Synthesis of New 5-Substituted Hydantoins and Symmetrical Twin-Drug Type Hydantoin Derivatives

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In connection with our studies on hydantoin derivatives, a conventional regioselective chemical transformation of 5-methylene hydantoins 4a–c to 5-aminomethyl-substituted hydantoins 5–10 or to 5-amino-5-methyl-disubstituted hydantoins 11–14 is described. Synthesis of bivalent twin-drug type hydantoin derivatives 19–24 and the binding property of a bivalent symmetrical hydantoin derivative 24b to sulfated glycosaminoglycans are also described.

Key words hydantoin; regioselective; antibacterial activity; isothermal titration calorimetry; bivalent twin-drug; sulfated glycosaminoglycan

The need for new antibacterial agents is largely due to the increase of bacterial infections with resistant strains, especially Gram-positive strains, in both community and hospital setting. Oxazolidinone antibacterial agents such as linezolid are a relatively new class of antibacterial agents, and the utility of this class includes activity against multidrug-resistant infections.1–3) In the early stage of invasion of bacteria or viruses, the surface glycans of organisms recognize various host cell lectins. In terms of molecular recognition, the participation of two-fold (C2) or three-fold (C3) symmetrical geometry macro-molecules is one of the common features in many biological responses,4–6) and small symmetric geometrical molecules frequently appear in many biological active compounds.7–9) From this interesting aspect of molecular symmetry, we have already reported a few examples of such types of symmetrical targeted molecules for the purpose of finding new bioactive leads or candidates.10–15)

Our previous studies on a bioisosteric replacement of the oxazolidinone ring in linezolid by a hydantoin nucleus provided a few interesting antibacterial leads.16–20) Among previously targeted hydantoin derivatives, some derivatives including a twin-drug type symmetrical hydantoin derivative20,21) showed significant antibacterial activity against Gram-positive organisms (Staphylococcus aureus). This finding of new antibacterially active molecules constructed on a hydantoin scaffold encouraged us to develop further modifications of this class of compounds.

In this article, we describe the regioselective chemical modification of 5-methylene hydantoins to 5-aminomethyl-substituted hydantoins 5–10 or to 5-amino-5-methyl-disubstituted hydantoins 11–14. Preparation of the bivalent twin-drug type hydantoin derivatives 19–24 from β-aminoalanine methyl ester (1)20) and a new carbohydrate recognition binding property of symmetrical twin-drug type hydantoin derivative 24b are also described.

Results and Discussion

In connection with our synthetic studies on new bioactive hydantoin derivatives, some molecular modifications of β-aminoalanine methyl esters (1) to bioisosteric hydantoin derivatives have been reported.16–20) As starting materials for further derivatizations in this series, 5-methylene hydantoins 4a–c were obtained from elimination (deamination) reactions of the corresponding 5-dialkylaminomethyl-hydantoins (3) (Chart 1) (see Experimental).

Two types of hydantoin derivatives (5–10 and 11–14) could be obtained from regioselective additions of amines to 5-methylene hydantoins 4a–c (Chart 2). Thus, reaction conditions without a solvent (neat) at room temperature (rt) (path a) resulted predominantly in the formation of 5-pyrrolidino-
methyl- or 5-benzylaminomethyl-hydantoin derivatives 5–10. In contrast, reactions in CH₂Cl₂ under rt or refluxing conditions (path b) afforded 5-amino-5-methylhydantoin derivatives 11–14 in moderate to good yields. The results are summarized in Tables 1 and 2. It is thought that the tautomeric isomer B of 5-methylene hydantoin in solution (A⁶B)¹⁷,¹⁹ is a crucial intermediate for the formation of 5,5-disubstituted hydantoins (11–14), as shown in Chart 2. When using an excess amount of an amine, a considerable amount of ring-opened urea derivatives 15–17 was isolated as a predominant reaction product (Chart 2).

All of the structures of the above hydantoin derivatives were easily confirmed by elemental analysis and spectroscopic data. The positive FAB mass spectroscopic behaviors of these hydantoin derivatives are particularly interesting, and diagnostically useful fragmentation processes were observed. The prominent fragment iminium ion [a] for 5-dialkylaminomethyl-hydantoin derivatives 5–10 is from fission of the C(5)–C bond (α-cleavage of the molecular ion). On the other hand, in the mass spectra of 5-methyl-5-dialkylamino-hydantoin derivatives 11–14, the formation of a strong ammonium ion peak [b] resulting from C(5)–N bond cleavage of the 5-amino substituent is observed (Fig. 1).

Furthermore, in NMR spectra of 5-methyl-5-dialkylaminosubstituted hydantoin derivatives, 5-methyl and 5-carbon ring signals of the products are easily distinguished. The ¹H-NMR spectrum of these 5,5-disubstituted derivatives showed 1.53–1.57 ppm as a singlet assignable to the 5-methyl group.

Table 1. Preparation of 5-Aminoethyl Hydantoins 5–10 from 5-Methylene Hydantoins 4a–c

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R¹</th>
<th>Amounts of aminos⁶</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>H</td>
<td>3</td>
<td>10 min</td>
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<td>6</td>
<td>H</td>
<td>1.4</td>
<td>2 h</td>
<td>78</td>
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<tr>
<td>7</td>
<td>Cl</td>
<td>2</td>
<td>2 h</td>
<td>64</td>
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<td>8</td>
<td>Cl</td>
<td>3</td>
<td>1 h</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>OMe</td>
<td>2.8</td>
<td>0.5 h</td>
<td>53</td>
</tr>
<tr>
<td>10</td>
<td>OMe</td>
<td>2</td>
<td>2 h</td>
<td>53</td>
</tr>
</tbody>
</table>

a) Molar ratio of the used amine to compound 4.
Amounts of amines

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Reaction temp.</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>H</td>
<td>-N-</td>
<td></td>
<td>rt</td>
<td>5</td>
<td>61</td>
</tr>
<tr>
<td>12</td>
<td>H</td>
<td>-NHCH₂Ph</td>
<td></td>
<td>Reflux</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>13</td>
<td>Cl</td>
<td>-N-</td>
<td></td>
<td>Reflux</td>
<td>2</td>
<td>69</td>
</tr>
<tr>
<td>14</td>
<td>OMe</td>
<td>-N-</td>
<td></td>
<td>rt</td>
<td>1</td>
<td>67</td>
</tr>
</tbody>
</table>

(a) Molar ratio of the used amine to compound 4.

and the ¹³C-NMR spectrum had two characteristic carbon signals at 22.9–24.0 and 73.4–75.1 ppm, easily ascribable to the substituent 5-methyl carbon and 5-position of the hydantoin ring carbon, respectively. From these data, we could easily confirm the structures of the products (see Experimental for details).

A novel N-acyl derivative 18 was obtained from direct N-acylation of isolated 5-aminomethyl-hydantoin 6 with acetic anhydride (Chart 3). This chemical modification of compound 18 also provided chemical evidence for the validity of the structure as a secondary amine 6 and a new promising route to 5-acylaminoethyl-hydantoins.

In addition to the above-described modifications, we also attempted to prepare twin-drug type hydantoin derivatives from β-aminoalanine methyl ester 1 in order to find more active antibacterial leads. The targeted bivalent twin-drug type 19–24 hydantoin derivatives were obtained from reactions of the corresponding diisocyanate derivatives and β-aminoalanine esters (I) (Chart 4). Details of the protocol for preparation of twin-drug type compounds are shown in Experimental. Double cyclization reactions affording bivalent hydantoin derivatives 19–24 easily occurred under conditions similar to those for preparation of 5-dialkylaminomethyl hydantoins described previously. The results for designed twin-drug type compounds are summarized in Table 3. All of the obtained compounds exhibited very simple symmetrical ¹³C-NMR spectra in DMSO-­⁴⁶, indicating little difference with respect to the signal assignable to substituted hydantoin rings and a linker moiety. The linker structures applied in these twin-drug type molecules are also shown in Table 3. The yields were good to excellent and the obtained products were stable solid or crystalline materials. Through these synthetic trials, we confirmed that the above-described procedure is a conventional route to prepare new types of bivalent symmetrical twin-drug type bivalent molecules.

It is thought that sulfated sugar chains play an important role in mediating adhesion of many types of bacterial organisms to host cells or tissues. Regarding the interaction of bacterial adhesion to glycans, a few examples of binding carbohydrate specificities have been demonstrated, and some bacteria are known to bind to sulfated glycosaminoglycans such as heparan sulfate. We have been interested in small molecules that interfere with such carbohydrate recognition stages in order to find new bioactive leads. With the aim of elucidating the chemical properties of the antibacterial active symmetrical twin drug type compound 24b, we carried out thermodynamic experiments on binding of sulfated glycosaminoglycans such as heparan sulfate and dermatan sulfate to a bivalent antibacterial active hydantoin derivative 24b by using isothermal titration calorimetry. Among the compounds tested, the binding reaction between twin-drug type compound 24b and heparan sulfate or dermatan sulfate was exothermic and the obtained thermodynamic parameters were K = 2.75 × 10⁴ 1/m and ΔH = −9.46 kJ/mol for heparan sulfate and K = 1.11 × 10³ 1/m and ΔH = −10.9 kJ/mol for dermatan sulfate at 298.15 K. A representative thermogram of a hydantoin derivative 24b titrated with heparan sulfate is shown in Fig. 2.

From the results of calorimetric experiments, we found that the twin-drug type small molecule 24b has an interesting binding property to sulfated glycosaminoglycans. Regarding the prepared hydantoin derivatives, symmetrical twin-drug type derivatives (24a and 23b) showed significant antibacterial activity against a Gram-positive strain (Staphylococcus aureus) (MIC = 0.026 mM and 0.116 mM, respectively), but these compounds were inactive against a Gram-negative strain (Escherichia coli) at a concentration of less than 0.211 mM. The difference in antibacterial activities seems to be affected by both structure of the linker and structure of the basic amine moiety in a twin-drug type molecule. Further details of an structure–activity relationship (SAR) study including other prepared hydantoin derivatives and additional thermodynamic experiments for the biological active compounds in this series.
Chart 3. Preparation of 5-N-Acylaminomethyl Hydantoin 18 from Compound 6

Chart 4. Synthesis of Twin-Drug Type Hydantoin Derivatives 19–24 from Compound 1

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Linker</th>
<th>(N^2R^2R^3)</th>
<th>Yield (%)</th>
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<tr>
<td>19a</td>
<td>(-(CH_2)_4-)</td>
<td>(N)</td>
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<td>19b</td>
<td>(-(CH_2)_4-)</td>
<td>(N)</td>
<td>62</td>
</tr>
<tr>
<td>20a</td>
<td>(-(CH_2)_6-)</td>
<td>(N)</td>
<td>40</td>
</tr>
<tr>
<td>20b</td>
<td>(-(CH_2)_6-)</td>
<td>(N)</td>
<td>43</td>
</tr>
<tr>
<td>21a</td>
<td>(-(CH_2)_8-)</td>
<td>(N)</td>
<td>71</td>
</tr>
<tr>
<td>21b</td>
<td>(-(CH_2)_8-)</td>
<td>(N)</td>
<td>84</td>
</tr>
<tr>
<td>22a</td>
<td>(-(CH_2)_{12}-)</td>
<td>(N)</td>
<td>78</td>
</tr>
<tr>
<td>22b</td>
<td>(-(CH_2)_{12}-)</td>
<td>(N)</td>
<td>71</td>
</tr>
<tr>
<td>23b</td>
<td>[]</td>
<td>(N)</td>
<td>40</td>
</tr>
<tr>
<td>24a</td>
<td>[]</td>
<td>(N)</td>
<td>45</td>
</tr>
<tr>
<td>24b(^a)</td>
<td>[]</td>
<td>(N)</td>
<td>65</td>
</tr>
</tbody>
</table>

\(^a\) The data for compound 24b were taken from ref. 19.
Experimental

Melting points are uncorrected. IR spectra were measured by a Shimadzu FT/IR-8100 spectrometer. The 1H- and 13C-NMR spectra were obtained by a JEOL JNM A-500 at 35°C. Chemical shifts are expressed in δ ppm downfield from an internal tetramethylsilane (TMS) signal. The assignments were confirmed by 1H–13C heteronuclear multiple quantum coherence (HMQC), 1H–13C heteronuclear multiple-bond connectivity (HMBC) spectra. High FAB-MS spectra were obtained by a JEOL JMS-HX110 mass spectrometer. Dermatan sulfate sodium salt (GAG-DS01) and heparan sulfate sodium salt (GAG-HS01) were purchased from Funakoshi Co., Ltd. All other chemicals used were of reagent grade.

Calorimetric Experiments

Heat of binding between a twin-drug type compound 24b and a sulfated glycosaminoglycan such as heparan sulfate was measured in water at 298.15 K by using an isothermal titration calorimeter (Thermal Activity Monitor 2270). Titrations were performed by stepwise injection of heparan sulfate solution or dermatan sulfate solution (0.2 mg/mL). In the calorimetric experiments, each binding reaction was exothermic and compound 24b solution (0.2 mg/mL) was titrated with heparan sulfate (0.2 mg/mL). The minimum inhibitory concentration (MIC) of dermatan sulfate was measured in water at 298.15 K by using an isothermal titration calorimeter (Thermal Activity Monitor 2270). Titrations were performed by stepwise injection of heparan sulfate solution or dermatan sulfate solution (0.2 mg/mL).

Assays for Antibacterial Activity

We used Staphylococcus aureus ATCC6538P and Escherichia coli NBRC14237 (NIHJ) (Gram-positive and Gram-negative bacteria, respectively) as target organisms. Synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) to a concentration of 1.280 μg/mL. The minimum inhibitory concentration (MIC) of a standard strain was measured by the authentic microdilution method to monitor the bacterial growth turbidity in Muller–Hinton broth according to the Japanese Society of Chemotherapy.

Preparation of 5-Methylene Hydantoins (4a–e)

These compounds were prepared according to the procedure reported previously. Physical and spectroscopic data of these compounds are shown below.

5-Methylene-3-phenylimidazolidine-2,4-dione (4a): Physical and spectroscopic data of this compound were reported in our previous paper.

5-Methylene-3-(4-chlorophenylimidazolidine-2,4-dione (4b): This compound was obtained in 68% yield; a white solid; mp >215°C. IR (KBr) cm⁻¹: 1775, 1728, 1671. FAB-MS (positive) m/z: 223 (M+H)⁺. 1H-NMR (DMSO-d₆) 6: 4.94, 5.26 (each 1H, d, J=2.4 Hz, Ar H-2, H-6), 7.47 (2H, d, J=2.1 Hz, Ar H-3, H-5), 10.8 (1H, br, NH). 13C-NMR (DMSO-d₆) 6: 128.3 (Ar C-3, C-5), 128.7 (Ar C-2, C-6), 130.6 (Ar C-4), 132.3 (Ar C-1), 134.9 (Hyd C-5), 153.1 (Hyd C-2), 158.7 (Ar C-4), 162.1 (Hyd C-4). Anal. Calcd for C₁₀H₈N₂O₃Cl: C, 53.95; H, 3.24; N, 12.65.

5-Methylene-3-(4-methoxyphenylimidazolidine-2,4-dione (4c): This compound was obtained in 85% yield; a white solid; mp >215°C. IR (KBr) cm⁻¹: 1789, 1765, 1714, 1665. FAB-MS (positive) m/z: 219 (M+H)⁺. 1H-NMR (DMSO-d₆) 6: 3.79 (3H, s, OMe), 4.91, 5.22 (each 1H, d, J=1.5 Hz, =CH₂), 7.02 (2H, d, J=8.8 Hz, Ar H-3, H-5), 7.30 (2H, d, J=8.8 Hz, Ar H-2, H-6), 10.66 (1H, br, NH). 13C-NMR (DMSO-d₆) 6: 55.3 (OMe), 94.4 (=CH₂), 114.0 (Ar C-3, C-5), 124.2 (Ar C-1), 128.1 (Ar C-2, C-6), 135.0 (Hyd C-5), 153.1 (Hyd C-2), 158.7 (Ar C-4), 162.1 (Hyd C-4). Anal. Calcd for C₁₀H₈N₂O₄Cl: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.42; H, 4.87; N, 12.58.

Typical Procedure for the Preparation of Products (5–10) from 5-Methylene Hydantoins (4a–e)

A mixture of a 5-methylene hydantoin 4a (0.050 g, 0.27 mmol) and pyrroolidine (0.057 g, 0.80 mmol) was allowed to stand for 10 min at rt. Et₃O was added to the mixture and the precipitate was collected by filtration to give 5 (0.043 g, 62%). A white solid; mp 118–119°C; IR (KBr) cm⁻¹: 1774, 1723, 1721. FAB-MS (positive) m/z: 260 (M+H)⁺, 84 (CH₃=Pyridine). 1H-NMR (DMSO-d₆) 6: 1.68 (4H, brs, Pyr H-3, H-4), 2.53–2.60 (4H, m, Pyr H-2, H-5), 2.81–2.83 (1H, m, CH₂-Pyr), 2.91–2.95 (1H, m, CH₂-Pyr).
(1H, m, CHH-Pyr), 4.27–4.28 (1H, m, Hyd H-5), 7.31–7.47
(5H, m, Ar H), 8.33 (1H, brs, Hyd-I). 1^1C-NMR (DMSO-d_6) δ:
23.2 (Pyr C-3, C-4), 54.2 (Pyr C-2, C-5), 56.3 (CH_2-Pyr), 56.9
(Hyd C-5), 126.2 (Ar C-2, C-6), 127.3 (Ar C-4), 128.4 (Ar C-3, C-5), 132.2 (Ar C-1), 155.5 (Hyd C-2), 172.2 (Hyd C-4). The hydrochloride of this compound was identical to an authentic sample. 15

5-(Benzylaminomethyl)-3-phenylimidazolidine-2,4-dione (6): A white solid; mp 151–152°C. IR (KBr) cm⁻¹: 1770, 1710. FAB-MS (positive) m/z: 296 (M+H)⁺, 120 (CH_2=NHCCHPh)⁺. 1^1H-NMR (DMSO-d_6) δ: 2.29 (1H, br, NHCHPh), 2.84 (1H, dd, J=12.5, 6.0 Hz, Hyd-CH=NH), 2.92 (1H, dd, J=12.5, 4.0 Hz, Hyd-CH=NH), 3.73, 3.78 (each 1H, d, J=6.5, 3.5 Hz, Hyd H-5), 7.21–7.48 (10H, m, Ar H), 8.37 (1H, t, J=6.0 Hz, ArHCONHCCH), 8.93 (1H, s, CONHCHPh). 1^1C-NMR (DMSO-d_6) δ: 42.0 (CONHCHPh), 50.9 (CH=CHNHCCHPh), 52.6 (CH=CHNHCCHPh), 52.8 (CH=CHNHCCHPh), 118.9 (Ar C-2, C-6 in 4-chlorophenyl), 124.5 (Ar C-4 in 4-chlorophenyl), 126.5, 126.6, 127.0, 127.8, 127.8, 128.0, 128.1, 128.4, 128.4 (Ar C), 139.2 (Ar C-1 in 4-chlorophenyl), 139.3 (Ar C-1 in CONHCCHPh), 140.4 (Ar C-1 in CH=CHNHCCHPh), 154.5 (NHCCH), 171.3 (CONHCCH). Anal. Calcd for C_{17}H_{16}N_{3}O_{2}Cl·0.5H_2O: C, 60.27; H, 5.06; N, 12.40. Found: C, 65.96; H, 5.95; N, 12.79.

3-(4-Methoxyphenyl)-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione (9): A white solid; mp 98.5–99.5°C. IR (KBr) cm⁻¹: 1773, 1710. FAB-MS (positive) m/z: 290 (M+H)⁺, 84 (CH_2=Pyrr)⁺. 1^1H-NMR (DMSO-d_6) δ: 1.67–1.69 (4H, brs, Pyrr H-3, H-4), 2.49–2.60 (4H, m, Pyrr H-2, H-5), 2.76–2.80, 2.88–2.92 (each 1H, m, CH=CHPyrr), 3.79 (3H, s, OMe), 4.27 (1H, dd, J=6.5, 3.5 Hz, Hyd H-5), 7.00–7.02 (2H, m, Ar H), 7.19–7.20 (2H, m, Ar H), 8.40 (1H, br, Hyd H-1). 1^1C-NMR (DMSO-d_6) δ: 23.3 (Pyr C-3, C-4), 54.3 (Pyr C-2, C-5), 56.4 (CH_2=Pyrr), 57.1 (Hyd C-5), 128.0, 128.0, 128.7, 128.7 (Ar C), 131.0 (Ar C-1 or C-4), 131.9 (Ar C-4 or Ar C-1), 155.4 (Hyd C-2), 172.2 (Hyd C-4). Anal. Calcd for C_{18}H_{19}N_{3}O_{3}: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.08; H, 6.62; N, 14.47.

5-((Benzylaminomethyl)-3-(4-methoxyphenyl)imidazolidine-2,4-dione (10): This compound was purified by centrifugal silica gel chromatography with AcOEt as a solvent; a white solid; mp 153–154°C. IR (KBr) cm⁻¹: 1771, 1707. FAB-MS (positive) m/z: 326 (M+H)⁺, 120 (CH_2=NHCCHPh)⁺. 1^1H-NMR (DMSO-d_6) δ: 2.37–2.50 (1H, br, NHCHPh), 2.85 (1H, dd, J=12.5, 6.0 Hz, NHCHPh), 2.91 (1H, dd, J=12.5, 4.0 Hz, NHCHPh), 3.74–3.79 (2H, m, Hyd H-5), 3.78 (3H, s, OMe), 4.25–4.27 (1H, m, Hyd H-5), 7.00–7.02 (1H, m, Ar H), 7.22–7.23 (3H, Ar H), 7.31–7.33 (4H, m, Ar H), 8.31 (1H, brs, Hyd H-1). 1^1C-NMR (DMSO-d_6) δ: 49.1 (NH=CH_2Ph), 52.7 (CH=CH_2Ph), 55.3 (Ome), 57.1 (Hyd C-5), 131.3 (Ar C-3, C-5 in 4-methoxyphenyl), 124.8 (Ar C-1 in 4-methoxyphenyl), 126.5, 127.8, 127.8, 127.9, 128.0, 128.0, 128.0 (Ar C), 140.5 (Ar C-1 in CH_2=Ph), 156.1 (Hyd C-2), 158.3 (Ar C-4 in 4-methoxyphenyl), 172.4 (Hyd C-4). Anal. Calcd for C_{19}H_{20}N_{3}O_{3}: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.50; H, 6.00; N, 12.88.

Typical Procedure for the Preparation of Products (11–14) from 5-Methylene Hydantoins (4a–e) 5-Methyl-3-phenyl-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione (11): A solution of a 5-methylene-hydantoin (4a) in AcOEt was added to a solution of 5-Methylene Hydantoin (4a) (0.050 g, 0.27 mmol) and pyrrolidine (0.019 g, 0.27 mmol) in CHCl_3 was stirred for 5h at room temperature. After concentration of the solvent, the solid material was purified by centrifugal silica gel chromatography using AcOEt as a solvent to afford 11 (0.042 g, 61%); a white solid; mp 142–143°C. IR (KBr) cm⁻¹: 1776, 1726. FAB-MS (positive) m/z: 260 (M+H)⁺, 72. 1^1H-NMR (DMSO-d_6) δ: 1.57 (3H, s, Me), 1.70–1.73 (4H, m, Pyrr H-3, H-4), 2.56–2.58 (2H, m, Pyrr H-2×1, H-5×1), 2.74–2.76 (2H, m, Pyrr H-2×1, H-5×1), 7.32–7.34 (2H, m, Ar H-2, H-6), 7.39–7.40.
1H, m, Ar H-4), 7.45–7.47 (2H, m Ar H-3, H-5), 8.62 (1H, brs, Hdyl H-1). 13C-NMR (DMSO-d6): 23.0 (Me), 23.2 (Pyr C-3, C-4), 45.2 (Pyr C-2, C-5), 75.0 (Hdyl C-5), 126.7 (Ar C-2, C-6), 127.7 (Ar C-4, Ar C-5), 128.7 (Ar C-3, C-5), 131.8 (Ar C-1), 154.2 (Hdyl C-2), 173.0 (Hdyl C-4). Anal. Caled for C16H18N2O2: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.78; H, 6.63; N, 16.11.

5-(Benzylamino)-5-methyl-3-phenylimidazolidine-2,4-dione (12): A white solid; mp 122–124°C. [The ratio of a mixture of three solvents (AcOEt–n-hexane–MeOH) changed stepwise (50:50:0→100:0→0:0:100:0:100%)] IR (KBr) cm⁻¹: 1782, 1718. FAB-MS (positive) m/z: 296 (M+H)⁺, 108. 1H-NMR (DMSO-d6): 1.53 (3H, s, Me), 3.40–3.42 (1H, m, NHCCHPh), 3.58 (1H, dd, J=13.0, 6.0 Hz, NHCCHPh). 3.72 (1H, dd, J=13.0, 6.0 Hz, NHCCHPh), 7.20–7.47 (10H, m, Ar H), 8.58 (1H, brs, Hdyl H-1). 13C-NMR (DMSO-d6): 24.0 (Me), 45.9 (NH-CH2Ph), 73.4 (Hdyl C-5), 126.5, 126.6, 127.6, 127.9, 128.5 (Ar H), 132.0 (Ar C-1 in Hdyl-Ph), 140.0 (Ar C-1 in CH2-Ph), 154.0 (Hdyl C-4), 173.4 (Hdyl C-4). Anal. Caled for C16H18N2O2: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.08; H, 5.76; N, 14.14.

1-(4-Chlorophenyl)-5-methyl-5-(pyridin-1-yl)-imidazolidine-2,4-dione (13): A white solid; mp 138–140°C (AcOEt–n-hexane=7:3). IR (KBr) cm⁻¹: 1781, 1723. FAB-MS (positive) m/z: 294 (M+H)+, 72. 1H-NMR (DMSO-d6): 1.57 (3H, s, Me), 1.70–1.72 (4H, m, Pyr H-3, H-4), 2.50–2.52, 2.72–2.77 (each 2H, m, Pyr H-2, H-5), 7.40 (2H, d, J=9.0Hz, Ar H-2, H-6 or H-3, H-5), 7.54 (2H, d, J=9.0Hz, Ar H-3, H-5 or H-2, H-6), 8.79 (1H, brs, Hdyl H-1). 13C-NMR (DMSO-d6): 22.9 (Me), 23.2 (Pyr C-3, C-4), 45.3 (Pyr C-2, C-5), 75.1 (Hdyl C-5), 128.3 (Ar C-2, C-3 or C-5, C-6), 128.7 (Ar C-3, C-5 or C-2, C-6), 130.7 (Ar C-1 or C-4), 130.7 (C-4 or Ar C-1), 153.9 (Hdyl C-2), 172.8 (Hdyl C-4). Anal. Caled for C14H16N3O2: C, 53.65; H, 5.56; N, 14.13. Found: C, 56.55; H, 5.32; N, 14.13.

3-(4-Methoxyphenyl)-5-methyl-5-(pyridin-1-yl)-imidazolidine-2,4-dione (14): A white solid; mp 128–130°C (AcOEt–n-hexane=7:3). IR (KBr) cm⁻¹: 1776, 1727. FAB-MS (positive) m/z: 290 (M+H)+, 72. 1H-NMR (DMSO-d6): 1.55 (3H, s, Me), 1.71 (4H, br, Pyr H-3, H-4), 2.50–2.52, 2.75–2.97 (each 2H, m, Pyr H-2, H-5), 3.78 (3H, s, OMe), 7.00–7.01, 7.21–7.23 (each 2H, d, J=8.5Hz, Ar H), 8.66 (1H, br, Hdyl H-1). 13C-NMR (DMSO-d6): 23.0 (Me), 23.2 (Pyr C-3, C-4), 45.2 (Pyr C-2, C-5), 55.3 (OMe), 74.9 (Me), 114.9 (Ar C-3, C-5), 124.4 (Ar C-1), 128.1 (C-2, C-6), 154.6 (Hdyl C-2), 158.6 (Ar C-4), 173.2 (Hdyl C-4). Anal. Caled for C18H17N3O4: 5.0H2O: C, 60.39; H, 6.76; N, 14.08. Found: C, 60.29; H, 6.54; N, 14.13.

1-(1-Oxo-1,3-di(pyridin-1-yl)propan-2-yl)phenylurea (16): A mixture of a 5-methylene-hydantoin (4a) (0.10 g, 0.53 mmol) and pyridoline (0.19 g, 2.68 mmol) was allowed to stand for 2 h at room temperature. The resulting solid material was filtered, washed with EtO, and dried to give 16 as a white solid (0.10 g, 57%). mp 193°C. IR (KBr) cm⁻¹: 3424, 1719. FAB-MS (positive) m/z: 338 (M+H)+. 1H-NMR (DMSO-d6): 2.07 (3H×0.6, s, Me), 2.18 (3H×0.4, s, Me), 3.60–3.78 (2H, m, CH2-N=Hyd H-5), 7.22–7.49 (10H, m, Ar H), 8.51 (1H×0.6, brs, Hdyl H-1). 13C-NMR (DMSO-d6): 21.5, 21.6 (Me), 47.2, 52.5 (CH2-Pyr), 47.2, 48.4 (Hyd-CH=N=), 54.6, 55.4 (Hdyl C-5), 126.3 (×3), 126.5 (×2), 126.6 (×3), 127.1, 127.3 (×2), 128.3 (×2), 128.5 (×3), 128.6 (×2), 131.9, 132.1 (Ar C-1 in Ph=H), 137.4, 137.5 (Ar C-1, in CH2-Pyr), 155.58, 156.63 (Hyd C-2), 171.57, 171.64 (Hdyl C-4). Anal. Caled for C12H17N3O4·0.5H2O: C, 66.75; H, 6.57; N, 12.26. Found: C, 66.59; H, 5.80; N, 12.05.

Preparation of Twin-Drug Type Molecules (19–24)

- Preparation of Phenylurea (3,3’-(Butane-1,4-diyli)bis(5-(pyridin-1-ylmethyl)-imidazolidine-2,4-dione) Dihydrochloride (19a): A solution of 1,4-diisocyanatobutane (0.25 g, 1.79 mmol) in CH2Cl2 was
added to a solution of β-aminoalanine methyl ester dihydrochloride 1a (1.00 g, 4.08 mmol) and TEA (0.41 g, 4.06 mmol) in CH₂Cl₂ (20 mL). The mixture was stirred for 3 h at rt and concentrated in vacuo. Concentrated HCl (7 mL) was added to the residue and the mixture was allowed to stand for 6 d at rt. After removal of the solvent under reduced pressure, the residue was washed with EtOH and collected by filtration to give 19a (0.59 g, 67%). An analytical sample was obtained by washing with MeOH–EtOH as a white solid; mp >260°C (dec). IR (KBr) cm⁻¹: 1769, 1716. FAB-MS (positive) m/z: 421 (M+ H)⁺. 1H-NMR (DMSO-d₆) δ: 1.51 (4H, s, butane H-2, H-3), 1.90–2.01 (8H, m, Pyr H-3, H-4), 3.06–3.09 (8H, m, Pyr H-2, H-5), 3.42–3.54 (4H, m, CH₂-Pyr), 3.64 (4H, br, butane H-1, H-4), 4.62–4.63 (2H, m, Hyd H-5), 8.37 (2H, bs, Hyd H-1), 10.73 (2H, br, NH⁺). 13C-NMR (DMSO-d₆): δ 22.5 (Pyr C-3, C-4), 24.3 (bthane C-2, C-3), 37.6 (bthane C-1, C-4), 52.9, 54.0 (Pyr C-2, C-5), 53.5 (Hyd C-5), 55.0 (CH₂-Pyr), 156.3 (Hyd C-2), 170.9 (Hyd C-4). Anal. Calc. for C₂₂H₃₈Cl₂N₆O₄·0.5H₂O: C, 49.81; H, 7.41; N, 15.84. Found: C, 49.99; H, 7.34; N, 16.00.

3,3’-(Hexane-1,6-diyl)bis[(5-piperidin-1-ylmethyl)-imidazolidine-2,4-dione) Dihydrochloride (20a): This compound was obtained from the reaction of 1a and 1,6-disocyanatooctane by a method similar to that for 19a as a white solid. An analytical sample was obtained by recrystallization from MeCN–MeOH; a white solid; mp 177–182°C (dec).

IR (KBr) cm⁻¹: 1766, 1706. FAB-MS (positive) m/z: 477 (M+ H)⁺. 1H-NMR (DMSO-d₆) δ: 1.24 (8H, brs, octane H-3–H-6), 1.50 (4H, ddd, J=14.0, 7.0, 7.0 Hz, octane H-2, H-5), 1.88–1.91 (4H, m, Pyr H-3, H-4), 2.02–2.04 (4H, m, Pyr H-3, H-4), 2.93–3.07 (4H, m, Pyr H-2, H-5), 3.34 (4H, t, J=7.0 Hz, octane H-1, H-8), 3.37–3.66 (8H, m, Pyr H-2, H-5, 5-Hetaryl H-Pyr), 4.66–4.68 (2H, m, Hyd H-5), 8.45 (2H, br, Hyd H-1), 11.07 (2H, br, NH⁺). 13C-NMR (DMSO-d₆): δ 22.4 (Pyr C-3 or C-4), 22.6 (Pyr C-4 or C-3), 25.8 (octane C-3, C-6), 27.2 (octane C-2, C-7), 28.2 (octane C-4, C-5), 38.0 (octane C-1, C-8), 53.1 (Pyr C-2 or C-5), 53.5 (Hyd C-5), 53.9 (Pyr C-5 or C-2), 55.2 (CH₂-Pyr), 156.2 (Hyd C-2), 170.8 (Hyd C-4). Anal. Calc. for C₂₆H₄₆Cl₂N₆O₄·0.8H₂O: C, 51.11; H, 7.79; N, 14.90. Found: C, 51.15; H, 7.66; N, 15.00.

3,3’-(Octane-1,8-diyl)bis[(5-piperidin-1-ylmethyl)-imidazolidine-2,4-dione) Dihydrochloride (21b): This compound was obtained from the reaction of 1b and 1,8-disiocyanatooctane by a method similar to that for 19a as a white solid. An analytical sample was obtained by recrystallization from MeCN–MeOH; a white solid; mp 188–195°C (dec). IR (KBr) cm⁻¹: 1786, 1712. FAB-MS (positive) m/z: 505 (M+ H)⁺. 1H-NMR (DMSO-d₆) δ: 1.17–1.24 (8H, m, octane H-3–H-6), 1.33–1.41 (2H, m, Pip H₄-4), 1.49 (4H, ddd, J=14.0, 7.0, 7.0 Hz, octane H-2, H-5), 1.70 (2H, d, J=13.5Hz, Pip H₄-4), 1.78–1.87 (8H, m, Pip H-3, H-5), 2.90–3.09 (4H, m, Pip H-2, H-6), 3.30–3.38 (6H, m, octane H-1, H-8+CHH-Pip), 3.40–3.43 (4H, m, CHH-Pip+Pip H₂-2 or H₂-6), 3.61 (2H, d, J=11.5 Hz, Pip H₂-6 or H₂-2), 4.78 (2H, d, J=9.51 Hz, Hyd H-5), 8.57 (2H, bs, br, Hyd H-1), 10.73 (2H, bs, NH⁺). 13C-NMR (DMSO-d₆): δ 21.0 (Pip C-4, 22.0 (Pip C-3 or C-5), 22.2 (Pip C-5 or C-3), 25.8 (octane C-3, C-6), 27.2 (octane C-2, C-7), 28.2 (octane C-4, C-5), 38.0 (octane C-1, C-8), 51.7 (Pip C-2 or C-5), 52.0 (Hyd C-5), 53.4 (Pip C-6 or C-2), 58.0 (CH₂-Pip), 156.1 (Hyd C-2), 171.0 (Hyd C-4). Anal. Calc. for C₂₅H₄₅Cl₂N₆O₅·1.0H₂O: C, 52.43; H, 8.12; N, 14.11. Found: C, 52.38; H, 7.96; N, 14.13.

3,3’-(Dodecan-1,12-diyl)bis[(5-piperidin-1-ylmethyl)-imidazolidine-2,4-dione) Dihydrochloride (22a): This compound was obtained from the reaction of 1a and 1,12-disocyanatododecane by a method similar to that for 19a as a white solid. An analytical sample was obtained by recrystallization from EtOH; a white solid; mp >200°C (dec). IR (KBr) cm⁻¹: 1782, 1709. FAB-MS (positive) m/z: 477 (M+ H)⁺. 1H-NMR (DMSO-d₆) δ: 1.23–1.26 (4H, m, hexane H-3, H-4), 1.38–1.40 (2H, m, Pip H₂-4), 1.49–1.51 (4H, m, hexane H-2, H-5), 1.7–1.72 (2H, m, Pip H₄-4), 1.80–1.90 (8H, m, Pip H₃-3, H-5), 2.93–3.01 (4H, m, Pip H₂-2, H₂-6), 3.33–3.62 (12H, m, Pip H₂-2, H₂-6+CHH-Pip+hexane H-1, H-6), 4.78 (2H, d, J=9.0Hz, Hyd H-5), 8.53 (2H, brs, Hyd H-1), 10.73 (2H, m, NH⁺). 13C-NMR (DMSO-d₆): δ 20.9 (Pip C-3 or C-5), 21.9 (Pip C-3 or C-5), 22.0 (Pip C-5 or C-3), 25.3 (hexane C-3, C-4), 27.0 (hexane C-2, C-5), 37.8 (hexane C-1, C-6), 51.7 (Pip C-2 or C-6), 51.9 (Hyd C-5), 53.4 (Pip C-6 or C-2), 57.9 (CH₂-Pip), 156.0 (Hyd C-2), 170.9 (Hyd C-4). Anal. Calc. for C₂₅H₄₅Cl₂N₆O₅·1.0H₂O: C, 50.79; H, 7.81; N, 14.81. Found: C, 50.49; H, 7.69; N, 14.74.
imidazolidine-2,4-dione) Dihydrochloride (C, 55.03; H, 8.35; N, 13.80. −from EtOH; a white solid; mp 160–163°C. IR (KBr) cm
solid. An analytical sample was obtained by recrystallization as a white
compound was obtained from the reaction of
and 1,12-diisocyanate by a method similar to that for
(DMSO-
and 4,4-compound was obtained from the reaction of
1a
245°C
(Dec). IR (KBr) cm
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1H-NMR (DMSO-d6, J = 7.0 Hz, dodecane H-2, H-11), 8.44 (2H, s, Hyd H-1), 11.0 (2H, br s, NH +). 13C-NMR (DMSO-d6) δ:
22.4 (Pyr C-3 or C-4), 22.6 (Pyr C-4 or C-3), 25.9 (dodecane C-3, C-10), 27.2 (dodecane C-2, C-11), 28.4, 28.7, 28.8 (dodecane C-4–C-9), 38.0 (dodecane C-1, C-12), 53.1 (Pyr C-2 or C-5), 53.5 (Hyd C-5), 53.9 (Pyr C-5 or C-2), 55.2 (CH2-Pyr), 156.2 (Hyd C-2), 170.8 (Hyd C-4). Anal. Calc. for C28H50Cl2N6O4·0.3H2O: C, 55.04; H, 8.35; N, 13.75. Found: C, 55.03; H, 8.35; N, 13.80.

3.3′-(Dodecyl-1,12-diyl)bis(5-(piperidin-1-ylmethyl)-imidazolidine-2,4-dione) Dihydrochloride (22b): This compound was obtained from the reaction of 1b and 1,12-diisocyanatododecane by a method similar to that for 19a as a white solid. An analytical sample was obtained by recrystallization from EtOH; a white solid; mp 160–163°C. IR (KBr) cm
1870, 1709. FAB-MS (positive) m/z: 561 (M+H)+. 1H-NMR (DMSO-d6) δ: 1.23 (16H, brs, dodecane H–H–I0), 1.36–1.38 (2H, m, Pip H-α), 1.49 (4H, t, J = 7.0 Hz, dodecane H-2, H-11), 1.62–1.72 (2H, m, Pip H-α), 1.80–1.87 (8H, m, Pip H-3, H-5), 2.91–3.01 (4H, m, Pip H-2, H-6), 3.31–3.38 (8H, m, dodecane H-1, H-12), 3.42–3.46 (4H, m, CH2-Pyr), 4.04 (2H, s, Ph-CH2-Ph), 4.81 (2H, t, /uni2032
= 5.5 Hz, Hyd H-5), 7.29–7.36 (8H, m, Ar H), 8.70 (2H, s, Hyd H-1), 11.13 (2H, brs, NH +). 13C-NMR (DMSO-d6) δ:
22.4 (Pyr C-3 or C-4), 22.7 (Pyr C-4 or C-3), 40.1 (Ph-CH2-Ph), 53.3 (Pyr C-2 or C-5), 53.7 (Hyd C-5), 54.0 (Pyr C-5 or C-2), 55.1 (CH2-Pyr), 126.7 (Ar C-2, C-2, C-6, C-6), 128.9 (Ar C-3, C-3, C-5, C-5), 129.8 (Ar C-, C-1’), 140.8 (Ar C-4, C-4’), 155.2 (Hyd C-2), 170.0 (Hyd C-4). Anal. Calc. for C32H36Cl2N6O6·0.3H2O: C, 57.20; H, 6.06; N, 13.80. Found: C, 57.19; H, 6.12; N, 13.81.

References and Notes


21) In our previous paper (refs. 19, 20), we showed the preparation of this symmetrical bivalent compound 24b and its antibacterial activity (MIC values against S. aureus and E. coli strains (MIC = 0.024 and 0.095 μg/ml, respectively).

From a stereochemical viewpoint, these products 19–24 can be considered to be a mixture of three twin-drug type molecules, i.e., two C$_2$-symmetrical molecules that have the same absolute configuration (R,R or S,S) regarding two chiral hydantoin rings in the molecules and a Cs-symmetrical meso compound having different absolute configurations (R,S). We distinguished the presence of three predominant stereoisomers in the free base of product 24b by an HPLC method (CHIRALPAK IA$^®$).20) We used stereoisomeric mixtures for calorimetric experiments and for the biological evaluation (antibacterial activity).


27) Regarding small molecule antagonists of glycosaminoglycan sulfates, it has been demonstrated that the identification of small molecule antagonists against such glycosaminoglycans may lead to the development of new pharmacological agents to treat infectious diseases that involve a glycosaminoglycan sulfate binding stage (for example, see following reference). Schuksz M., Fuster M. M., Brown J. R., Crawford B. E., Ditto D. P., Lawrence R., Glass C. A., Wang L., Tor Y., Esko J. D., Proc. Natl. Acad. Sci. U.S.A., 105, 13075–13080 (2008).
