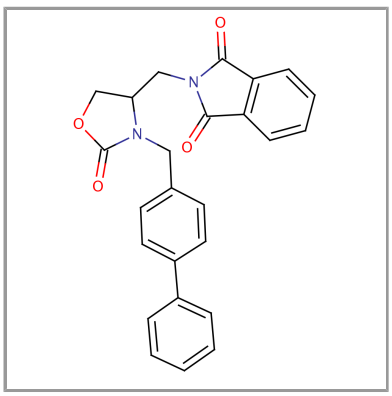


Compound Details Structure Search

8a



Compound Details Structure Search

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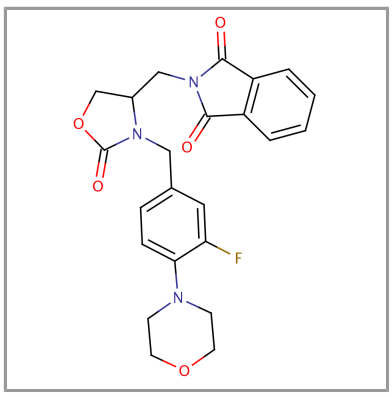

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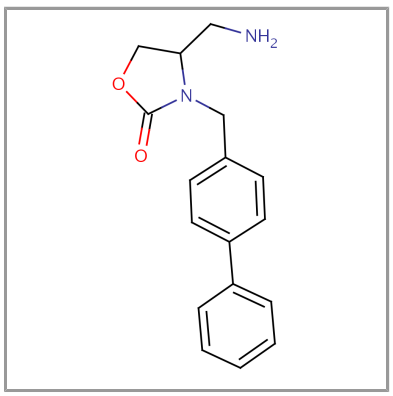
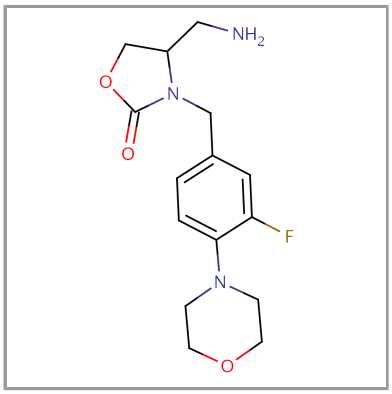
9a



Compound Details Structure Search

9b



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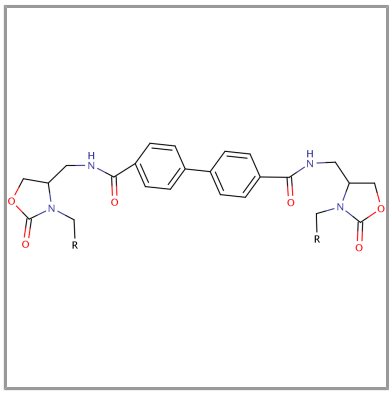

Compound Details Structure Search

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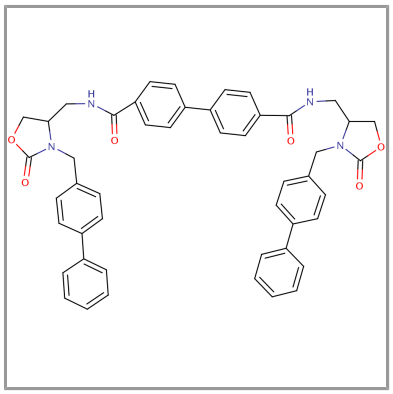

Compound Details Structure Search

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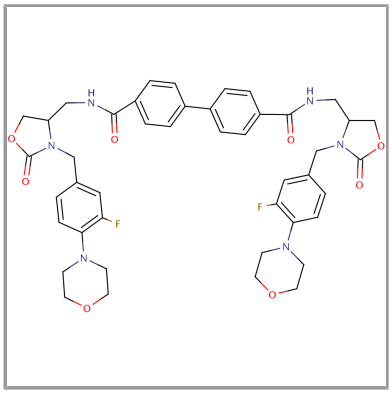

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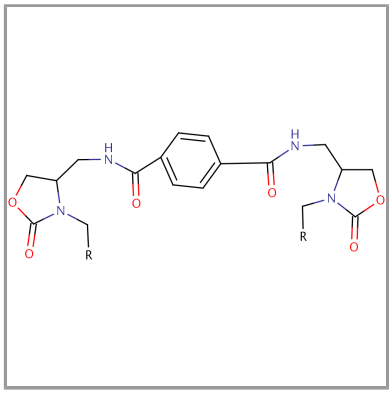
11



Compound Details Structure Search

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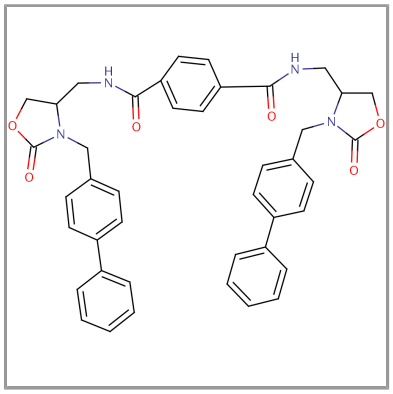

Compound Details Structure Search

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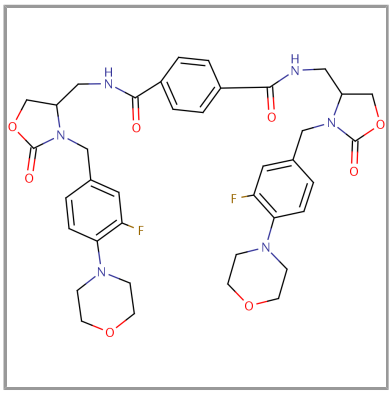

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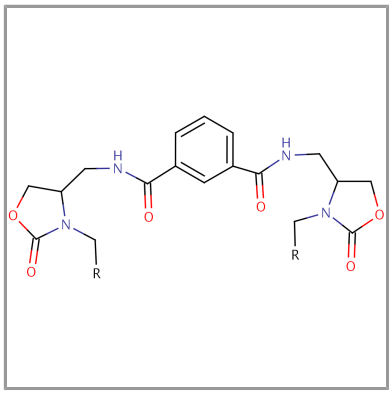

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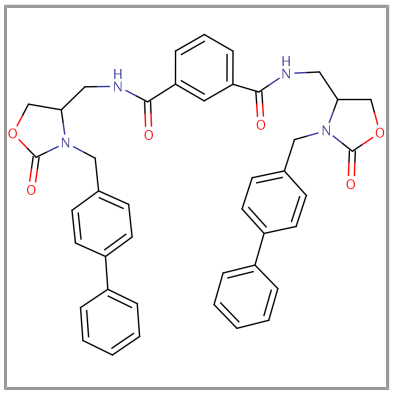
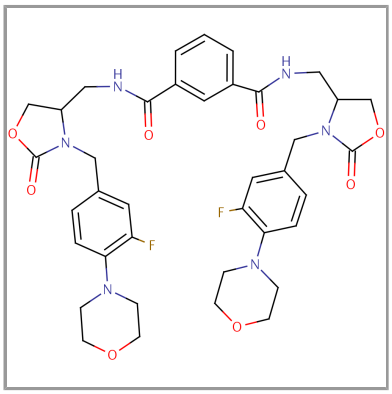
12a



Compound Details Structure Search

12b



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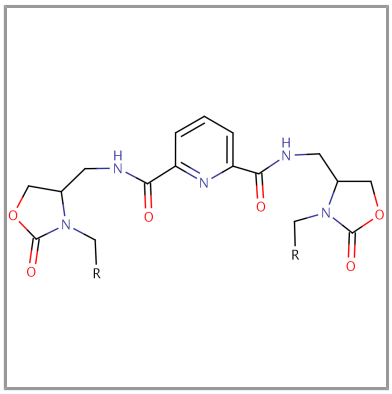

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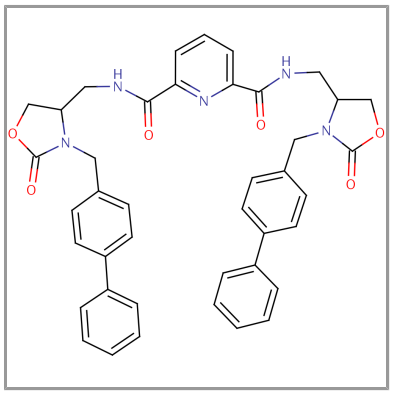

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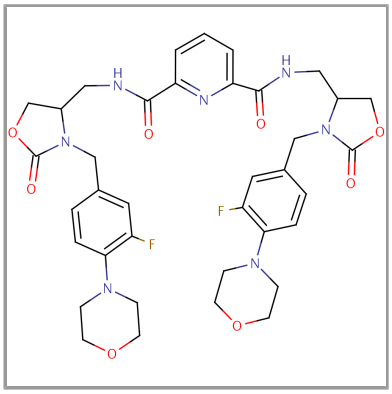

Compound Details Structure Search

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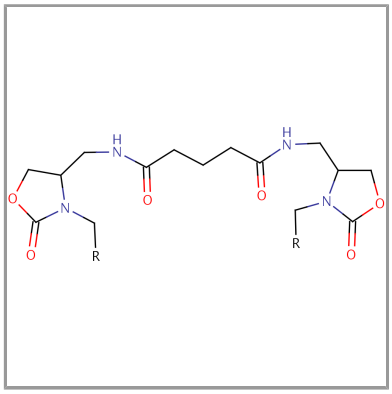

Compound Details Structure Search

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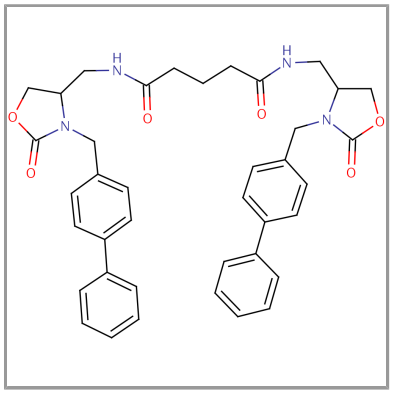

Compound Details Structure Search

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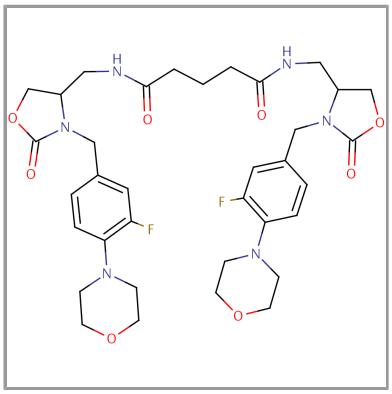

Compound Details Structure Search