HETEROCYCLES, Vol. 75, No. 7, 2008, pp. 1681 - 1694. © The Japan Institute of Heterocyclic Chemistry
Received, 28th January, 2008, Accepted, 28th February, 2008, Published online, 4th March, 2008. COM-08-11350

A NEW ROUTE FOR THE SYNTHESIS OF LINEZOLID MIMETIC 3,4-DISUBSTITUTED OXAZOLIDIN-2-ONE DERIVATIVES

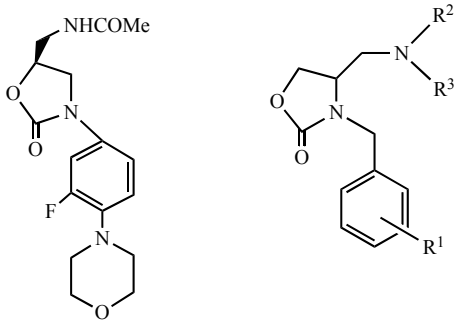
Fumiko Fujisaki, Nobuhiro Abe, and Kunihiro Sumoto*

Faculty of Pharmaceutical Sciences, Fukuoka University; Nanakuma, Jonan-Ku, Fukuoka 814-0180, Japan. e-mail: kunihiro@cis.fukuoka-u.ac.jp

Abstract – New oxazolidin-2-ones (**3**), which mimic the clinically useful antibacterial agent (**1**) (Linezolid) were prepared by using a cyclization procedure with diethyl carbonate from aminoalcohol (**7**) starting with DL-serine methyl ester hydrochloride (**4**) and aromatic carboxylic acid derivatives (**5**).

INTRODUCTION

In a search for biologically active compounds,[1-4] a molecule (**2**) was designed staring with *β*–aminoalanine derivatives. The protocol for the preparation for this class of compounds has been established in this laboratory.[2,5] The derivatives of 3,4-disubstituted oxazolodin-2-one (**2**) prepared previously possess dialkylaminomethyl (-$CH_2NR^1R^2$) functionality at the 4-position of oxazolidin-2-one ring of the molecule shown in the structure (**2**) (Figure 1). Unfortunately, all of the compounds (**2**)

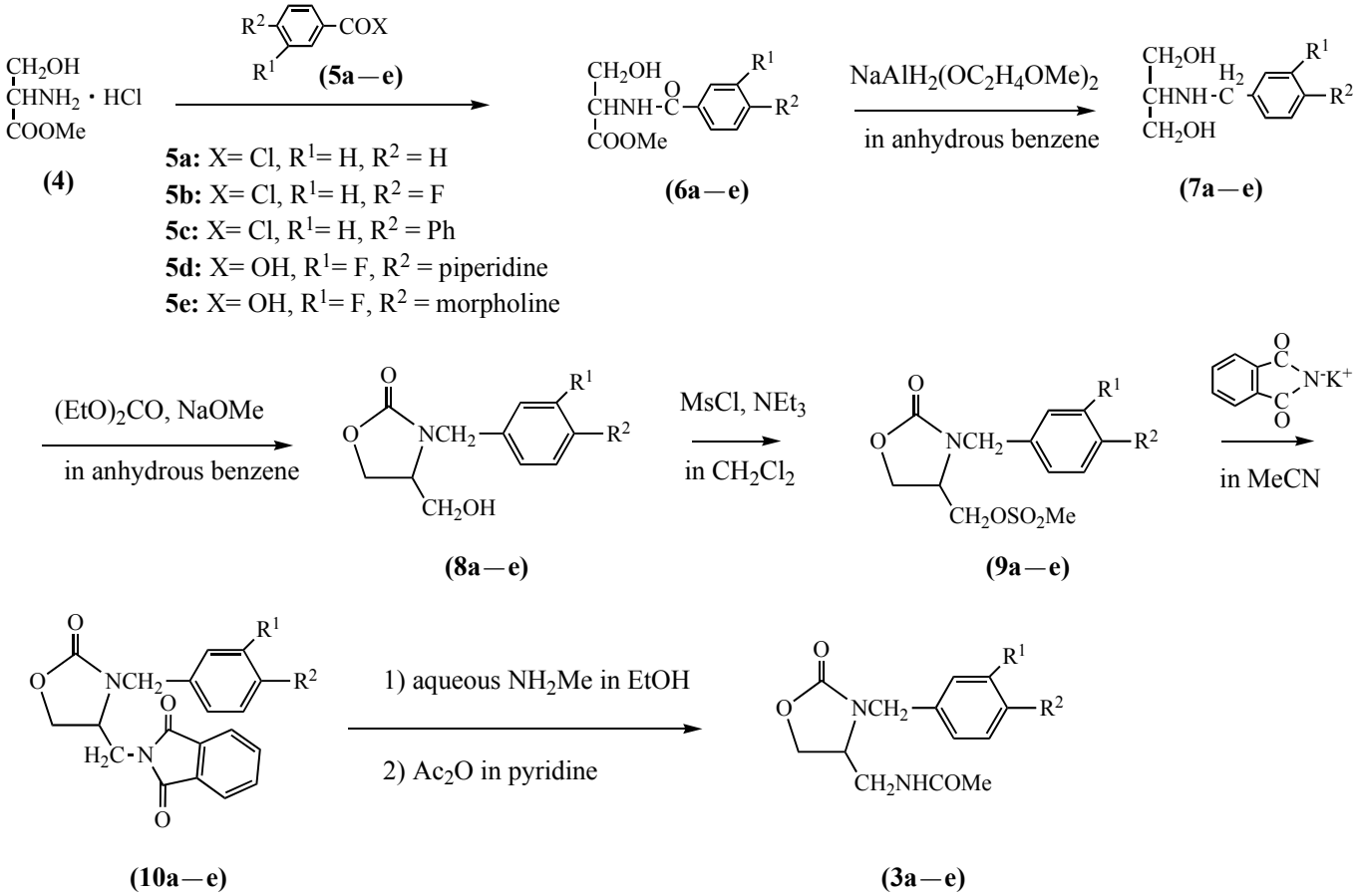


Linezolid (**1**) (**2**)

Figure 1

synthesized in the previous report showed no significant antibacterial activity. Using the procedure reported previously, no compounds could be obtained which had -NHAc functionality as a —$CH_2NR^1R^2$

group in the represented molecule (**2**) mimicking the structural framework of Linezolid.[6, 7] The synthesis of this class of compounds seems to be an interesting molecular modification[8] in terms of the effectiveness of the disjunctive approach in medicinal chemistry; because the structure (**2**) is a Linezolid mimetic structural fragment. This paper describes a new synthetic route to obtain oxazolidin-2-one analogues of the structure (**3**) with -NHAc functionality, which consists of multistage reactions and involves a similar cyclization procedure with diethyl carbonate of the aminoalcohol (**7**) shown in Scheme 1.



Scheme 1

RESULTS AND DISCUSSION

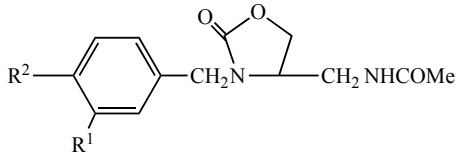
Since the introduction of –NHAc moiety as a part of – $CH_2NR^1R^2$ group could not be achieved by the previous method,[2] DL-serine methyl ester hydrochloride (**4**) and the carboxylic acid derivatives (**5**) were used as the starting materials to obtain the key intermediate aminoalcohols (**7**) for the preparation of the new 3,4-disubstituted oxazolidin-2-ones (**3**). Therefore, the transformation to the precursors (**6**) to the compounds (**7**) was effectively achieved by the coupling procedure reported recently,[1,5] or by a Schotten-Baumann procedure.[3] The aminoalcohols (**7**) were easily cyclized to the desired

3,4-disubstituted oxazolidin-2-ones ring system (**8**) from the cyclization reaction with $(EtO)_2CO$.

The hydroxymethyl groups at the C-4 position of oxazolidin-2-one ring in the molecule (**8**) were successfully converted to the corresponding methansulfonates (**9**). The transformation of the hydroxy groups to the corresponding phthalimide group by substitution reaction was easily achieved with potassium phthalimide in MeCN. After deprotection of the phthalimide derivatives (**10**) with a large excess of methylamine in the usual manner, the generated primary amines (**11**) *in situ* were easily acetylated with Ac_2O in pyridine to give the target new 3,4-disubstituted oxazolidin-2-ones (**3**). All steps were successfully completed and resulted in good yields (summarized in Scheme 1 and see Experimental). The structures of all these products were established by a spectroscopic and elemental analysis. The physical data and elemental analysis for the target new oxazolidin-2-ones (**3**) were summarized in Table 1. NMR spectroscopic data are also listed in Tables 2 and 3. Each reaction procedure for the preparation of the target compounds (**3a—e**) was recorded in detail as a typical example (**3d**; see Experimental).

Further molecular modification and the details of evaluations for antibacterial activity of the new linezolid mimetic compounds synthesized above will be described elsewhere.

Table 1. Physical and Analytical Data for 3,4-Disubstituted Oxazolidin-2-ones (**3**)



Compd. No	R^1	R^2	Yield[a] (%)	mp (°C)[b]	Formula	FAB-MS (positive)	IR(KBr) cm^{-1}	Anal. Calcd (Found)
3a	H	H	53	oil[c]	$C_{13}H_{16}N_2O_3 \cdot 0.2\ H_2O$	249[h]	1744 1655	61.99 6.56 11.12 (61.86 6.69 11.07)
3b	H	F	51	oil[d]	$C_{13}H_{15}N_2O_3F \cdot 0.5\ H_2O$	267[h]	1744 1655	56.72 5.86 10.18 (56.75 5.58 9.99)
3c	H	Ph	79	oil[e]	$C_{19}H_{20}N_2O_3 \cdot 0.3\ H_2O$	325[h]	1740 1655	69.20 6.30 8.49 (69.34 6.42 8.45)
3d	F		78	oil[f]	$C_{18}H_{24}N_3O_3F \cdot 0.1\ H_2O$	349[i]	1741 1655	61.56 6.95 11.96 (61.66 6.97 11.69)
3e	F		63	115–117[g]	$C_{17}H_{22}N_3O_4F \cdot 0.2\ H_2O$	351[i]	1747 1673	57.52 6.36 11.84 (57.40 6.38 12.09)

a) The yields (**3**) were based on the phthalimide derivatives (**10**). b) Purified by a silica gel column chromathography using as the solvent c) ~g) c) AcOEt, d) MeCN, e) AcOEt-MeCN, f) AcOEt-MeOH, g) AcOEt-MeOH
h) $(M+H)^+$ i) $(M)^+$

Table 2. ^{1}H-NMR Spectral Data for 3,4-Disubstituted Oxazolidin-2-ones (**3**)

No.	^{1}H-NMR (in DMSO-d_6) δ (ppm)
3a[a)]	1.93 (3H, s, Me), 3.25 (1H, ddd, *J* = 14.5, 9.0, 4.5 Hz, CHHNHCO), 3.55 (1H, ddd *J* = 14.5, 7.5, 3.0 Hz, CHHNHCO), 3.78 (1H, m, Oxaz H-4), 4.11 (1H, dd, *J* = 9.0, 6.0 Hz, Oxaz H-5), 4.26—4.30 (2H, m, Oxaz H-5 and CHHPh), 4.64 (1H, d, *J* = 5.0 Hz, CHHPh), 6.54 (1H, br s, NH), 7.30—7.41 (5H, m, Ar H)
3b	1.83 (3H, s, Me), 3.27 (2H, dd, *J* = 6.0, 4.5 Hz, CH_2NHCO), 3.65—3.67 (1H, m, Oxaz H-4), 4.04 (1H, dd, *J* = 9.0, 5.5 Hz, Oxaz H-5), 4.22 (1H, d, *J* = 15.5 Hz, CHHPh), 4.28 (1H, t, *J* = 9.0 Hz, Oxaz H-5), 4.56 (1H, d, *J* = 15.5 Hz, CHHPh), 7.18 (2H, t, *J* = 9.0 Hz, Ar H-3, H-5), 7.34 (2H, dd, *J* = 8.5, 5.5 Hz, Ar H-2, H-6), 7.98 (1H, t-like, NH)
3c	1.84 (3H, s, Me), 3.33 (2H, t, *J* = 5.0 Hz, CH_2NHCO), 3.70—3.73 (1H, m, Oxaz H-4), 4.06 (1H, t, *J* = 9.0 Hz, Oxaz H-5), 4.27 (1H, d, *J* = 5.5 Hz, CHHPh), 4.31 (1H, t, *J* = 9.0 Hz, Oxaz H-5), 4.64 (1H, d, *J* = 5.5 Hz, CHHPh), 7.35—7.39 (3H, m, Ar H), 7.46 (2H, t, *J* = 7.0 Hz, Ar H), 7.65—7.67 (4H, m, Ar H), 8.02 (1H, t, *J* = 6.0 Hz, NH)
3d	1.51—1.54 (2H, m, Ppd H-4), 1.62—1.66 (4H, m, Ppd H-3, H-5), 1.82 (3H, s, CH_3), 2.95 (4H, t, *J* = 5.0 Hz, Ppd H-2, H-6), 3.27 (2H, t, *J* = 6.0 Hz, CH_2NHCO), 3.64—3.67 (1H, m, Oxaz H-4), 4.00—4.04 (1H, m, Oxaz H-5), 4.18, 4.49 (each 1H, d, *J* = 5.5 Hz, CH_2Ph), 4.28 (1H, t, *J* = 9.0 Hz, Oxaz H-5), 6.99—7.04 (3H, m, Ar H), 7.98 (1H, t-like, *J* = 6.0 Hz, NH)
3e	1.82 (3H, s, Me), 2.99 (4H, t, *J* = 4.5 Hz, Mor H-2, H-6), 3.26—3.28 (2H, m, CH_2NHCO), 3.65—3.68 (1H, m, Oxaz H-4), 3.73 (4H, t, *J* = 4.5 Hz, Mor H-3, H-5), 4.02 (1H, dd, *J* = 8.5, 5.5 Hz, Oxaz H-5), 4.15, 4.50 (each 1H, d, *J* = 15.5 Hz, CH_2Ph), 4.29 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 6.99—7.08 (3H, m, Ar H), 7.98 (1H, t, *J* = 6.0 Hz, NH)

a) in $CDCl_3$

Table 3. ^{13}C-NMR Spectral Data for 3,4-Disubstituted Oxazolidin-2-ones (**3**)

No.	^{13}C-NMR (in DMSO-d_6) δ (ppm)
3a[a)]	22.8 (Me), 38.5 (CH_2NHCO), 46.2 (CH_2Ph), 54.3 (Oxaz C-4), 65.1 (Oxaz C-5), 128.0 (x2), 128.1, 128.9, 129.0 (Ar C-2—C-6), 135.8 (Ar C-1), 158.7 (Oxaz C=O), 171.3 (NHCOMe)
3b	22.4 (Me), 38.4 (CH_2NHCO), 44.3 (CH_2Ph), 53.5 (Oxaz C-4), 65.0 (Oxaz C-5), 115.3 (d, *J* = 22 Hz, Ar C-3, C-5), 129.7 (d, *J* = 8 Hz, Ar C-2, C-6), 132.6 (Ar C-1), 157.7 (Oxaz C=O), 161.5 (d, *J* = 243 Hz, Ar C-4), 170.0 (NHCOMe)
3c	22.5 (Me), 38.3 (CH_2NHCO), 44.7 (CH_2Ph), 53.6 (Oxaz C-4), 65.0 (Oxaz C-5), 126.5 (x2), 126.9 (x2), 127.4, 128.3 (x2), 128.9 (x2), 135.6, 139.4, 139.7 (Ar C), 157.7 (Oxaz C=O), 170.0 (NHCOMe)
3d	22.4 (Me), 23.6 (Ppd C-4), 25.6 (Ppd C-3, C-5), 38.3 (CH_2NHCO), 44.1 (CH_2Ph), 51.4 (Ppd C-2, C-6), 53.5 (Oxaz C-4), 64.9 (Oxaz C-5), 115.3 (d, *J* = 22 Hz, Ar C-2), 119.4 (d, *J* = 3 Hz, Ar C-5), 124.0 (d, *J* = 3 Hz, Ar C-6), 130.3 (d, *J* = 7 Hz, Ar C-1), 140.1 (d, *J* = 9 Hz, Ar C-4), 154.7 (d, *J* = 245 Hz, Ar C-3), 157.7 (Oxaz C=O), 169.9 (NHCOMe)
3e	22.4 (Me), 38.3 (CH_2NHCO), 44.1 (CH_2Ph), 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* = 22 Hz, Ar C-2), 119.4 (d, *J* = 3 Hz, Ar C-5), 124.1 (d, *J* = 3 Hz, Ar-C-6), 130.9 (d, *J* = 7 Hz, Ar C-1), 138.9 (d, *J* = 8 Hz, Ar C-4), 154.7 (d, *J* = 244 Hz, Ar C-3), 157.7 (Oxaz C=O), 169.9 (NHCOMe)

a) in $CDCl_3$

EXPERIMENTAL

The melting points are uncorrected. The IR spectra were measured with a Shimadzu FT/IR-8100 spectrometer. The ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL JNM A-500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) at 35 °C. The chemical shifts are expressed as δ ppm downfield from an internal tetramethylsilane (TMS) signal. The signal assignments were confirmed with ^{1}H-^{1}H two-dimensional (2D) correlation spectroscopy (COSY), ^{1}H-^{13}C heteronuclear multiple quantum coherence (HMQC), ^{1}H-^{13}C heteronuclear multiple-bond connectivity (HMBC) spectra. FAB-MS spectra were obtained with a JEOL JMS-HX110 mass spectrometer. The following abbreviations in the brackets were used for the piperidine ring (Ppd), morpholine ring (Mor), phthalimide ring (PhI) and for the oxazolidinone ring (Oxaz), respectively.

3-Fluoro-4-(1-piperidinyl)benzoic acid (5d)

This compound was prepared according to the procedure by A-H Khuthier *et al*.[9]

A mixture of 3,4-difluorobenzoic acid (15 g, 94.8 mmol) and piperidine (27 g, 318 mmol) in DMSO (80 mL) was stirred for 26 h at 110—115 °C under a nitrogen atmosphere. The reaction mixture was diluted with water and acidified (pH 3) with 1 *N* hydrochloric acid and the resulting precipitated material was collected by filtration. The recrystallization of the isolated product from EtOH gave 3-fluoro-4-piperidinebenzoic acid (**5d**) in 68.0 % yield (14.38 g), mp 201—202 °C (decomp.). IR (KBr) cm^{-1}: 2940, 2826, 1698, 1615. FAB-MS (positive) *m/z*: 223 (M^+). ^{1}H-NMR (DMSO-d_6) *δ:* 1.55—1.58 (2H, m, Ppd H-4), 1.58—1.67 (4H, m, Ppd H-3, H-5), 3.10 (4H, t, *J* = 5.0 Hz, Ppd H-2, H-6), 7.05 (1H, t, *J* = 8.5 Hz, Ar H-2), 7.54 (1H, dd, *J* = 4.0, 2.0 Hz, Ar H-5), 7.66 —7.68 (1H, m, Ar H-6), 12.5 (1H, br, COOH). ^{13}C-NMR (DMSO-d_6) *δ:* 23.6 (Ppd C-4), 25.4 (Ppd C-3, C-5), 50.6 (Ppd C-2, C-6), 116.6 (d, *J* = 22 Hz, Ar C-5), 118.3 (*J* = 3 Hz, Ar C-2), 123.1 (*J* = 7 Hz, Ar C-1), 126.4 (*J* = 3 Hz, Ar C-6), 144.2 (d, *J* = 8 Hz, Ar C-4), 153.5 (d, *J* = 244 Hz, Ar C-3), 166.2 (COOH). *Anal*. Calcd for $C_{12}H_{14}NO_2F \cdot 0.1\ H_2O$: C, 64.04; H, 6.36; N, 6.22. Found: C, 64.05; H, 6.18; N, 6.16.

3-Fluoro-4-(morpholinyl)benzoic acid (5e)

Compound (**5e**) was prepared by the same procedure as described for (**5d**). The yield was 79.0 %, mp 218—219 °C (decomp: EtOH). IR (KBr) cm^{-1}: 1665, 1617. FAB-MS (positive) *m/z*: 225 (M^+). ^{1}H-NMR (DMSO-d_6) *δ:* 3.13 (4H, t, *J* = 4.5 Hz, Mor H-2, H-6), 3.75 (4H, t, *J* = 4.5 Hz, Mor H-3, H-5), 7.08 (1H, t, *J* = 9.0 Hz, Ar H-2), 7.56—7.59 (1H, m, Ar H-5), 7.70 (1H, dd, *J* = 7.5, 2.0 Hz, Ar H-6), 12.5—13.5 (1H, br, COOH). ^{13}C-NMR (DMSO-d_6) *δ:* 49.7 (Mor C-2, C-6), 65.9 (Mor C-3, C-5), 116.6 (d, *J* = 22 Hz, Ar C-5), 118.1 (*J* = 3 Hz, Ar C-2), 123.8 (*J* = 7 Hz, Ar C-1), 126.4 (*J* = 2 Hz, Ar C-6), 143.2 (*J* = 8 Hz, Ar C-4), 153.5 (d, *J* = 244 Hz, Ar C-3), 166.1 (COOH). *Anal*. Calcd for $C_{11}H_{12}NO_3F$: C, 58.66; H, 5.37; N, 6.22. Found: C, 58.48; H, 5.36; N, 6.06.

Coupling reaction of (5d) with DL-serine methyl ester hydrochloride. (Preparation of the compound 6d)

2-[3-Fluoro-4-(1-piperidinyl)benzoylamino]-3-hydroxypropionic acid methyl ester (6d)

1-Hydroxy-1*H*-benzotriazole monohydrate (HO-Bt) (4.15 g, 27.1 mmol) in DMF (20 mL) and *N*-methylmorpholine (2.74 g, 27.1 mmol) was added to an ice cooled solution of 3-fluoro-4-piperidinebenzoic acid (**5d**) (5.48 g, 24.6 mmol) and DL-serine methyl ester hydrochloride (4.22 g, 27.1 mmol) in DMF (80 mL). 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCI) (5.20 g, 27.1 mmol) was added to the above mixture, and the resulting mixture was then allowed to stand at 0 °C for 10 min and then kept overnight at rt with stirring. The reaction mixture was evaporated and the residue was combined with CH_2Cl_2 (80 mL). The resulting mixture was extracted with 1*N*-hydrochloric acid and the extracted aqueous layer was washed with CH_2Cl_2 and the pH was normalized with K_2CO_3, and then the compound was re-extracted with CH_2Cl_2. The CH_2Cl_2 layer extract was washed with water and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the product was purified by chromatography on silica gel column with AcOEt as an eluate to afford the compound (**6d)** in 62.3 % (4.98 g), mp 82—83 °C. IR (KBr) cm^{-1}: 3434, 3299, 1750, 1636. FAB-MS (positive) *m/z*: 324 $(M)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 1.54—1.58 (2H, m, Ppd H-4), 1.63—1.67 (4H, m, Ppd H-3, H-5), 3.08 (4H, t, *J* = 5.0 Hz, Ppd H-2, H-6), 3.64 (3H, s, Me), 3.78 (2H, t, *J* = 6.0 Hz, C<u>H</u>$_2$OH), 4.52 (1H, dd, *J* = 13.0, 5.5 Hz, CONHC<u>H</u>CH$_2$), 4.99 (1H, t, *J* = 6.0 Hz, OH), 7.06 (1H, t, *J* = 9.0 Hz, Ar H-5), 7.63—7.68 (2H, m, Ar H-2, H-6), 8.39 (1H, d, *J* = 7.0 Hz, NH). ^{13}C-NMR (DMSO-d_6) *δ:* 23.6 (Ppd C-4), 25.4 (Ppd C-3, C-5), 50.8 (Ppd C-2, C-6), 51.7 (Me), 55.5 (CONH<u>C</u>HCH$_2$), 61.0 (CH$_2$OH), 115.0 (d, *J* = 23 Hz, Ar C-2), 118.3 (d, *J* = 3 Hz, Ar C-5), 124.3 (d, *J* = 2 Hz, Ar C-6), 126.3 (d, *J* =7 Hz, Ar C-1), 143.2 (d, *J* = 8 Hz, Ar C-4), 153.7 (d, *J* = 243 Hz, Ar C-3), 165.0 (NHCO), 171.0 (<u>C</u>OOMe). *Anal*. Calcd for $C_{16}H_{21}N_2O_4F$: C, 59.25; H, 6.53; N, 8.64. Found: C, 59.41; H, 6.73; N, 8.61.

2-Benzoylamino-3-hydroxypropionic acid methyl ester (6a)

A solution of benzoyl chloride (1.8 g, 12.8 mmol) in CH_2Cl_2 (20 mL) was added while stirring into a solution of DL-serine methyl ester hydrochloride (2.0 g, 12.9 mmol) and triethylamine (2.6 g, 25.7 mmol) in CH_2Cl_2 (20 mL). The solution was stirred for 30 min and concentrated under reduced pressure. The residue was triturated with Et_2O and the solvent was dried over anhydrous $MgSO_4$. The concentration of the solvent under reduced pressure gave 2.76 g of **6a** (95.8 %) as an oil. IR (KBr) cm^{-1}: 3410, 1744, 1647. FAB-MS (positive) *m/z*: 224 $(M + H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.66 (3H, s, Me), 3.81 (2H, t, *J* = 6.0 Hz, C<u>H</u>$_2$OH), 4.54—4.58 (1H, m, C<u>H</u>NHCO), 5.02 (1H, t, *J* = 6.0 Hz, OH), 7.48 (2H, t, *J* = 8.0 Hz, Ar H-2, H-6), 7.56 (1H, t, *J* = 7.5 Hz, Ar H-4), 7.90 (2H, d, *J* = 7.0 Hz, Ar H-3, H-5), 8.51 (1H, d, *J* = 7.0 Hz, NH). ^{13}C-NMR (DMSO-d_6) *δ:* 51.8 (Me), 55.6 (<u>C</u>HNHCO), 61.0 (CH$_2$OH), 127.3 (Ar C-3, C-5), 128.2

(Ar C-2, C-6), 131.4 (Ar C-4), 133.7 (Ar C-1), 166.5 (COPh), 171.0 (COOMe). *Anal*. Calcd for $C_{11}H_{13}NO_4 \cdot 0.2\ H_2O$: C, 58.25; H, 5.95; N, 6.18. Found: C, 58.49; H, 6.05; N, 6.06.

2-(4-Fluorobenzoylamino)-3-hydroxypropionic acid methyl ester (6b)

This compound was prepared with 4-fluorobenzoyl chloride (10.19 g, 64.3 mmol) and DL-serine methyl ester hydrochloride (10.0 g, 64.3 mmol) using essentially the same procedure as described for (**6a**). The yield was 73.0 %, mp 62—65 °C (benzene). IR (KBr) cm^{-1}: 3328, 3299, 1601, 1510. FAB-MS (positive) *m/z*: 242 $(M + H)^+$. ^{1}H-NMR ($CDCl_3$) *δ:* 3.17 (1H, br s, OH), 3.79 (3H, s, Me), 4.00 (1H, dd, *J* = 11.0, 3.0 Hz, CHHOH), 4.06 (1H, dd, *J* = 11.0, 4.0 Hz, CHHOH), 4.81—4.84 (1H, m, CHNH), 7.08 (2H, t, *J* = 8.5 Hz, Ar H-3, H-5), 7.18 (1H, br d, *J* = 7.0 Hz, NH), 7.81—7.83 (2H, m, Ar H-2, H-6). ^{13}C-NMR ($CDCl_3$) *δ:* 52.8 (Me), 55.2 (CHNHCO), 63.2 (CH_2OH), 115.6 (d, *J* = 23 Hz, Ar C-3, C-5), 129.6 (d, *J* = 8 Hz, Ar C-2, C-6), 164.0 (Ar C-4), 166.0 (Ar C-1), 166.7 (COPh), 171.0 (COOMe). *Anal*. Calcd for $C_{11}H_{12}NO_4F$: C, 54.77; H, 5.01; N, 5.81. Found: C, 54.69; H, 5.02; N, 5.76.

2-[4-(Phenyl)benzoylamino]-3-hydroxypropionic acid methyl ester (6c)

This compound was prepared with 4-phenylbenzoylchloride (10.0 g, 46.3 mmol) and DL -serine methyl ester hydrochloride (7.18 g, 46.1 mmol) by the same procedure as described for (**6a**). The yield was 83.3 %, mp 151—152 °C (benzene). IR (KBr) cm^{-1}: 3426, 3376, 1754, 1636. FAB-MS (positive) *m/z*: 300 $(M + H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.67 (3H, s, Me), 3.82—3.84 (2H, m, CH_2OH), 4.57—4.61 (1H, m, CHNH), 5.04 (1H, t, *J* = 6.0 Hz, OH), 7.41 (1H, t, *J* = 7.0 Hz, Ar H), 7.48—7.52 (2H, m, Ar H), 7.74 (2H, dd, *J* = 12.0, 8.5 Hz, Ar H), 7.80 (2H, d, *J* = 8.5 Hz, Ar H), 8.00 (2H, d, *J* = 8.5 Hz, Ar H), 8.58 (1H, d, *J* = 7.0 Hz, NH). ^{13}C-NMR (DMSO-d_6) *δ:* 51.8 (Me), 55.6 (CHNHCO), 61.0 (CH_2OH), 126.4 (x2), 126.8 (x 2), 128.0 (x 3), 128.9 (x 2), 132.5, 139.1, and 143.0 (Ar C), 166.1 (COPh), 171.0 (COOMe). *Anal*. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.33; H, 5.84; N, 4.66.

2-[3-Fluoro-4-(4-morpholinyl)benzoylamino]-3-hydroxypropionic acid methyl ester (6e)

This compound was prepared with 3-fluoro-4-(morpholinyl)benzoic acid (**5e**) (5.52 g, 24.5 mmol) and DL-serine methyl ester hydrochloride (4.22 g, 27.1 mmol) using the same procedure as that described for (**6d**). The yield was 59.2 %. IR (KBr) cm^{-1}: 3466, 3302, 1744. FAB-MS (positive) *m/z*: 327 $(M + H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.11 (4H, t, *J* = 4.5 Hz, Mor H-2, H-6), 3.65 (3H, s, Me), 3.75 (4H, t, *J* = 4.5 Hz, Mor H-3, H-5), 3.79 (2H, t, *J* = 6.0 Hz, CH_2OH), 4.52 (1H, dd, *J* = 12.0, 5.0 Hz, CHNHCO), 5.00 (1H, t, *J* = 6.0 Hz, CH_2OH), 7.09 (1H, t, *J* = 9.0 Hz, Ar H-5), 7.67—7.70 (2H, m, Ar H-2, H-6), 8.44 (1H, d, *J* = 6.0 Hz, NH). ^{13}C-NMR (DMSO-d_6) *δ:* 49.9 (Mor C-2, C-6), 51.7 (Me), 55.6 (CONHCH), 61.0 (CH_2OH), 65.0 (Mor C-3, C-5), 115.1 (d, *J* = 22 Hz, Ar C-2), 118.0 (*J* = 3 Hz, Ar C-5), 124.4 (*J* = 3 Hz, Ar C-6), 126.9 (*J* = 6 Hz, Ar C-1), 142.2 (*J* = 8 Hz, Ar C-4), 153.7 (d, *J* = 244 Hz, Ar C-3), 164.9 (NHCO), 170.9 (COOMe). *Anal*. Calcd for $C_{15}H_{19}N_2O_5F$: C, 55.21; H, 5.87; N, 8.58. Found: C, 55.02; H, 5.82; N, 8.48.

Preparation of 4-hydroxymethyl derivatives (7d)

2-{[3-Fluoro-4-(1-piperidinyl)phenyl]methylamino}propane-1,3-diol (7d)

Ester (**6d**) (5.9 g, 18.2 mmol) was added with stirring to a solution of sodium bis(2-methoxyethoxy)aluminium hydride (103.8 mmol) in anhydrous benzene (100 mL). The reaction mixture was refluxed for 4 h and carefully decomposed with 30 mL of water. The benzene layer was separated and the hydroxide precipitate was washed with benzene. The solution were combined and dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo* to afford a crude product. The purification of the residue by chromatography on silica gel column afforded the compound (**7d**) in 74.0 % (3.8 g). The solvents for elution for the chromatography were used initially AcOEt, MeCN, and then 50 % (V/V) MeCN -EtOH, mp 62—67 °C. IR (KBr) cm^{-1}: 3403, 3287. FAB-MS (positive) *m/z*: 305 $(M+Na)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 1.49—1.54 (2H, m, Ppd H-4), 1.62—1.66 (4H, m, Ppd H-3, H-5), 2.52 [1H, t, *J* = 15.5 Hz, C<u>H</u>$(CH_2OH)_2$], 2.92 (4H, t, *J* = 5.0 Hz, Ppd H-2, H-6), 3.32—3.42 (4H, m, C<u>H</u>$_2$OH x 2), 3.39 (1H, br s, NH), 3.70 (2H, s C<u>H</u>$_2$Ph), 4.34 (2H, br s, CH_2O<u>H</u> x 2), 6.93 (1H, t, *J* = 8.5 Hz, Ar H-5), 7.02—7.03 (1H, m, Ar H-6), 7.08 (1H, dd, *J* = 14.0, 2.0 Hz, Ar H-2). ^{13}C-NMR (DMSO-d_6) *δ:* 23.7 (Ppd C-4), 25.6 (Ppd C-3, C-5), 49.7 (<u>C</u>H$_2$Ph), 51.6 (Ppd C-2, C-6), 60.1 [<u>C</u>H$(CH_2OH)_2$], 61.0 (<u>C</u>H$_2$OH x 2), 115.1 (d, *J* = 21 Hz, Ar C-2), 118.9 (d, *J* = 3 Hz, Ar C-5), 123.7 (d, *J* = 3 Hz, Ar C-6), 125.8 (d, *J* = 6 Hz, Ar C-1), 139.2 (d, *J* = 9 Hz, Ar C-4), 154.8 (d, *J* = 244 Hz, Ar C-3). *Anal*. Calcd for $C_{15}H_{23}N_2O_2F \cdot 0.1$ H_2O: C, 63.4; H, 8.23; N, 9.86. Found: C, 63.49; H, 8.36; N, 9.83.

Compounds **(7a—c**, and **7e)** were also prepared according to the above procedure. The data of the products are shown below.

2-(Phenylmethylamino)propane-1,3-diol (7a)

The yield was 79.2 %, mp 72—73 °C (Et_2O). IR (KBr) cm^{-1}: 3299. FAB-MS (positive) *m/z*:182 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) *δ:* 2.43 (3H, br s, N<u>H</u> and O<u>H</u> x 2), 2.78 [1H, dt, *J* = 9.5, 5.0 Hz, C<u>H</u>$(CH_2OH)_2$], 3.57 (2H, dd, *J* = 11.0, 5.0 Hz, C<u>H</u>HOH x 2), 3.70 (2H, dd, *J* = 11.0, 5.0 Hz, CH<u>H</u>OH x 2), 3.81 (2H, s, C<u>H</u>$_2$Ph), 7.31 (5H, s, Ar H). ^{13}C-NMR ($CDCl_3$) *δ:* 51.2 (<u>C</u>H$_2$Ph), 59.0 [<u>C</u>H(CH_2OH_2)], 62.2 (CH_2OH x 2), 127.2 (Ar C-4), 128.1 (Ar C-2, C-6), 128.5 (Ar C-3, C-5), 140.0 (Ar C-1). *Anal*. Calcd for $C_{10}H_{15}NO_2 \cdot$ 0.1 H_2O: C, 65.62; H, 8.37; N, 7.65. Found: C, 65.68; H, 8.29; N, 7.62.

2-[(4-Fluorophenyl)methylamino]propane-1,3-diol (7b)

The yield was 31.0 %, mp 94—94.5 °C (benzene). IR (KBr) cm^{-1}: 3328, 3299, 1601. FAB-MS (positive) *m/z*: 200 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 2.53 [1H, t, *J* = 5.5 Hz, C<u>H</u>$(CH_2OH)_2$], 3.30 (1H, br s, NH), 3.35, 3.42 (each 2H, dd, *J* = 10.5, 5.0 Hz, C<u>H</u>$_2$OH x 2), 3.74 (2H, s, C<u>H</u>$_2$Ph), 4.36 (2H, br s, OH x 2), 7.11 (2H, t, *J* = 9.0 Hz, Ar H-3, H-5), 7.35–7.38 (2H, m, Ar H-2, H-6). ^{13}C-NMR ($CDCl_3$) *δ:* 49.9 (<u>C</u>H$_2$Ph),

60.2 [CH(CH_2OH)$_2$], 61.1 (CH_2OH x 2), 114.6 (d, J = 23.0 Hz, Ar C-3, C-5), 129.6 (d, J = 8.0 Hz, Ar C-2, C-6), 137.5 (d, J = 3 Hz, Ar C-1), 160.9 (d, J = 243 Hz, Ar C-4). *Anal*. Calcd for $C_{10}H_{14}NO_2F$: C, 60.29; H, 7.08; N,7.03. Found: C, 60.51; H, 7.19; N, 6.93.

2-[(4-(Biphenyl-4-yl)methylamino)propane-1,3-diol (7c)

The yield was 61.4 %, mp 128—129 °C (benzene). IR (KBr) cm^{-1}: 3333, 3292. FAB-MS (positive) *m/z*: 258 (M + H)$^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 2.57—2.62 [1H, m, CH(CH_2OH)$_2$], 3.31 (1H, br s, NH), 3.39, 3.46 (each 2H, dd, J = 10.5, 5.5 Hz, CH_2OH), 3.82 (2H, s, CH_2Ph), 4.39 (2H, br s, OH x 2), 7.32—7.36 (1H, m, Ar H), 7.42—7.47 (4H, m, Ar H), 7.60, 7.65 (each 2H, d, J = 7.0 Hz, Ar H). ^{13}C-NMR ($CDCl_3$) *δ:* 50.4 (CH_2Ph), 60.2 [CH(CH_2OH)$_2$], 61.1 (CH_2OH x 2), 126.3 (x2), 126.4 (x2), 127.1, 128.3 (x2), 128.8 (x2), 138.3, 140.1, and 140.6 (Ar C). *Anal*. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.67; H, 7.42; N, 5.31.

2-{[3-Fluoro-4-(4-morpholinyl)phenyl]methylamino}propane-1,3-diol (7e)

The yield was 57.5 %, mp 87—91 °C (benzene). IR (KBr) cm^{-1}: 3391. FAB-MS (positive) *m/z*: 307 (M + Na)$^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 2.52 [1H, t, J = 5.5 Hz, CH(CH_2OH)$_2$], 2.97 (4H, t, J = 4.5 Hz, Mor H-2, H-6), 3.29 (1H, br s, NH), 3.34, 3.41 (each 2H, dd, J = 10.5, 5.5 Hz, CH_2OH), 3.70 (2H, s, CH_2Ph), 3.73 (4H, t, J = 5.0 Hz, Mor H-3, H-5), 4.36 (2H, br s, OH x 2), 6.95 (1H, t, J = 8.5 Hz, Ar H-5), 7.05—7.07 (1H, m, Ar H-6), 7.11—7.14 (1H, m, Ar H-2). ^{13}C-NMR (DMSO-d_6) *δ:* 49.6 (CH_2Ph), 50.6 (Mor C-2, C-6), 60.0 (CHCH_2OH), 61.0 (CH_2OH x 2), 66.1 (Mor C-3, C-5), 115.3 (d, J = 20 Hz, Ar C-2), 118.5 (d, J = 3 Hz, Ar C-5), 123.9 (d, J = 3 Hz, Ar C-6), 136.2 (d, J = 6 Hz, Ar C-1), 138.0 (d, J = 8 Hz, Ar C-4), 154.7 (d, J = 244 Hz, Ar C-3). *Anal*. Calcd for $C_{14}H_{21}N_2O_3 \cdot 0.1\ H_2O$: C, 58.77; H, 7.47; N, 9.79. Found: C, 58.68; H, 7.48; N, 9.80.

Cyclization to oxazolidin-2-one (8d) with $(EtO)_2C=O$

3-[3-Fluoro-4-(1-piperidinyl)phenylmethyl]-4-hydroxymethyloxazolidin-2-one (8d)

A solution of diethyl carbonate (1.79 g, 15.2 mmol) and the aminoalcohol (**7d**; 3.63 g, 12.9 mmol) in anhydrous benzene (80 mL) was heated in an oil bath (110 °C) with stirring for 30 min. After the addition of sodium methoxide (0.01 g), the resulting mixture was then again heated to 140 °C for 30 min with stirring, and then kept the temperature at 120 °C for 2 h. The reaction mixture was combined with MeCN and the precipitated insoluble material was filtered off. The filtrate was concentrated *in vacuo* and the resulting residue was purified by a silica gel column using AcOEt-hexane as a solvent to afford the compound (**8d**) in 71.0 % (2.81 g). An analytical sample was obtained by recrystallization from AcOEt, mp 98—99 °C. IR (KBr) cm^{-1}: 3428, 1719. FAB-MS (positive) *m/z*: 308 (M)$^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 1.52—1.53 (2H, m, Ppd H-4), 1.54—1.656 (4H, m, Ppd H-3, H-5), 2.94 (4H, t, J = 5.0 Hz Ppd H-2, H-6), 3.39—3.43 (1H, m, CHHOH), 3.53—3.57 (1H, m, CHHOH), 3.61—3.66 (1H, m, Oxaz H-4), 4.06—4.09

(1H, m, Oxaz H-5), 4.11 (1H, d, *J* = 15.0 Hz, C<u>H</u>HPh), 4.30 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.49 (1H, d, *J* = 15.0 Hz, CH<u>H</u>Ph), 4.97 (1H, t, *J* = 5.5 Hz, OH), 6.97—7.05 (3H, m, Ar H). ^{13}C-NMR (DMSO-d_6) *δ:* 23.6 (Ppd C-4), 25.6 (Ppd C-3, C-5), 44.2 (<u>C</u>H_2Ph), 51.4 (Ppd C-2, C-6), 55.2 (Oxaz C-4), 59.4 (CH_2OH), 64.2 (<u>C</u>H_2Ph), 115.2 (d, *J* = 21 Hz, Ar C-2), 119.3 (d, *J* = 3 Hz, Ar C-5), 123.9 (d, *J* = 2 Hz, Ar C-6), 130.7 (d, *J* = 6 Hz, Ar C-1), 140.0 (d, *J* = 8 Hz, Ar C-4), 154.7 (d, *J* =245 Hz, Ar C-3), 157.9 (C=O). *Anal*. Calcd for $C_{16}H_{21}N_2O_3F$: C, 62.32; H, 6.86; N, 9.08. Found: C, 62.18; H, 6.83; N, 9.04.

Compounds (**8a—c**, and **8e**) were also obtained by the above procedure. The results for the products are shown below.

3-Phenylmethyl-4-hydroxymethyloxazolidin-2-one (8a)

The yield was 56.6 %, mp 66—68 °C (SiO_2/AcOEt-EtOH). IR (KBr) cm^{-1}: 3422, 1721. FAB-MS (positive) *m/z*: 208 (M + H)$^+$. ^{1}H-NMR ($CDCl_3$) *δ:* 2.84 (1H, br s, OH), 3.52—3.55 (1H, m, C<u>H</u>HOH), 3.68—3.74 (2H, m, CH<u>H</u>OH and Oxaz H-4), 4.24—4.32 (3H, m, C<u>H</u>HPh and Oxaz H-5), 4.70 (1H, d, *J* = 4.5 Hz, CH<u>H</u>Ph), 7.26—7.36 (5H, m, Ar H). ^{13}C-NMR ($CDCl_3$) *δ:* 46.4 (<u>C</u>H_2Ph), 55.9 (Oxaz C-4), 60.5 (CH_2OH), 64.5 (Oxaz C-5), 128.0 (Ar C-2, C-4, C-6), 128.9 (Ar C-3, C-5), 136.1 (Ar C-1), 159.1 (Oxaz C=O). *Anal*. Calcd for $C_{11}H_{13}NO_3 \cdot 0.1\ H_2O$: C, 63.21; H, 6.37; N, 6.70. Found: C, 63.28; H, 6.55; N, 6.66.

3-[(4-Fluorophenyl)methyl]-4-hydroxymethyloxazolidin-2-one (8b)

The yield was 44.5 %, mp 105—107 °C (SiO_2/AcOEt-EtOH). IR (KBr) cm^{-1}: 3461, 1728. FAB-MS (positive) *m/z*: 226 (M + H)$^+$. ^{1}H-NMR ($CDCl_3$) *δ:* 2.42 (1H, br s, OH), 3.57 (1H, dd, *J* = 11.0, 3.0 Hz, C<u>H</u>HOH), 3.69—3.75 (2H, m, CH<u>H</u>OH and Oxaz H-4), 4.22 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.27, 4.66 (each 1H, d, *J* = 15.0 Hz, C<u>H</u>$_2$Ph), 4.32 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 7.04 (2H, t, *J* = 8.5 Hz, Ar H-3, H-5), 7.26—7.35 (2H, m, Ar H-2, H-6). ^{13}C-NMR ($CDCl_3$) *δ:* 45.8 (<u>C</u>H_2Ph), 55.9 (Oxaz C-4), 60.9 (<u>C</u>H_2OH), 64.5 (Oxaz C-5), 115.8 (d, *J* = 22.0 Hz, Ar C-3, C-5), 129.9 (d, *J* = 8.0 Hz, Ar C-2, C-6), 131.9 (d, *J* = 3 Hz, Ar C-1), 159.0 (Oxaz C=O) 162.5 (d, *J* = 246 Hz, Ar C-4), *Anal*. Calcd for $C_{11}H_{12}NO_3F$: C, 58.66; H, 5.37; N, 6.22. Found: C, 58.86; H, 5.46; N, 6.16.

3-[4-(Biphenyl-4-yl)methyl]-4-hydroxymethyloxazolidin-2-one (8c)

The yield was 71.5 %, mp 128—129 °C (SiO_2/AcOEt-EtOH). IR (KBr) cm^{-1}: 3422, 1717. FAB-MS (positive) *m/z*: 284 (M + H)$^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.43—3.47, 3.59—3.62 (each 1H, m, C<u>H</u>$_2$OH), 3.68—3.70 (1H, m, Oxaz H-4), 4.12 (1H, dd, *J* = 8.5, 6.0 Hz, Oxaz H-5), 4.25 (1H, d, *J* = 8.5 Hz, C<u>H</u>HPh), 4.33 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.64 (1H, d, *J* = 5.5 Hz, CH<u>H</u>Ph), 5.02 (1H, t, *J* = 5.0 Hz, CH_2O<u>H</u>), 7.35—7.41 (3H, m, Ar H), 7.45—7.48 (2H, m, Ar H), 7.64—7.67 (4H, m, Ar H). ^{13}C-NMR ($CDCl_3$) *δ:* 44.8 (<u>C</u>H_2Ph), 55.3 (Oxaz C-4), 59.4 (CH_2OH), 64.3 (Oxaz C-5), 126.5 (x2), 126.8 (x2), 127.3,

128.3 (x2), 128.8 (x2), 135.9, 139.3, and 139.8 (Ar C), 158.0 (Oxaz C=O). *Anal*. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.95; H, 6.16; N, 4.89.

3-[3-Fluoro-4-(4-morpholinyl)phenyl]methyl]-4-hydroxymethyloxazolidin-2-one (8e)

The yield was 57.1 %, mp 117—119 °C (SiO_2/AcOEt). IR (KBr) cm^{-1}: 3424, 1717. FAB-MS (positive) *m/z*: 310 $(M)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 2.99 (4H, t, *J* = 5.0 Hz, Mor H-2, H-6), 3.39—3.43 (1H, m, CHHOH), 3.53—3.57 (1H, m, CHHOH), 3.64—3.65 (1H, m, Oxaz H-4), 3.73 (4H, t, *J* = 5.0 Hz, Mor H-3, H-5), 4.08 (2H, dd, *J* = 8.5, 6.0 Hz, Oxaz H-5), 4.13, 4.50 (each 1H, d, *J* = 15.5 Hz, CH_2Ph), 4.30 (1H, t, *J* = 8.5, Hz, Oxaz H-5), 4.97 (1H, t, *J* = 5.0 Hz, CH_2OH), 6.99—7.09 (3H, m, Ar H). ^{13}C-NMR (DMSO-d_6) *δ:* 44.2 (CH_2Ph), 50.4 (Mor C-2, C-6), 55.2 (Oxaz C-4), 59.4 (CH_2OH), 64.2 (Oxaz C-5), 66.1 (Mor C-3, C-5), 115.3 (d, *J* = 22 Hz, Ar C-2), 118.9 (d, *J* = 4 Hz, Ar C-5), 124.0 (d, *J* = 2 Hz, Ar C-6), 131.3 (d, *J* = 6 Hz, Ar C-1), 138.8 (d, *J* = 8 Hz, Ar C-4), 154.6 (d, *J* = 245 Hz, Ar C-3), 157.9 (Oxaz C=O). *Anal*. Calcd for $C_{15}H_{19}N_2O_4F$: C, 58.06; H, 6.17; N, 9.03. Found: C, 57.93; H, 6.25; N, 8.93.

Preparation of the compound (10d) from the 4-hydroxymethyl derivatives (8d)

2-{3-[3-Fluoro-4-(1-piperidinyl)phenylmethyl]-2-oxooxazolidin-4-ylmethyl}-1*H*-isoindole-1,3(2*H*)-dione (10d)

Methanesulfonyl chloride (0.94 g, 8.2 mmol) was added in a dropwise manner to a mixture of (**8d**) (2.1 g, 6.8 mmol) and triethylamine (0.83 g, 8.2 mmol) in 80 mL of CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 40 min and then kept at rt for 3 h. Additional methanesulfonyl chloride (1.41 g, 12.3 mmol) and triethylamine (1.25 g, 12.4 mmol) was added to this mixture, and thereafter the resulting mixture was stirred for 2 h. The reaction mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2. AcOEt was added to the combined extracts. The solution was dried over $MgSO_4$ and then concentrated *in vacuo* to give an oily residue (**9d**). This material was dissolved into 100 mL of acetonitrile, and 1 mL of water and potassium phthalimide (3.79 g, 20.5 mmol) was added then to this solution. This mixture was heated to reflux for 4 d. After filtration of insoluble material, the filtrate was concentrated *in vacuo* and the residue was again dissolved into AcOEt, washed with water, and then 5 % Na_2CO_3. After drying over $MgSO_4$, the solution was concentrated *in vacuo* to obtain a solid material, which was purified by silica gel column using AcOEt/hexane as solvent. The phthalimide derivative (**10d**) was obtained in 67.8 % (2.02 g). An analytical sample was recrystallized from MeCN, mp 166—167 °C. IR (KBr) cm^{-1}: 1771, 1740, 1713. FAB-MS (positive) *m/z*: 437 $(M)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 1.51—1.54 (2H, m, Ppd H-4), 1.62—1.66 (4H, m, Ppd H-3, H-5), 2.94 (4H, t, *J* = 5.5 Hz, Ppd H-2, H-6), 3.81—3.83 (2H, m, CH_2-PhI), 3.92—3.94 (1H, m, Oxaz H-4), 4.17 (1H, dd, *J* = 9.0, 4.5 Hz, Oxaz H-5), 4.29, 4.52 (each 1H, d, *J* = 15.5 Hz, CH_2Ph), 4.33 (1H, d, *J* = 9.0 Hz, Oxaz H-5), 7.01—7.05 (3H, m, Ar H), 7.81—7.89 (4H, m, PhI). ^{13}C-NMR (DMSO-d_6) *δ:* 23.6 (Ppd C-4), 25.6 (Ppd C-3, C-5), 38.1

(CH_2PhI), 44.4 (CH_2Ph), 51.3 (Ppd C-2, C-6), 53.1 (Oxaz C-4), 65.8 (Oxaz C-5), 115.3 (d, *J* = 22 Hz, Ar C-2), 119.3 (d, *J* = 3 Hz, Ar C-5), 122.8, 123.1 (PhI C-3, C-6), 124.0 (d, *J* = 3 Hz, Ar C-6), 130.1 (d, *J* = 7 Hz, Ar C-1), 131.4 (PhI C-2a, C-6a), 134.1 and 134.5 (PhI C-4, C-5), 140.1 (d, *J* = 8 Hz, Ar C-4), 154.7 (d, *J* = 245 Hz, Ar C-3), 157.4 (Oxaz C=O), 168.1 (x 2) (PhI C=O). *Anal*. Calcd for $C_{24}H_{24}N_3O_4F$: C, 65.89; H, 5.53; N, 9.61. Found: C, 65.71; H, 5.55; N, 9.76.

Compounds (**10a—c**, and **10e**) were also prepared by above procedure. The data for the products are shown below.

2-[2-Oxo-3-(phenylmethyl)oxazolidin-4-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione (10a)

The yield was 80.2 %, mp 167.5—168.5 °C (MeCN). IR (KBr) cm^{-1}: 1775, 1742, 1721. FAB-MS (positive) *m/z*: 337 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.78—3.86 (2H, m, CH_2-PhI), 3.90—3.94 (1H, m, Oxaz H-4), 4.19 (1H, dd, *J* = 9.0, 4.5 Hz, Oxaz H-5), 4.33 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.38 (1H, d, *J* = 15.5 Hz, CHHPh), 4.62 (1H, d, *J* = 15.5 Hz, CHHPh), 7.28—7.37 (5H, m, Ar H), 7.82—7.89 (4H, m, PhI). ^{13}C-NMR (DMSO-d_6) *δ:* 38.1 (CH_2-PhI), 45.3 (CH_2Ph), 53.2 (Oxaz C-4), 65.8 (Oxaz C-5), 123.1 (PhI C-3, C-6), 127.5 (Ar C-4), 127.6 (Ar C-2, C-6), 128.6 (Ar C-3, C-5), 131.4 (PhI C-2a, C-6a), 134.5 (PhI C-4, C-5), 136.3 (Ar C-1), 157.4 (Oxaz C=O), 168.1 (x 2) (PhI C=O). *Anal*. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.79; H, 4.90; N, 8.16.

2-{3-[4-(Fluorophenyl)methyl]-2-oxooxazolidin-4-ylmethyl}-1*H*-isoindole-1,3(2*H*)-dione (10b)

The yield was 65.1 %, mp 164—166 °C (MeCN). IR (KBr) cm^{-1}: 1775, 1740, 1723. FAB-MS (positive) *m/z*: 355 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.81—3.83 (2H, m, CH_2-PhI), 3.91—3.93 (1H, m, Oxaz H-4), 4.18 (1H, dd, *J* = 9.0, 4.5 Hz, Oxaz H-5), 4.32 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.39, 4.58 (each 1H, d, *J* = 15.5 Hz, CH_2Ph), 7.16 (2H, t, *J* = 9.0 Hz, Ar H-3, H-5), 7.35—7.38 (2H, m, Ar H-2, H-6), 7.83—7.89 (4H, m, PhI). ^{13}C-NMR (DMSO-d_6) *δ:* 38.1 (CH_2-PhI), 44.6 (CH_2Ph), 53.2 (Oxaz C-4), 65.9 (Oxaz C-5), 115.3 (d, *J* = 21 Hz, Ar C-3, C-5), 123.1 (PhI C-3, C-6), 129.8 (d, *J* = 8 Hz, Ar C-2, C-6), 131.4 (PhI C-2a, C-6a), 132.6 (d, *J* = 3 Hz, Ar C-1), 134.5 (PhI C-4, C-5), 157.4 (Oxaz C=O), 161.5 ((d, *J* = 243 Hz, Ar C-4), 168.1 (x 2) (PhI C=O). *Anal*. Calcd for $C_{19}H_{15}N_2O_4F$: C, 64.4; H, 4.27; N, 7.91. Found: C, 64.12; H, 4.46; N, 7.93.

2-{3-[4-(Biphenyl-4-yl)methyl]-2-oxooxazolidin-4-ylmethyl}-1*H*-isoindole-1,3(2*H*)-dione (10c)

The yield was 84.7 %, mp 208—210 °C (MeCN). IR (KBr) cm^{-1}: 1773, 1736, 1717. FAB-MS (positive) *m/z*: 413 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.81—3.89 (2H, m, CH_2-PhI), 3.96—3.99 (1H, m, Oxaz H-4), 4.20 (1H, dd, *J* = 9.0, 4.0 Hz, Oxaz H-5), 4.35 (1H, t, *J* = 8.5 Hz, Oxaz H-5), 4.42, 4.65 (each 1H, d, *J* = 15.5 Hz, CH_2Ph), 7.34—7.41 (3H, m, Ar H), 7.46 (2H, d, *J* = 7.0 Hz, Ar H), 7.63—7.66 (4H, m, Ar H), 7.84—7.90 (4H, m, PhI). ^{13}C-NMR (DMSO-d_6) *δ:* 38.1 (CH_2-PhI), 45.0 (CH_2Ph), 53.2 (Oxaz C-4), 65.8 (Oxaz C-5), 123.1 (PhI C-3, C-6), 126.5 (x 2), 126.9 (x 2,), 127.4, 128.3 (x 2), and 128.8 (x 2), (Ar H),

131.4 (PhI C-2a, C-6a), 134.5 (PhI C-4, C-5), 135.5, 139.4, and 139.6 (Ar C), 157.5 (Oxaz C=O), 168.1 (x 2) (PhI C=O). *Anal*. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.8; H, 4.89; N, 6.79. Found: C, 72.87; H, 4.94; N, 6.83.

2-{3-[3-Fluoro-4-(4-morpholinyl)phenylmethyl]-2-oxooxazolidin-4-ylmethyl}-1*H*-isoindole-1,3(2*H*)-dione (10e)

The yield was 61.4 %, mp 196—199 °C (MeCN). IR (KBr) cm^{-1}: 1773, 1736, 1713. FAB-MS (positive) *m/z*: 439 $(M)^+$. ^{1}H-NMR ($CDCl_3$) *δ:* 3.06—3.09 (4H, m, Mor H-2, H-6), 3.83—3.88 (7H, m, Oxaz H-4, Mor H-3, H-5 and C$\underline{H}_2$-PhI), 4.27—4.37 (2H, m, Oxaz H-5), 4.34, 4.78 (each 1H, d, *J* = 15.0 Hz, C$\underline{H}_2$Ph), 6.89 (1H, t, *J* = 8.5 Hz, Ar H-5), 7.03—7.08 (2H, m, Ar H-2, H-6), 7.74—7.78 (2H, m, PhI), 7.86—7.88 (2H, m, PhI). ^{13}C-NMR (DMSO-d_6) *δ:* 38.3 ($\underline{C}H_2$N-PhI), 45.5 ($\underline{C}H_2$Ph), 50.8 (Mor C-2, C-6), 53.8 (Oxaz C-4), 66.0 (Oxaz C-5), 67.0 (Mor C-3, C-5), 116.2 (d, *J* = 22 Hz, Ar C-2), 118.9 (d, *J* = 3 Hz, Ar C-5), 123.5 and 123.7 (PhI C-3, C-6), 124.5 (d, *J* = 3 Hz, Ar C-6), 130.3 (d, *J* = 7 Hz, Ar C-1), 131.6 and 132.7 (PhI C-2a, C-6a), 134.2 and 134.4 (PhI C-4, C-5), 139.8 (d, *J* = 8 Hz, Ar C-4), 155.6 (d, *J* = 248 Hz, Ar C-3), 158.1 (Oxaz C=O), 168.0 and 168.3 (PhI C=O). *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.

Preparation of the target oxazolidin-2-one (3d) from the compound (10d)

***N*-{3-[3-Fluoro-4-(1-piperidinyl)phenylmethyl]-2-oxooxazolidin-4-ylmethyl}acetamide (3d)**

A mixture of (**10d**; 1.0 g, 2.3 mmol) and aqueous 40 % methylamine (2.6 mL) and EtOH (40 mL) was refluxed for 2 h and then the reaction mixture was concentrated under a reduced pressure. The residue was dissolved in pyridine (13 mL), the resulting mixture was cooled to 0 °C and then acetic anhydride (4.5 mL) was added. The reaction mixture was allowed to stand at rt with stirring. After evaporation of the solvents under reduced pressure, the residue was dissolved in 10 % MeOH-AcOEt and the resulting mixture was again concentrated *in vacuo*. The residue was stirred in AcOEt and the insoluble material was filtered off. The filtrate was concentrated and purified by a silica gel column using a MeOH -AcOEt (0—5 % MeOH) as solvent. The target 3,4-disubstituted oxazolidin-2-one (**3d**) was obtained with a 77.6 % yield (0.62 g). Other target compounds (**3a—c** and **3e**) were also prepared according to the above procedure. The physical and spectroscopic results of the products are summarized in Tables 1 — 3.

REFERENCES

1. F. Fujisaki, M. Oishi, and K. Sumoto, *Chem. Pharm. Bull*., 2007, **55**, 829.
2. F. Fujisaki, N. Abe, and K. Sumoto, *Chem. Pharm. Bull*., 2004, **52**, 1238.
3. F. Fujisaki, N. Abe, and K. Sumoto, *Chem. Pharm. Bull*., 2002, **50**, 129.
4. N. Abe, F. Fujisaki, and K. Sumoto, *Chem. Pharm., Bull*., 1998, **46**, 142.
5. F. Fujisaki, M. Oishi, and K. Sumoto, *Chem. Pharm. Bull*., 2007, **55**, 124.

6. C.-H. Park, D. R. Brittelli, C. L.-J. Wang, F. D. Marsh, W. A. Gregory, M. A. Wuonola, R. J. McRipley, V. S. Eberly, A. M. Slee, and M. Forbes, *J. Med. Chem.*, 1992, **35**, 1156.
7. S. J. Brickner, D. K. Hutchinson, M. R. Barbachyn, P. R. Manninen, D. A. Ulanowicz, S. A. Garmon, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford, and G. E. Zurenko, *J. Med. Chem.*, 1996, **39**, 673.
8. M. A. Tlekhusezh, L. A. Badovskaya, and Z. I. Tyukhteneva, *Khim. Geterotsikl. Soedin.,* 1996, 711.
9. A.-H. Khuthier, K. Y. Al-Mallah, S. Y. Hanna, and N.-A. I. Abdulla, *J. Org. Chem.,* 1987, **52**, 1710.