HETEROCYCLES, Vol. 87, No. 1, 2013, pp. 133 - 145. © 2013 The Japan Institute of Heterocyclic Chemistry
Received, 21st September, 2012, Accepted, 26th October, 2012, Published online, 31st October, 2012
DOI: 10.3987/COM-12-12592

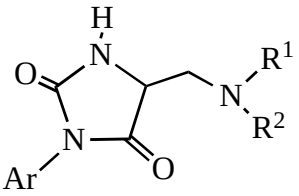
SYNTHESIS OF SOME NEW 5-DIALKYLAMINOMETHYLHYDANTOINS AND RELATED COMPOUNDS

Fumiko Fujisaki, Mayu Egami, Keiko Toyofuku, and Kunihiro Sumoto*

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

Abstract – In this paper, we describe the synthesis of new 5-dialkylaminomethyl-substituted hydantoin derivatives (**3** and **9**) from *β*-aminoalanines (**1** or **6**) and some chemical properties of the synthesized compounds. A synthetic trial for the preparation of a new twin-drug type molecule (**12**) is also described.

In connection with studies on new antibacterial compounds, many synthetic studies on molecular modifications have been carried out to find new promising candidates. Many reports on molecular recognition properties of artificial molecules have appeared, and many chemists are naturally interested in studying such biologically active substances. We have been interested in substances that interfere with molecular recognition process[1-4] in order to find new leads for antibacterial agents. We have already examined molecular modification of a bioisosteric replacement of the oxazolidinone ring in linezolid by a hydantoin nucleus.[5-7] Regarding biological activities of synthesized hydantoin derivatives, we have observed that most of the 5-dialkylaminomethy-3-arylhydantoin derivatives **(A)** show a wide range of significant antibacterial activities against either gram-positive or gram-negative strains.[7] For this attractive bioactivity of 5-dialkylaminomethyl-substituted hydantoins, further molecular modifications of this class of compounds seemed to be interesting.

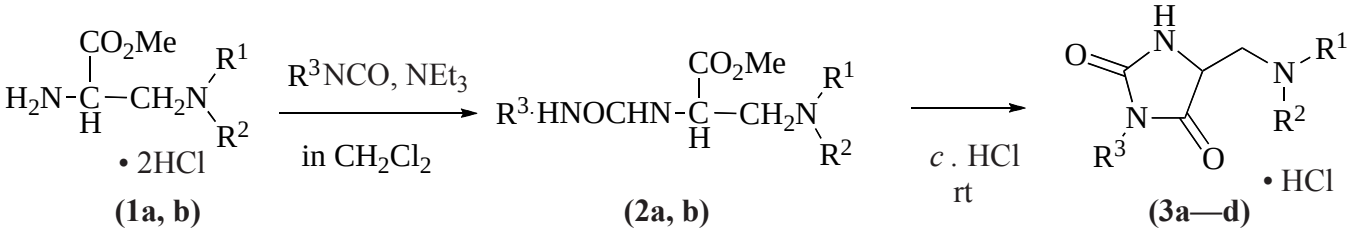


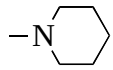
(A)

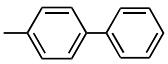
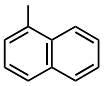
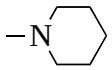
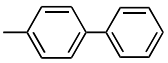
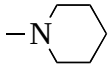
In this article, we describe a novel synthetic route for new 5-dialkylaminomethylhydantoin-related heterocycles and some chemical properties of the synthesized hydantoin derivatives.

SYNTHESIS OF 5-DIALKYLAMINOMETHYLHYDANTOINS

The new 3-aryl-substituted hydantoins were obtained from methyl ester of *β*-aminoalanines **1** and arylisocyanates as starting materials.[5,6] Details of the preparation of the new 3-aryl-substituted hydantoin derivatives **(3a—3d)** and their physical or spectroscopic data are presented in the Experimental section. The overall preparation stages **(1→2→3)** for the new target 5-dialkylaminomethyl-3-arylhydantoins **(3a—d)** are shown in Chart 1.



Compounds	$-N\begin{matrix}R^1\\R^2\end{matrix}$
1a, 2a =	
1b, 2b =	

Compounds	$-N\begin{matrix}R^1\\R^2\end{matrix}$	R^3	Yield [%]
3a =			69.8[a)]
3b =			22.7[b)]
3c =			86.0[b)]
3d =		$-(CH_2)_2\cdot Cl$	74.4[b)]

a) The yield was based on the compound **2a**. b) The yield was based on the compound **1**.

Chart 1

A new *N*(3)-alkyl-substituted hydantoin derivative **3e** was prepared (see Chart 2). The cyclization reaction of the urea intermediate **2c** to the hydantoin derivative **3e** was sensitive to reaction temperature. Room temperature for the cyclization stage is adequate for preparation of the target hydantoin derivative. By heating the urea intermediate **2c** with concentrated HCl, elimination of the corresponding dialkylamine also occurred easily to give 5-methylenehydantoin **4** together with the formation of a migration product **5**. Compound **5** was probably formed from a tautomeric isomer **4'** (see Chart 2). The structures of these substituted hydantoins were confirmed by spectroscopic and elemental analyses (see Experimental).

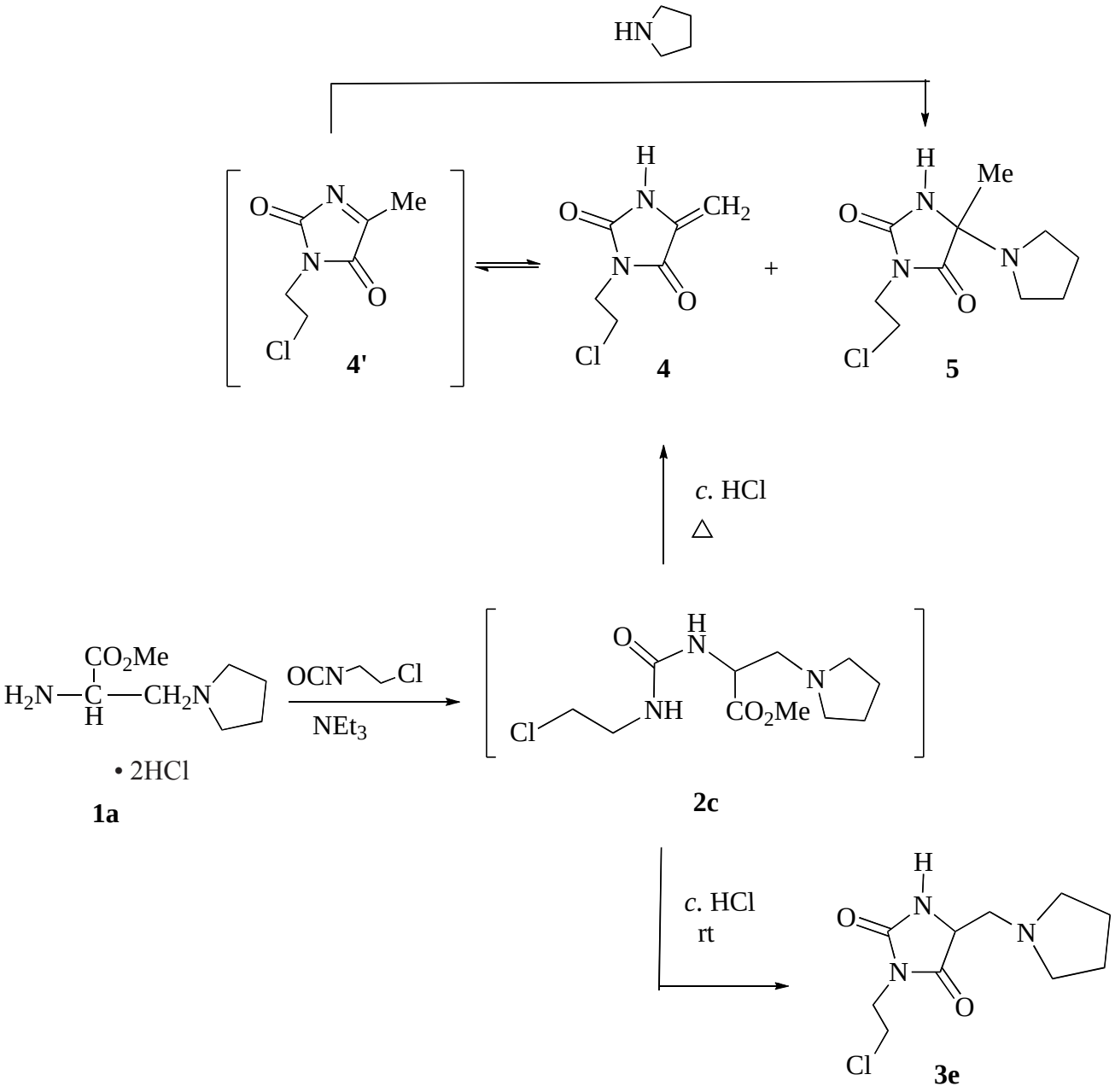
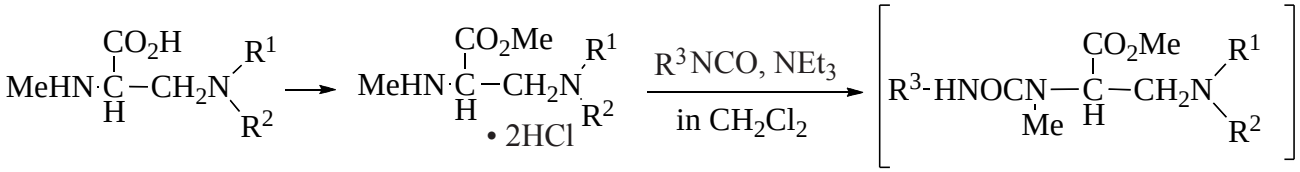


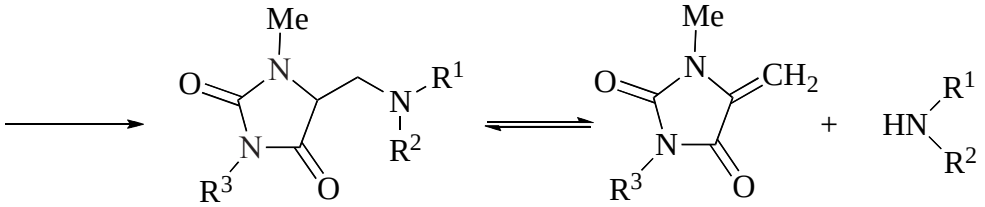
Chart 2

Some new *N*(1)-methyl hydantoin analogues **9a—9c** were also prepared from *N*-methyl-*β*–aminoalanine methyl ester derivatives **7** as starting materials (see Chart 3).

Interestingly, compounds **9a—9c** having an *N*(1)-methyl substituent in a hydantoin ring were unstable even at rt in a commonly used organic solvent, such as CH_2Cl_2, AcOEt or DMSO, and gradually afforded a corresponding 5-methylene derivative **10**[8] with elimination of a secondary amine. This characteristic chemical behavior of some *N*(1)-unsubstituted 5-dialkylaminomethylhydantoins has been observed previously in some *N*(1)-unsubstituted hydantoins.[5,6]



6 **7** **8**



9a—9c **10**

Compounds	—N R1 R2	R3	Yield[a)] [%]
9a:	—N	Cl	32.2
9b:	—N		35.3
9c:	—N		25.8

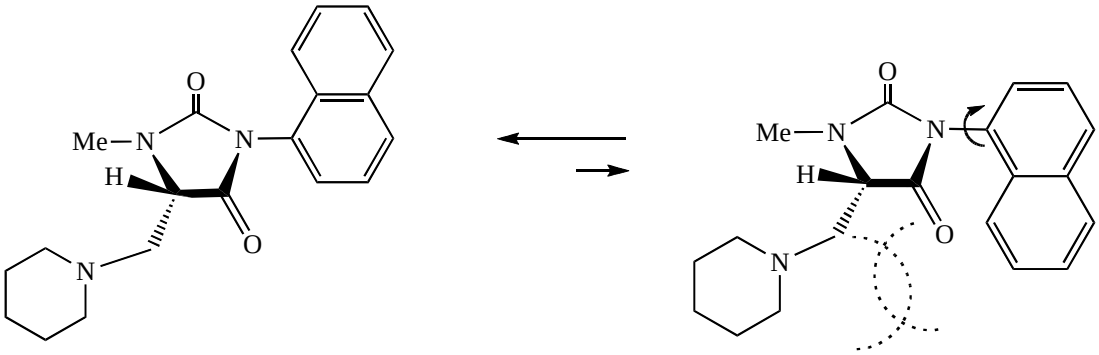
Compounds	—N R1 R2
6a, 7a:	—N
6b, 7b:	—N

a) The yields were based on the compound **7**.

Chart 3

Among the compounds shown in Chart 3, it is expected that bulky 3-naphthyl-substituted 5-dialkylaminomethylhydantoin derivatives (**3b** and **9c**) have two diastereomeric rotational isomers, since restricted internal rotation of a bulky group in the molecules against the planarity of the 5-substituted hydantoin ring system has been pointed out in a few derivatives.[9,10] NMR data of our compounds (**3b** and **9c**) in DMSO clearly showed the existence of two diastereomeric rotational isomers. The ratio of the two isomers for the compound **3b** was estimated to be ca. 1:1 [from the integration of C(5)-H signals (4.97—4.99 ppm, 5.12—5.14 ppm) on the hydantoin ring]. Interestingly, compound **9c** having *N*(1)-methyl and C(5)-piperidinomethyl substituents showed the existence of two rotational isomers in a

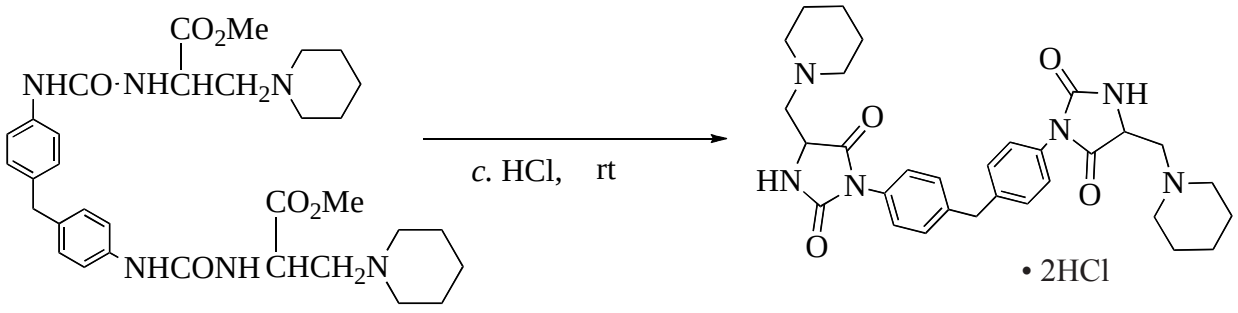
ratio of 7:3 [by comparison of each integration of *N*(1)-methyl protons in the hydantoin ring] (see Experimental). Structures of the two rotational isomers are shown in Figure 1. We speculate that the represented rotational isomer **9c-A** is a more stable conformer than **9c-B** because the conformer **9c-B** has a more sterically hindered interaction between a bulky C(5)-substituent and a plane of the naphthalene ring.



9c-A **9c-B**

Figure 1

In connection with the synthesis of some identical twin-drug or triplet-drug type symmetrical molecules,[11] a twin-drug type symmetrical hydantoin derivative **12** was also prepared for the purpose of comparison of chemical and biological properties. Twin-drug type compound **12** could be obtained from double cyclization of the corresponding urea intermediate **11** (see Chart 4). The symmetrical feature in solution of this compound **12** is elucidated by the ^{13}C-NMR spectrum, showing a magnetically equivalent spectroscopic signal pattern[12] (see Experimental).



11 **12**

Chart 4

Through these synthetic studies on hydantoin derivatives, we have established conventional procedures for a few new types of 3-and 5-disubstituted hydantoin derivatives. Assays for antibacterial activity of the prepared compounds by using gram-negative bacteria and gram-positive bacteria as target organisms are

now under investigation. Biological results for these compounds will be described in detail in a separate paper.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured by a Shimadzu FT/IR-8100 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained by a JEOL JNM A-500 at rt. The chemical shifts were expressed in δ ppm downfield from an internal tetramethylsilane (TMS) signal. The signal assignments were confirmed by ^{1}H - ^{1}H two-dimensional (2D) correlation spectroscopy (COSY), ^{1}H -^{13}C heteronuclear multiple quantum coherence (HMQC), and ^{1}H -^{13}C heteronuclear multiple-bond connectivity (HMBC) spectra. High FAB-MS spectra were obtained by a JEOL JMS-HX110 mass spectrometer. The following abbreviations in parentheses were used for pyrrolidine ring (Pyr), piperidine ring (Pip), 1-naphthyl ring (Np) and hydantoin ring (Hyd).

Synthesis of 2-amino-3-(*sec*-amino)propanoic acid methyl esters (1a—b)

According to the procedure reported previously, esterification of *β*-aminoalanine[13,14] (0.01 mol) with methanolic hydrogen chloride (5—10%) (150 mL) gave the corresponding methyl ester **(1a—b)**. The obtained materials were used for the subsequent reaction stage without further purification.

3-(Biphenyl-4-yl)-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione Hydrochloride (3a)

TEA (0.90 g, 8.9 mmol) was added to a suspension of methyl 2-amino-3-(pyrrolidin-1-yl)propanoic acid methyl ester dihydrochloride **1a** (1.0 g, 4.08 mmol) in toluene (10 mL) at 0 °C. After 5 min, a solution of 4-biphenylyl isocyanate (0.80 g, 4.10 mmol) in CH_2Cl_2 was added dropwise to the mixture and stirred for 4 h at rt. Water (25 mL) was added to the mixture and insoluble material was collected by filtration to give 2-(3-biphenyl-4-ylureido)-3-(pyrrolidin-1-yl)propanoic acid **2a** (1.02 g, 70.8%), mp 192 °C (dec). IR (KBr) cm^{-1}: 1691. HR-FAB-MS (positive) *m/z*: 354.1817. Calcd for $C_{20}H_{24}N_3O_3$: 354.1818. This urea derivative **2a** was used without further purification. Concentrated HCl (15 mL) was added to the urea derivative (0.75 g, 2.12 mmol) and the mixture was allowed to stand 1 week at rt and then the precipitated solid material was collected by filtration to give the crude compound (0.55 g, 69.8% from the corresponding urea derivative). An analytical sample was obtained by recrystallization from EtOH/MeOH as colorless feathers, mp 183—185 °C (with dec). IR (KBr) cm^{-1}: 1779, 1717. FAB-MS (positive) *m/z*: 336 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.91, 1.93 (each 2H, br, Pyr H-3, H-4), 3.10—3.11 (2H, br, Pyr H-2 x1, H-5 x 1), 3.67—3.71 (4H, br, C$\underline{H}_2$-Pyr and Pyr H-2 x1, H-5 x 1), 4.84—4.86 (1H, m, Hyd H-5), 7.39—7.51 (4H, m, Ar H), 7.69—7.80 (5H, m, Ar H), 8.78 (1H, s, Hyd H-1), 11.05 (1H, br, NH^+). ^{13}C-NMR (DMSO-d_6) δ: 22.5 (Pyr C-3 or C-4), 22.8 (Pyr C-4 or C-3), 53.5 (Pyr C-2 or C-5), 53.8 (Hyd C-5), 54.1 (Pyr C-5 or C-2), 55.1 ($\underline{C}H_2$-Pyr), 126.8 x 2 (Ar C), 127.0 x 2 (Ar C), 127.0 (Ar C-4'), 127.7 x 2 (Ar C), 129.0 x 2 (Ar C), 131.1 (Ar C-1), 139.3 (Ar C-4), 139.8 (Ar C-1'), 155.3 (Hyd C-2), 170.1 (Hyd

C-4). Anal. Calcd for $C_{20}H_{22}ClN_3O_2$: C, 64.60; H, 5.96; N, 11.30. Found. C, 64.51; H, 5.98; N, 11.19.

Compound **3b** ~ **3d** were also obtained by a similar method described above.

3-(Naphthalen-1-yl)-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione Hydrochloride (3b)

This compound was obtained from compound **1a** in 22.7% yield as colorless crystals, mp 195 °C (dec). The same proportion of two rotational isomers is indicated by ^{1}H-NMR spectrum in DMSO-d_6 at 34.6 °C. IR (KBr) cm^{-1}: 1793, 1725. FAB-MS (positive) *m/z*: 310 (M+H).$^+$ ^{1}H-NMR (DMSO-d_6) δ: 1.90—1.96 (4H, m, Pyr H-3, H-4), 3.14—3.17 (2H, br, Pyr H-2, H-5), 3.69—3.94 (4H, m, C$\underline{H}_2$-Pyr and Pyr H-2, H-5), 4.97—4.99 (0.5H, m, Hyd H-5), 5.12—5.14 (0.5H, m, Hyd H-5), 7.53—7.65 (4H, m Np H), 7.73—7.74 (0.5H, m, Np H), 7.84—7.86 (0.5H, m, Np H), 8.04—8.08 (2H, m, Np H), 8.85 (0.5H, br s, Hyd H-1), 8.89 (0.5H, br s, Hyd H-1), 11.28—11.31 (1H, m, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 22.5, (Pyr C-3, C-4), 22.7 (Pyr C-3, C-4), 53.2, 54.0 (C$\underline{H}_2$-Pyr), 54.1 and 54.5 (Hyd C-5), 55.1 (Pyr C-2, C-5), 55.6 (Pyr C-2, C-5), 122.4, 122.6, 125.4, 125.5, 126.5 (x 2), 126.9 (x 2), 127.0, 127.1, 128.1, 128.2, 129.4 (x 2) (Np C), 129.6 (x 2) (Np C-8'), 129.7 (x 2) (Np C-4'), 133.6 (x 2) (Np C-1), 155.4 and 155.7 (Hyd C-2), 170.5 and 170.6 (Hyd C-4). Anal. Calcd for $C_{18}H_{20}ClN_3O_2 \cdot 0.3\ H_2O$: C, 61.55; H, 5.91; N, 11.96. Found. C, 61.51; H, 5.80; N, 11.91.

3-(Biphenyl-4-yl)-5-(piperidin-1-ylmethyl)imidazolidine-2,4-dione Hydrochloride (3c)

This compound was obtained from compound **1b** in 86.0% yield as colorless crystals, mp >215 °C (dec). IR (KBr) cm^{-1}: 1781, 1718. FAB-MS (positive) *m/z*: 350 (M+H).$^+$ ^{1}H-NMR (DMSO-d_6) δ: 1.38—1.41 (1H, m, Pip H-4), 1.72—1.75 (1H, m, Pip H-4), 1.81—1.91 (4H, m, Pip H-3, H-5), 2.98—3.07 (2H, m, Pip H-2 H-6), 3.45—3.48 (1H, m, Pip H-2 or H-6), 3.55—3.56 (2H, m C$\underline{H}_2$-Pip), 3.66—3.68 (1H, m, Pip H-6 or H-2), 4.97—4.99 (1H, m, Hyd H-5), 7.38—7.42 (1H, m, Ar H), 7.46—7.51 (4H, m, Ar H), 7.70—7.72 (2H, m, Ar H), 7.77—7.80 (2H, m, Ar H), 8.90 (1H, s, Hyd H-1), 10.76 (1H, br s, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 21.1 (Pip C-4), 22.2 (Pip C-3 or C-5), 22.3 (Pip C-5 or C-3), 51.9 (Pip C-2 or C-6), 52.3 (Hyd C-5), 53.6 (Pip C-6 or C-2), 58.1 (C$\underline{H}_2$-Pip), 126.8 (x 2) (Ar C), 127.0 (x 4) (Ar C), 127.7 (Ar C-4'), 129.0 (x 2) (Ar C), 131.1 (Ar C-1), 139.3 (Ar C-4), 139.8 (Ar C-1'), 155.1 (Hyd C-2), 170.2 (Hyd C-4). Anal. Calcd for $C_{21}H_{24}ClN_3O_2$: C, 65.36; H, 6.27; N, 10.89. Found. C, 65.22; H, 6.30; N, 10.87.

3-(2-Chloroethyl)-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione Hydrochloride (3d)

This compound was obtained from compound **1b** in 74.4% yield as a white solid, mp 176—182 °C (EtOH/H$^+$). IR (KBr) cm^{-1}: 1786, 1714. FAB-MS (positive) *m/z*: 260 (M+H).$^+$ ^{1}H-NMR (DMSO-d_6) δ: 1.35—1.38 (1H, m, Pip H-4), 1.70—1.86 (5H, m, Pip H-3 x 2, Pip H-4, Pip H-5 x 2), 2.92—3.02 (2H, m, Pip H-2 x 1, H-6 x 1), 3.30—3.32 (1H, m, C$\underline{H}$H-Pip), 3.43—3.47 (2H, m, CH$\underline{H}$-Pip + Pip H-2 x 1 or H-6 x 1), 3.55—3.58 (1H, m, Pip H-6 x 1 or H-2 x 1), 3.62—3.79 (4H, m, C$\underline{H}_2$C$\underline{H}_2$Cl), 4.88—4.89 (1H, d, *J* = 9.0 Hz, Hyd H-5), 8.73 (1H, s, Hyd H-1), 10.76 (1H, br s, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 21.1 (Pip C-4),

22.1, 22.3 (Pip C-3, C-5), 39.8 ($\underline{C}H_2CH_2Cl$), 40.9 ($CH_2\underline{C}H_2Cl$), 51.7 (Pip C-2 or C-6), 52.1 (Hyd C-5), 53.4 (Pip C-6 or C-2), 58.0 ($\underline{C}H_2$-Pip), 155.7 (Hyd C-2), 171.0 (Hyd C-4). Anal. Calcd for $C_{11}H_{19}Cl_2N_3O_2$: C, 44.61; H, 6.47; N, 14.19. Found. C, 44.39; H, 6.41; N, 14.21.

3-(2-Chloroethyl)-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione Hydrochloride (3e)

This compound was obtained from compound **1a** in 21.2% yield as a white solid, mp 160—165 °C. IR (KBr) cm^{-1}: 1784, 1713. FAB-MS (positive) *m/z*: 246 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.90—2.02 (4H, m, Pyr H-3, H-4), 3.05 (2H, br, Pyr H-2 x 1, H-5 x 1), 3.42—3.46 (1H, m, C$\underline{H}$H-Pyr), 3.57—3.68 (3H, m, CH$\underline{H}$-Pyr, Pyr H-2 x 1, and H-5 x 1), 3.70—3.73 (2H, m, $C\underline{H}_2CH_2Cl$), 3.77—3.80 (2H, m, $CH_2C\underline{H}_2Cl$), 4.72 (1H, d, *J* = 8.0 Hz, Hyd H-5), 8.57 (1H, s, Hyd H-1), 11.02 (1H, br s, NH^+). ^{13}C-NMR (DMSO-d_6) δ: 22.4 (Pyr C-3 or C-4), 22.6 (Pyr C-4 or C-3), 39.8 ($\underline{C}H_2CH_2Cl$), 40.8 ($CH_2\underline{C}H_2Cl$), 53.3 (Pyr C-2 or C-5), 53.6 (Hyd C-5), 54.0 (Pyr C-5 or C-2), 55.1 ($\underline{C}H_2$-Pyr), 155.8 (Hyd C-2), 170.8 (Hyd C-4). Anal. Calcd for $C_{10}H_{17}Cl_2N_3O_2$: C, 42.57; H, 6.07; N, 14.89. Found. C, 42.46; H, 6.04; N, 14.60.

[Preparation of compounds 4 and 5]

A solution of 2-chloroethyl isocyanate (0.22 g, 2.09 mmol) in CH_2Cl_2 was added to a solution of compound **1a** (0.50 g, 2.04 mmol) and TEA (0.41 g, 4.06 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h at rt and concentrated *in vacuo*. Concentrated HCl (4 mL) and water (1 mL) were added to the residue and the mixture was allowed to stand for 16 h at rt and subsequently heated for 6 min (100 °C). After removal of the solvent, the residue was dissolved in water and the resulting solution was made alkaline (*ca.* pH = 11) with K_2CO_3. The resulting mixture was extracted with AcOEt and the extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a mixture of compounds **4** and **5**. Separation by centrifugal silica gel chromatography using AcOEt as a solvent gave the two compounds **4** (0.180 g, 50.7%) and **5** (0.043 g, 8.6%) as a white solid. The data for compounds **4** and **5** are shown below.

3-(2-Chloroethyl)-5-methyleneimidazolidine-2,4-dione (4)

Mp 107—109 °C. IR (KBr) cm^{-1}: 1781, 1725, 1699. FAB-MS (positive) *m/z*: 175 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.77—3.80 (4H, m, $C\underline{H}_2C\underline{H}_2Cl$), 4.87 (1H, s, = C$\underline{H}$H), 4.88 (1H, s, = CH$\underline{H}$), 10.63 (1H, br s, Hyd H-1). ^{13}C-NMR (DMSO-d_6) δ: 39.6 ($\underline{C}H_2CH_2Cl$), 41.1 ($CH_2\underline{C}H_2Cl$), 94.7 (=$\underline{C}H_2$), 134.9 (Hyd C-5), 153.7 (Hyd C-2), 162.7 (Hyd C-4). HR-FAB-MS (positive) *m/z:* 175.0272 (Calcd for $C_6H_8ClN_2O_2$: 175.0274).

3-(2-Chloroethyl)-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione (5)

Mp 103—104 °C. IR (KBr) cm^{-1}: 1787, 1727, 1712. FAB-MS (positive) *m/z*: 246 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.45 (3H, s, $C\underline{H}_3$), 1.67 (4H, s, Pyr H-3, H-4), 2.47—2.51 (2H, m, Pyr H-2 x 1, H-5 x 1), 2.62—2.66 (2H, m, Pyr H-2 x 1, H-5 x 1), 3.69—3.72 (2H, m, $C\underline{H}_2CH_2Cl$), 3.78—3.81 (2H, m, $CH_2C\underline{H}_2Cl$), 8.55 (1H, br s, Hyd H-1). ^{13}C-NMR (DMSO-d_6) δ: 23.19 (CH_3), 23.22 (Pyr C-3, C-4), 39.3

($\underline{C}H_2CH_2Cl$), 41.3 ($CH_2\underline{C}H_2Cl$), 45.3 (Pyr C-2, C-5), 75.2 (Hyd C-5), 155.1 (Hyd C-2), 173.9 (Hyd C-4). Anal. Calcd for $C_{10}H_{16}ClN_3O_2 \cdot 0.2\ H_2O$: C, 48.18; H, 6.63; N, 16.85. Found. C, 48.14; H, 6.45; N, 16.94.

[Preparation of 2-(methylamino)-3-(pyrrolidin-1-yl)propanoic acid (6a)]

Preparation of diethyl 2-(benzyl(methyl)amino)propanedioate. To a solution of diethyl bromomalonate (0.105 mol) in 40 mL of absolute EtOH was added dropwise methylbenzylamine (0.209 mol). The mixture was refluxed for 1 h, and the solvent was evaporated under reduced pressure. Et_2O was added to the residue and insoluble material was filtered off. The obtained organic layer was washed with brine and dried over anhydrous Mg_2SO_4. After concentration of the solvent, the residue was purified with an aluminum oxide column using AcOEt-n-hexane-Et_2O (1:4:5) as a solvent to give diethyl 2-(benzyl(methyl)amino)propanedioate as a colorless oil (98.2%). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, t, J = 7.0 Hz, $CH_2C\underline{H}_3$ x 2), 2.46 (3H, s, $NC\underline{H}_3$), 3.82 (2H, s, $NC\underline{H}_2Ph$), 4.16 (1H, s, $C\underline{H}COOCH_2CH_3$), 4.25 (4H, q, J = 7.0 Hz, $C\underline{H}_2CH_3$ x 2), 7.22—7.39 (5H, m, Ar H).

Preparation of diethyl 2-(methylamino)propanedioate. A solution of diethyl 2-(benzyl(methyl)amino)propanedioate (30 g, 0.108 mol) in EtOH (200 mL) was rapidly stirred under 2~3 atmospheric pressure of hydrogen in the presence of 5% Pd-C (12 g). After absorption of hydrogen ceased, the catalyst was removed by filtration through Celite 545. The filtrate was evaporated to dryness under reduced pressure. The residue was purified with an aluminum oxide column using n-hexane-Et_2O (1:4:5) as a solvent to give diethyl 2-(methylamino)propanedioate as a colorless oil (17.5 g, 86.1%). The product gave a single spot on TLC analysis. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (6H, t, J = 7.0 Hz, $CH_2C\underline{H}_3$ x 2), 2.17 (1H, br, NH), 2.45 (3H, s, $NC\underline{H}_3$), 3.94 (1H, s, $C\underline{H}COOCH_2CH_3$), 4.25 (4H, q, J = 7.0 Hz, $C\underline{H}_2CH_3$ x 2). HR-FAB-MS (positive) *m/z:* 190.1071 (Calcd for $C_7H_{15}NO_4$: 190.1079).

Preparation of compound 6a. Diethyl 2-(methylamino)propanedioate (34.3 g, 0.181 mol) was added to a mixture of pyrrolidine (14.1 g, 0.199 mol) and formaldehyde (37%) (16.2 g, 0.200 mol), and the resulting mixture was stirred at rt for 10 min and then heated in a water bath for a few min. Concentrated HCl (500 mL) was added to the reaction mixture under cooling and then the mixture was allowed to stand at rt for 1 month. The resulting mixture was heated at 90 °C in a water bath for 1 h and concentrated *in vacuo*. The oily residue was passed through a column packed with ion-exchanged resin (AG 11A8®, Bio Rad Laboratories) in order to obtain free amino acid. The obtained precipitate was purified with a silica gel column using (EtOH-NH_3 (28% aq) =97/3) as a solvent to give a crude crystalline product. Washing the crystalline product with EtOH gave **6a** (11.98 g, 38.4%). An analytical sample could be obtained by recrystallization from EtOH as colorless crystals, mp >218 °C (dec). IR (KBr) cm^{-1}: 3453, 2876, 2838, 2778, 1582. FAB-MS *m/z:* 173 ($M+H^+$). ^{1}H-NMR (D_2O) δ: 2.00—2.03(4H, m, Pyr H-3, H-4), 2.44 (3H, s, $NC\underline{H}_3$), 3.18—3.28 (6H, m, Pyr H-2, H-5 and $C\underline{H}_2$-Pyr), 3.37 (1H, dd, J = 7.5, 6.5 Hz, $C\underline{H}COOH$).

^{13}C-NMR (D_2O) δ: 25.6 (Pyr C-3, C-4), 35.9 (N<u>C</u>H$_3$), 57.3 (Pyr C-2, C-5), 58.9 (<u>C</u>H$_2$-Pyr), 64.2 (<u>C</u>HCOOH), 180.0 (<u>C</u>OOH). Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.73; H, 9.08; N, 16.14.

In a similar fashion, compound **6b** was also obtained. The data for *N*-methyl *β*-aminoalanines **6b** is shown below.

2-(Methylamino)-3-(piperidin-1-yl)propanoic acid (6b)

The yield from diethyl 2-(methylamino)propanedioate was 30.4%. The analytical sample was obtained by recrystallization from EtOH as colorless crystals, mp >194 °C (dec). IR (KBr) cm^{-1}: 2824, 1648, 1604. FAB-MS *m/z:* 187 (M+H$^+$). ^{1}H-NMR (D_2O) δ: 1.56—1.61 (2H, m, Pip H-4), 1.73—1.78 (4H, m, Pip H-3, H-5), 2.49 (3H, s, NC<u>H</u>$_3$), 2.95—3.07 (5H. m, C<u>H</u>H-Pip and Pip H-2, H-5), 3.09 (1H, dd, *J* = 13.5, 6.0 Hz, CH<u>H</u>-Pip), 3.49 (1H, dd, *J* = 8.0, 6.0 Hz, C<u>H</u>COOH). ^{13}C-NMR (D_2O) δ: 24.7 (Pip C-4), 26.4 (Pip C-3, C-5), 35.8 (N<u>C</u>H$_3$), 56.7 (Pip C-2, C-6), 60.5 (<u>C</u>H$_2$-Pip), 62.8 (<u>C</u>HCOOH), 178.7 (<u>C</u>OOH). Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 58.00; H, 9.85; N, 14.89.

Preparation of 2-(methylamino)-3-(pyrrolidin-1-yl)propanoic acid methyl esters: 7a—b

Methanolic hydrogen chloride (5—10%) (150 mL) was added to a solution of compounds **6a—b** (0.01 mol) in anhydrous MeOH, and the mixture was kept for 3 d at rt under anhydrous conditions and then evaporated to dryness *in vacuo*. After treatment with methanolic hydrogen chloride three times, the residue was used for the subsequent reaction step without further purification.

3-(4-Chlorophenyl)-1-methyl-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione (9a)

A solution of *p*-chlorophenyl isocyanate (0.31 g, 2.02 mmol) in CH_2Cl_2 was added to a solution of *N*-methyl amino acid methyl ester dihydrochloride **7a** (0.50 g, 1.93 mmol) and TEA (0.82 g, 8.12 mmol) in CH_2Cl_2, and the reaction mixture was stirred for 1 h at rt. The mixture was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column with AcOEt as a solvent to give compound **9a** as a white solid (0.19 g, 32.2%), mp 93—95 °C. IR (KBr) cm^{-1}: 1777, 1716. FAB-MS (positive) *m/z*: 308 (M+H).$^+$ ^{1}H-NMR (DMSO-d_6) δ: 1.63—1.69 (4H, m, Pyr H-3, H-4), 2.45—2.51 (2H, br, Pyr H-2 x 1, H-5 x 1), 2.54—2.59 (2H, br, Pyr H-2 x 1, H-5 x 1), 2.94—2.98 (1H, m, C<u>H</u>H-Pyr), 2.97 (3H, s, NC<u>H</u>$_3$), 3.01—3.05 (1H, m, CH<u>H</u>-Pyr), 4.24 (1H, dd, *J* = 4.5, 3.5 Hz, Hyd-H-5), 7.35—7.47 (2H, m, Ar H-2, H-6), 7.53—7.57 (2H, m, Ar H-3, H-5). ^{13}C-NMR (DMSO-d_6) δ: 23.4 (Pyr C-3, C-4), 27.9 (N<u>C</u>H$_3$), 53.8 (<u>C</u>H$_2$-Pyr), 54.4 (Pyr C-2, C-5), 61.1 (Hyd C-5), 127.8 x 2 (Ar C-2, C-6), 128.8 x 2 (Ar C-3, C-5), 131.1 (Ar C-4), 132.0 (Ar C-1), 154.8 (Hyd C-2), 171.0 (Hyd C-4). Anal. Calcd for $C_{15}H_{18}ClN_3O_2$: C, 58.54; H, 5.89; N, 13.65. Found. C, 58.44; H, 5.90; N, 13.50.

3-(Biphenyl-4-yl)-1-methyl-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione (9b)

Compound **9b** was prepared in a manner similar to that for **9a** in 35.3% yield as a white solid, mp 108—110 °C. IR (KBr) cm^{-1}: 1779, 1708. FAB-MS (positive) *m/z*: 350 (M+H).$^+$ ^{1}H-NMR (DMSO-d_6) δ:

1.65—1.70 (4H, m, Pyr H-3, H-4), 2.47—2.61 (4H, m, Pyr H-2, H-5), 2.99 (3H, s, NCH_3), 2.97—3.07 (2H, m, $C\underline{H}_2$-Pyr), 4.25—4.27 (1H, m, Hyd H-5), 7.37—7.42 (3H, m, Ar H), 7.47—7.52 (2H, m, Ar H), 7.68—7.72 (2H, m, Ar H), 7.75—7.79 (2H, m, Ar H). ^{13}C-NMR (DMSO-d_6) δ: 23.4 (Pyr C-3, C-4), 27.9 (NCH_3), 53.8 ($\underline{C}H_2$-Pyr), 54.4 (Pyr C-2, C-5), 61.0 (Hyd C-5), 126.6, 126.7 x 2 (Ar C), 126.9, 127.0 (Ar C), 127.6 (Ar C-4'), 127.7, 128.9 x 2 (Ar C), 131.6 (Ar C-1), 139.3 (Ar C-4), 139.5 (Ar C-1'), 155.1 (Hyd C-2), 171.2 (Hyd C-4). Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found. C, 71.90; H, 6.61; N, 11.64.

1-Methyl-3-(naphthalen-1-yl)-5-(piperidin-1-ylmethyl)imidazolidine-2,4-dione (9c)

This compound was obtained from the reaction of 1-naphthyl isocyanate and compound **7b** by a method similar to that for **9a** in 25.8% yield as a white solid, mp 159—160 °C. A ratio of the two rotational isomers (major/minor) of 7:3 was indicated by the ^{1}H-NMR spectrum in DMSO-d_6 at 34.6 °C. IR (KBr) cm^{-1}: 1774, 1714. FAB-MS (positive) *m/z*: 338 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.39—1.46 (2H, m, Pip H-4), 1.51—1.60 (4H, m, Pip H-3, Pip H-5), 2.40—2.59 (4H, m, Pip H-2, H-6), 2.86—2.93 (2H, m, $C\underline{H}_2$-Pip), 3.01 (3H x 0.7, s, NCH_3 for major rotational isomer), 3.04 (3H x 0.3, s, NCH_3 for minor rotational isomer), 4.30 —4.31 (1H x 0.7, m, Hyd H-5 for major rotational isomer), 4.47—4.48 (1H x 0.3, m, Hyd H-5 for minor rotational isomer), 7.37 (1H x 0.3, d, J = 6.5 Hz, Np H for minor rotational isomer), 7.47 (1H x 0.7, dd J = 7.0, 1.0 Hz, Np H for major rotational isomer), 7.52—7.64 (3H, m, Np H for major and minor rotational isomers), 7.80 (1H x 0.3, d, J = 8.0 Hz, Np H for minor rotational isomer), 8.00 (1H x 0.7, d, J = 8.5 Hz, Np H for major rotational isomer), 8.03—8.09 (2H, m, Np H for major and minor rotational isomers). ^{13}C-NMR (DMSO-d_6) δ: 23.5 (Pip C-4), 25.7 (Pip C-3, C-5), 28.3 (NCH_3), 54.9 ($\underline{C}H_2$-Pip), 55.8 (Pip C-6, C-2), 62.4 (Hyd C-5), 128.9 (Np C-8'), 129.9 (Np C-4'), 133.7 (Np C-1), 155.9 (Hyd C-2), 171.7 (Hyd C-4). These signals are ascribable to the major rotational isomer. δ: 23.6 (Pip C-4), 25.9 (Pip C-3, C-5), 28.5 (NCH_3), 55.8 (Pip C-6, C-2), 57.1 ($\underline{C}H_2$-Pip), 60.6 (Hyd C-5), 129.0 (Np C-8'), 130.0 (Np C-4'), 133.7 (Np C-1), 155.7 (Hyd C-2), 172.0 (Hyd C-4). These signals are ascribable to the minor rotational isomer. δ: 122.9, 123.1, 125.5 (x 2), 126.4, 126.5 (x 2), 126.7, 127.0, 128.1 (x 2), 129.1 (x 2), 129.2 (Np C). These signals are for both rotational isomers. Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found. C, 71.05; H, 6.95; N, 12.17.

3,3'-(4,4'-Methylenebis(4,1-phenylene))bis(5-(piperidin-1-ylmethyl)imidazolidine-2,4-dione) Dihydrochloride (12)

A solution of 3,4'-methylenebis(isocyanatobenzene) (0.22 g, 0.88 mmol) in CH_2Cl_2 was added to a solution of compound **1b** (0.50 g, 1.93 mmol) and TEA (0.39 g, 3.86 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h at rt and washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give diurea derivative **11** (0.41 g, 65.1%), mp 119 °C (dec). IR (KBr) cm^{-1}: 3338, 1744, 1652. HR-FAB-MS (positive) *m/z*: 623.3558. Calcd for $C_3H_{47}N_6O_6$: 623.3557. Concentrated HCl (3 mL) was

added to this urea intermediate (0.38 g, 0.61 mmol) and the mixture was allowed to stand for 8 d at rt and then the solvent was removed under reduced pressure to give compound **12** as a white solid (0.40 g, 97.6% from compound **11**). This product was very hygroscopic, mp 178—180 °C. IR (KBr) cm^{-1}: 1782, 1719. FAB-MS (positive) *m/z*: 559 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.36—1.39 (2H, m, Pip H-4), 1.71—1.82 (2H, m, Pip H-4), 1.85—1.91 (8H, m, Pip H-3 x 4, H-5 x 4), 2.95—3.05 (4H, m, Pip H-2 x 2, H-6 x 2), 3.43—3.53 (6H, m, CHH-Pip x 2, Pip H-2 x 2, and Pip H-6 x 2), 3.64—3.67 (2H, m CHH-Pip x 2), 4.04 (2H, s, Ph-CH_2-Ph), 4.95—4.97 (2H, m, Hyd H-5 x 2), 7.28—7.37 (8H, m, Ar H), 8.86 (2H, s, Hyd H-1 x 2), 10.86 (2H, br s, NH^+ x 2). ^{13}C-NMR (DMSO-d_6) δ: 21.1(Pp C-4), 22.1, (Pip C-3 or C-5), 22.3 (Pip C-5 or C-3), 40.1 (Ph-CH_2-Ph), 51.8 (Pip C-2 or C-6), 52.2 (Hyd C-5), 53.6 (Pip C-6 or C-2), 58.1 (CH_2-Pip), 126.7 (Ar C-2, C-2', C-6, C-6'), 129.0 (Ar C-3, C-3', C-5, C-5'), 129.9 (Ar C-, C-1'), 140.9 (Ar C 4, C-4'), 155.1 (Hyd C-2), 170.1 (Hyd C-4). Anal. Calcd for $C_{31}H_{40}Cl_2N_6O_4 \cdot 2.3H_2O$: C, 55.32; H, 6.68; N, 12.49. Found. C, 55.32; H, 6.74; N, 12.22.

REFERENCES AND NOTES

1. A. P. Davis, *Org. Biomol. Chem.*, 2009, **7**, 3629.
2. J. B. Locke, J. Finn, M. Hilgers, G. Morales, S. Rahawi, G. C. Kedar, J. J. Picazo, W. Im, K. J. Shaw, and J. L. Stein, *Antimicrob. Agents Chemother.*, 2010, **54**, 5337 and related references cited therein.
3. S.-C. Hsu, C.-H. Chen, S.-H. Tsai, H. Kawasaki, C.-H. Hung, Y.-T. Chu, H.-W. Chang, Y. Zhou, J. Fu, B. Plunkett, S.-N. Su, S. Vieths, R. T. Lee, Y. C. Lee, and S.-K. Huang, *J. Biol. Chem.*, 2010, **285**, 7903.
4. A. Varki, R. D. Cummings, J. D. Esko, H. H. Freeze, P. Stanley, C. R. Bertozzi, G. W. Hart, and M. E. Etzler, 'Essentials of Glycobiology' 2nd ed. Cold Spring Harbor Laboratory Press, Cold Spring Harbor N. Y, 2009, p. 719.
5. F. Fujisaki, K. Shoji, and K. Sumoto, *Heterocycles*, 2009, **78**, 213.
6. F. Fujisaki, K. Shoji, and K. Sumoto, *Chem. Pharm. Bull.*, 2009, **57**, 1415.
7. F. Fujisaki, K. Shoji, M. Shimodouzono, N. Kashige, F. Miake, and K. Sumoto, *Chem. Pharm. Bull.*, 2010, **58**, 1123.
8. For example, in the ^{1}H-NMR spectrum of compound **9b**, characteristic methylene signals were observed at 5.10 (d, J = 2.5 Hz) and 5.37 (d, J = 2.5 Hz) ppm, indicating the corresponding hydantoin derivative **10**.
9. L. D. Colebrook, *Can. J. Chem.*, 1991, **69**, 1957.
10. R. Benassi, A. Bregulla, D. Henning, M. Heydenreich, G. Kempter, E. Kleinpeter, and F. Taddei, *J. Mol. Struct.*, 1999, **475**, 105.
11. F. Fujisaki, H. Usami, S. Nakashima, S. Iwashita, Y. Kurose, N. Kashige, F. Miake, and K. Sumoto,

Heterocycles, 2011, **83**, 1843.

12. The cyclization of compound **11** to hydantoin derivative **12** is not stereoselective ring closure, and the obtained compound **12** can therefore be considered to be a mixture of a *meso* compound and two enatiomeric C_2-symmetrical molecules that have the same absolute configuration regarding two C(5) chiral carbons in two hydantoin rings in the molecule **12**. With reference to this stereochemistry of the product **12**, we have no experimental data to prove the product to be a mixture of three stereoisomeric forms.
13. N. Abe, F. Fujisaki, and K. Sumoto, *Chem. Pharm. Bull.*, 1998, **46**, 142.
14. F. Fujisaki, N. Abe, and K. Sumoto, *Chem. Pharm. Bull.*, 2002, **50**, 129.