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SYNTHESIS OF THE IDENTICAL LINKER MODE TWIN-DRUG TYPE C2-SYMMETRICAL MOLECULES

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Abstract – In connection with our studies on antibacterial active compounds against gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) strains, some molecular modifications were attempted. In this study, molecular transformations of aminoguanidines and related amines to the represented C2-symmetrical molecules (**Aa**–**b**, **Ba**–**b**, and **Ca**–**b**) were investigated. In addition, some C3-symmetrical compounds (**Da**–**b**) were also prepared.

INTRODUCTION

With reference to work on new antibacterial compounds, extensive efforts have been made to find new promising candidates. Many reports on molecular recognition properties of symmetrical macromolecules have appeared,[1] and it is well known that many receptors or membrane proteins in the native state often have a high order of symmetrical interface. In the infection process by bacteria or virus, microorganisms usually use sugar-binding proteins such as lectins.[2] We have been interested in compounds that interfere with such a recognition process in order to find new leads for antibacterial agents.[3] Since molecular recognition via complexes of C2- or C3-symmetry (2-fold or 3-fold symmetrical geometry) is a common feature of several important receptors,[4] we have designed twin-drug type symmetrical molecules in connection with our studies on antibacterial compounds.[5] In this article, syntheses of target designed C2- or C3-symmetrical molecules in the search for biologically active leads are described.

DESIGN OF TARGET SYMMETRICAL MOLECULE

In terms of molecular symmetry, small symmetrical molecules frequently appear in various synthetic twin-drug type molecules[5] and biologically active compounds. Biologically active C2-symmetrical molecules are usually constructed on a symmetrical alkyl linker or another symmetrical aromatic template.[5,6] For linker mode twin-drug symmetrical molecules, the nature of a linker plays an important role in binding to the receptor site for biological activity.[5,6] It was thought worthwhile to undertake a synthetic molecular modification study with the aim of obtaining new canditates with antibacterial activity. From this point of view, molecular modification of aminoguanidines seemed to be interesting because some aminoguanidine derivatives are known to interfere with the cross-linking of sugar chains.[7] Furthermore, a number of bacteria utilize heparan sulfate proteoglycans such as syndecans as attachment factors for host epithelia for coursing infections in many body sites. Heparan sulfate sugar chains have a repeated sulfated structure of sugar units.[8] These facts encouraged us to design C2-symmetrical structures having two guanidine groups in the target molecules, because a guanidine functionality (a guanidinium ion structure in physiological conditions) is expected to interfere with anionic sulfate moieties of heparan sulfate sugar chains by charge-charge (ionic) interactions.[5] We therefore carried out synthetic investigation of new C2-symmetrical derivatives (**Aa**, and **Ab**) (Figure 1). Molecular modification of the represented C2-symmetrical molecules (**A**) can be considered to be an identical twin-drug type approach utilizing a biphenyl scaffold as a linker.

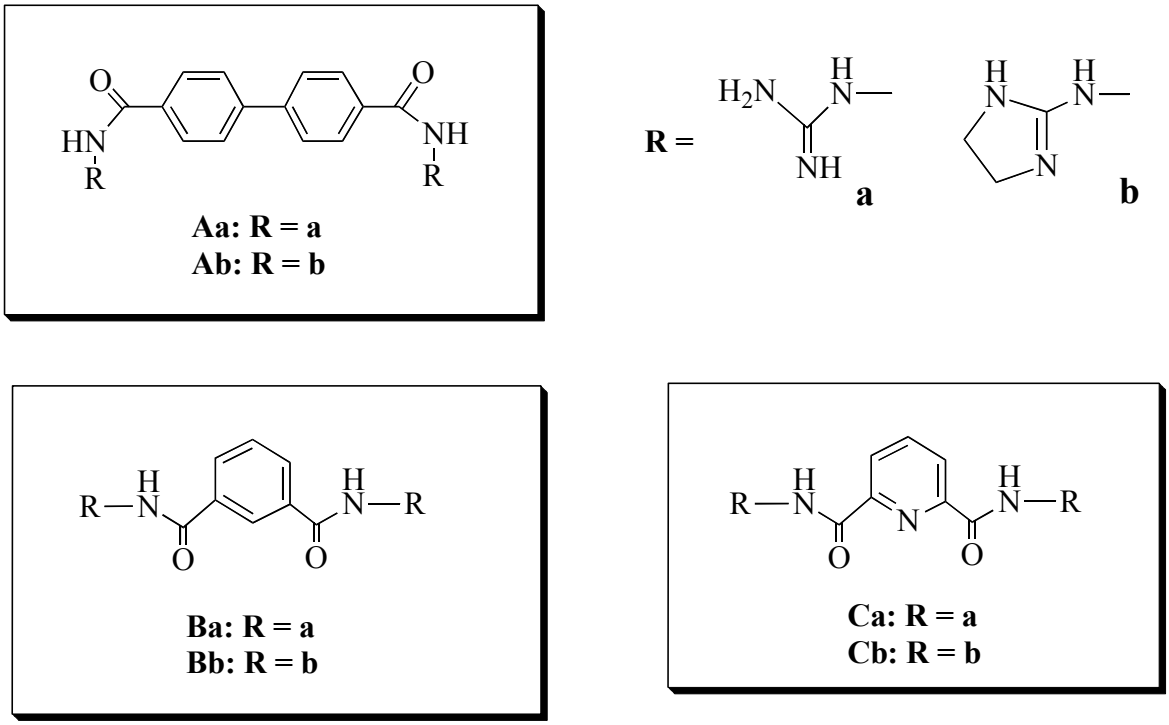
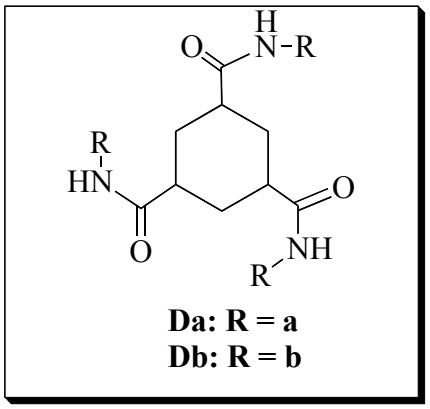


Figure 1

We also designed C2-symmetrical molecules represented as structure **B** or **C** (Figure 1). In addition, we prepared C3-symmetrical cis-1,3,5-trisubstituted molecules **Da** and **Db** (Figure 2) from the reaction of 1,3,5-cis-cyclohexanetricarbonyl chloride[9] and corresponding aminoguanidines for bioassay and comparison of antibacterial activity with that of C2-symmetrical target molecules. These modifications to C3-symmetrical molecules can also be considered to be an identical triplet-drug type approach in the search for bioactive leads.



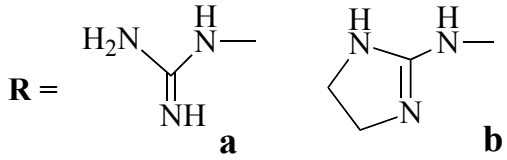


Figure 2

CHEMISTRY AND RESULTS

Synthesis of identical linker mode twin-drug type C2-symmetrical molecules (**A**, **B**, and **C**) could be achieved by condensation reaction of the corresponding dicarbonyl chloride as templates and aminoguanidines or corresponding amines. The C2-symmetrical structures of the synthesized compounds were easily confirmed by ^{13}C-NMR spectroscopic analysis. All of the twin-drug type compounds showed magnetically equivalent spectroscopic signal patterns (appearance of signals assignable to half of the symmetrical molecules), indicating a C2-symmetrical molecular feature in solution (see Experimental). Symmetrical target compound (**Ba**) could be obtained from the reaction of isophthaloyl chloride with aminoguanidine.

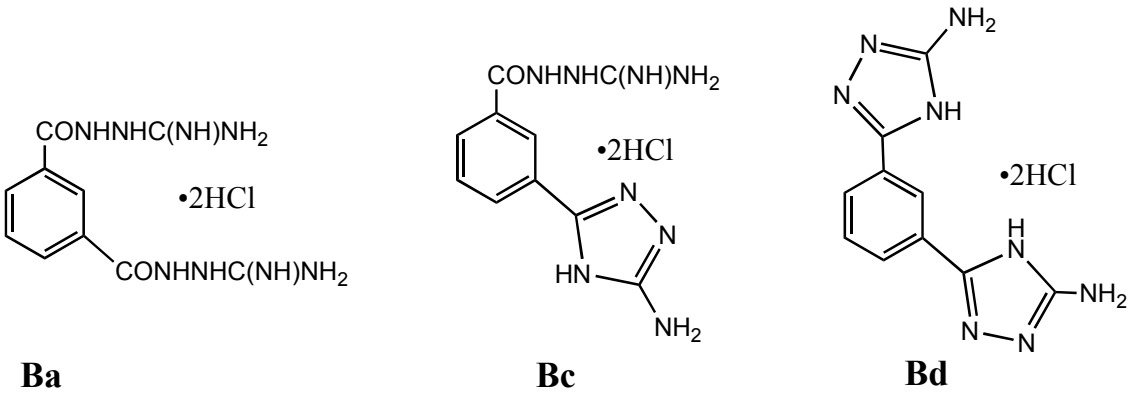


Figure 3

TLC analysis of the reaction products of isophthaloyl chloride with aminoguanidine indicated the formation of three types of derivatives (Figure 3**)**. Compound **Ba** was easily dehydrated to give cyclized heterocyclic compounds (**Bc** and **Bd)**, and the ratio of the three products was dependent on the reaction conditions. At an elevated reaction temperature, a condensed target derivative (**Ba**) further proceeded the intramolecular dehydration reaction of both acyl aminoguanidines in the molecule, and compound **Bd** was obtained as a sole product. At a lower reaction temperature, a monodehydrated unsymmetrical product (**Bc**) could be isolated (see Experimental). By NMR spectroscopic analysis of signal patterns, compound **Bd** also showed a C2-symmetrical molecular feature in solution (see Experimental). C3-symmetrical compounds (**Da** and **Db**) were also prepared from the reaction of 1,3,5-*cis*-cyclohexanetricarbonyl chloride with corresponding amines. The C3-synmetrical structures of the products were easily confirmed by ^{13}C-NMR spectroscopic analysis (see Experimental data).

A bioassay for antibacterial activity [determination of the minimum concentrations (MICs) of the compounds] was carried out by authentic methods according to the Japanese Society of Chemotherapy. Most of the synthesized C2- or C3-symmetrical molecules showed no remarkable antibacterial activity against either *Escherichia coli* (gram-negative) or *Staphylococcus aureus* (gram-positive). However, two compounds (**Aa** and **Ab**) that used biphenyl as a linker showed significant antibacterial activity (MIC = 0.330 and 0.225 μM/mL, respectively) against *E. coli* but did not show remarkable antibacterial activity against *S. aureus* strain.

Further synthetic applications on the basis of the above chemical and biological information for related symmetrical derivatives, particularly in the search for biological active lead compounds, are under investigation.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured by a Shimadzu FT/IR-8100 spectrometer. The ^{1}H- and ^{13}C-NMR spectra were obtained by a JEOL JNM A-500 at 35 °C. 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.

Assays for Antibacterial Activity

We used *S. aureus* ATCC6538P and *E. coli* NBRC14237 (NIHJ) (gram-positive and gram-negative bacteria, respectively) as target organisms. Synthesized compounds (**A, B, C, and D**) 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.[10,11]

2,2'-(4, 4'-Biphenyl-1,1'-dicarbonyl)bis(hydrazinecarboximidamide) Dihydrochloride (Aa)

A mixture of biphenyl-4,4'-dicarbonyl dichloride (0.50 g, 1.79 mmol) and aminoguanidine hydrochloride (0.79 g, 7.14 mmol) in a round-bottomed flask was heated slowly up to 200 °C in an oil bath and kept for 10 min. After cooling, the mixture was triturated with water. Insoluble material **Aa** (0.53 g, 69.3%) was collected by filtration. Mp >200 °C (dec). IR (KBr) cm^{-1}: 3372, 3293, 3211, 3139, 1660, 1626, 1597. FAB-MS (positive) *m/z*: 355 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 7.4–8.2 (8H, br, C=($N^+\underline{H}_2$)N$\underline{H}_2$), 7.92 (4H, d, J = 8.5 Hz, Ar H-3, H-5, H-3', H-5'), 8.07 (4H, d, J = 8.5 Hz, Ar H-2, H-6, H-2', H-6'), 9.75 (2H, br, CONHN$\underline{H}$), 10.75 (2H, br, CON$\underline{H}$NH), ^{13}C-NMR (DMSO-d_6) δ: 126.7 (Ar C-3, C-5, C-3', C-5'), 128.6 (Ar C-2, C-6, C-2', C-6'), 131.2 (Ar C-1, C-1'), 142.3 (Ar C-4, C-4'), 158.8 (NH$\underline{C}$(=NH)NH_2), 166.0 ($\underline{C}$O). *Anal*. Calcd for $C_{16}H_{18}N_8O_2$ • 2HCl: C, 44.97; H, 4.72; N, 26.22. Found: C, 44.70; H, 4.77; N, 26.50.

***N*'^{4},*N*'$^{4'}$-Bis(4,5-dihydro-1*H*-imidazol-2-yl)biphenyl-4,4'-dicarbohydrazide Dihydribromide (Ab)**

A mixture of biphenyl-4,4'-dicarbonyl dichloride (0.80 g, 2.86 mmol) and 2-hydrazinoimidazoline hydrobromide (1.14 g, 6.30 mmol) in a round-bottomed flask was heated slowly up to 190 °C in an oil bath and kept for 40 min. After cooling, the precipitated material was recrystallized from water to give **Ab** dihydrobromide (0.88 g, 54.0%). The mother liquor was made alkaline with K_2CO_3 and the precipitated material was filtered to give an **Ab** free base. To a solution of this free base in MeOH (10 mL) was added a solution of 10% hydrochloride in MeOH (4 mL). Concentration of the solvent gave **Ab** hydrochloride (0.48 g, 35.0%, mp >230 °C). Total yield was 89.0%. The following data was shown as dihydrobromide. Mp >230 °C. IR (KBr) cm^{-1}: 3181, 1683, 1652. FAB-MS (positive) *m/z*: 407 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 3.70 (8H, s, imidazole H-4, H-5), 7.94 (4H, d, J = 8.5 Hz, Ar H-3, H-5, H-3', H-5'), 8.06 (4H, d, J = 8.5 Hz, Ar H-2, H-6, H-2', H-6'), 8.2–9.2 (4H, br, imidazole -N$\underline{H}$-C=$N^+\underline{H}$-), 10.40 (2H, br, CONHN$\underline{H}$), 10.92 (2H, br, CON$\underline{H}$NH), ^{13}C-NMR (DMSO-d_6) δ: 42.8 (imidazole C-4, C-5), 126.8 (Ar C-3, C-5, C-3', C-5'), 128.6 (Ar C-2, C-6, C-2', C-6'), 131.0 (Ar C-1, C-1'), 142.4 (Ar C-4, C-4'), 160.9 (imidazole C-2), 166.0 ($\underline{C}$O). *Anal*. Calcd for $C_{20}H_{22}N_8O_2$ • 2HBr: C, 42.27; H, 4.26; N, 19.72. Found: C, 42.35; H, 4.22; N, 19.66.

Reaction of Isophthaloyl Dichloride with Aminoguanidine Hydrochloride:

Formation of (Ba) and (Bc)

A mixture of isophthaloyl chloride (0.50 g, 2.46 mmol) and aminoguanidine hydrochloride (0.66 g, 5.97 mmol) in a round-bottomed flask was heated slowly up to 177 °C in an oil bath and kept for 10 min. After cooling, EtOH (5 mL) was added to the reaction mixture and insoluble material **Ba** (0.44 g, 50.9%) was

collected by filtration. The filtrate was concentrated *in vacuo* and the residue was recrystallized from EtOH to give **Bc** (0.10 g, 12.2%).

2,2'-(1,3-Phenylenedicarbonyl)bis(hydrazinecarboximidamide) Dihydrochloride (Ba)

Mp 233 °C (dec). IR (KBr) cm^{-1}: 1658. FAB-MS (positive) *m/z*: 279 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 7.64–7.67 (1H, m, Ar H-5), 7.7–8.0 {8H, br, C=(N^+H_2)NH_2}, 8.15–8.16 (2H, m, Ar H-4, H-6), 8.61 (1H, s, Ar H-2), 9.81 (2H, s, CONHNH), 10.87 (2H, br, CONHNH), ^{13}C-NMR (DMSO-d_6) *δ:* 127.9 (Ar C-2), 128.3 (Ar C-5), 131.3 (Ar C-4, C-6), 131.9 (Ar C-1, C-3), 158.8 {NHC(=NH)NH}, 165.9 (CO). *Anal*. Calcd for $C_{10}H_{14}N_8O_2$ • 2HCl • H_2O: C, 32.53; H, 4.91; N, 30.35. Found: C, 32.50; H, 4.84; N, 30.36.

2-(3-(5-Amino-4*H*-1,2,4-triazol-3-yl)phenylcarbonyl)hydrazinecarboximidamide Dihydrochloride (Bc)

Mp >240 °C (EtOH). IR (KBr) cm^{-1}: 1688, 1670, 1651. FAB-MS (positive) *m/z*: 261 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 7.2–8.2 [8H, m, {C=(N^+H_2)NH_2} + {triazole –NH + -N^+H_3}], 7.67 (1H, t, *J* = 7.9 Hz, Ar H-5), 8.08 (1H, t, *J* = 7.9 Hz, Ar H-6), 8.15–8.19 (1H, m, Ar H-4), 8.55 (1H, br s, Ar H-2), 9.81 (1H, br s, CONHNH), 10.84 (1H, br s, CONHNH), ^{13}C-NMR (DMSO-d_6) *δ:* 125.7 (Ar C-2), 126.6 (Ar C-3), 129.0 (Ar C-5), 129.3 (Ar C-4), 129.6 (C-6), 132.6 (Ar C-1), 149.8 (triazole C-3), 153.1 (triazole C-5), 158.8 {NHC(=NH)NH}, 165.9 (CO). *Anal*. Calcd for $C_{10}H_{12}N_8O$ • 2HCl • $1.4H_2O$: C, 33.51; H, 4.72; N, 31.26. Found: C, 33.43; H, 4.61; N, 31.43.

***N*'^{1},*N*'^{3}-Bis(4,5-dihydro-1*H*-imidazol-2-yl)benzene-1,3-dicarbohydrazide Dihydrobromide (Bb)**

A mixture of isophthaloyl chloride (0.50 g, 2.46 mmol) and 2-hydrazinoimidazoline hydrobromide (1.06 g, 5.86 mmol) in a round-bottomed flask was heated slowly up to 220 °C in an oil bath and kept for 3 min. After cooling, the precipitate material was recrystallized from MeOH (5 mL) to give **Bb** (0.66 g, 54.5%). Mp >245 °C (dec). IR (KBr) cm^{-1}: 3227, 3154, 1690, 1658, 1618. FAB-MS (positive) *m/z*: 331 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.69 (8H, s, imidazole H-4, H-5), 7.69 (1H, t, *J* = 7.9 Hz, Ar H-5), 8.14–8.16 (2H, m, Ar H-4, H-6), 8.52 (1H, s, Ar H-2), 8.69 (4H, br, imidazole -NH-C=N^+H-), 10.46 (2H, s, CONHNH), 10.92 (2H, s, CONHNH), ^{13}C-NMR (DMSO-d_6) *δ:* 42.8 (imidazole C-4, C-5), 127.7 (Ar C-2), 128.4 (Ar C-5), 131.3 (Ar C-4, C-6), 131.9 (Ar C-1, C-3), 160.8 (imidazole C-2), 165.8 (CO). *Anal*. Calcd for $C_{14}H_{18}N_8O_2$ • 2HBr • 1.6 H_2O: C, 32.28; H, 4.49; N, 21.51. Found: C, 32.29; H, 4.68; N, 21.64.

3,3'-(1,3-Phenylene)bis(4*H*-1,2,4-triazol-5-amine) Dihydrochloride (Bd)

A mixture of isophthaloyl chloride (0.69 g, 3.40 mmol) and aminoguanidine hydrochloride (0.83 g, 7.51 mmol) in a round-bottomed flask was heated slowly up to 210 —240 °C in an oil bath and kept for 3.5 h. After cooling, MeOH (30 mL) was added to the reaction mixture and separated insoluble material was collected by filtration. The solid material was recrystallized from c-HCl. The crystal material was dissolved in water and the aqueous solution was made alkaline with K_2CO_3. The precipitated material was

filtered and purified by silica gel column chromatography with EtOH-28% ammonia solution (100 : 3) as a solvent to afford **Bd** as a free base. Treatment with 10% methanolic hydrochloride (4 mL) gave **Bd** dihydrochloride (0.45 g, 42.1%). Mp >240 °C (dec). IR (KBr) cm^{-1}: 1689. FAB-MS (positive) *m/z*: 243 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 7.0–9.0 (8H, br, NH + -N^+H_3), 7.72 (1H, t, *J* = 7.9 Hz, Ar H-5), 8.13 (2H, dd, *J* = 7.9, 1.8 Hz, Ar H-4, H-6), 8.52 (1H, t, *J* = 1.8 Hz, Ar H-2). ^{13}C-NMR (DMSO-d_6) *δ:* 123.3 (Ar C-2), 126.8 (Ar C-1, C-3), 128.0 (Ar C-4, C-6), 129.8 (Ar C-5), 149.1 (triazole C-3), 152.7 (triazole C-5). *Anal*. Calcd for $C_{10}H_{10}N_8 \cdot 2HCl \cdot 0.2H_2O$: C, 37.68; H, 3.92; N, 35.15. Found: C, 37.81; H, 3.87; N, 34.87.

2,2'-(1,3-Pyridinedicarbonyl)bis(hydrazinecarboximidamide) Dihydrochloride (Ca)

A mixture of pyridine-2,6-dicarbonyl dichloride (0.50 g, 2.45 mmol) and aminoguanidine hydrochloride (0.67 g, 6.06 mmol) in a round-bottomed flask was heated slowly up to 145 °C in an oil bath and kept for 3 min. After cooling, the reaction mixture was triturated with water and concentrated *in vacuo*. The solid residue was recrystallized from MeOH to give **Ca** (0.24 g, 27.9%). Mp 240 °C (dec). IR (KBr) cm^{-1}: 3364, 3154, 1682. FAB-MS (positive) *m/z*: 280 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 7.5–8.0 {8H, br, C=(N^+H_2)NH_2}, 8.27–8.28 (3H, m, Pyridine H-3, H-4, H-5), 10.07 (2H, s, CONHNH), 11.38 (2H, s, CONHNH), ^{13}C-NMR (DMSO-d_6) *δ:* 125.3 (Pyridine C-3, C-5), 139.6 (Pyridine C-4), 147.4 (Pyridine C-2, C-6), 158.9 {NHC(=NH)NH}, 163.0 (CO). *Anal*. Calcd for $C_9H_{13}N_9O_2 \cdot 2HCl \cdot 1.5H_2O$: C, 28.51; H, 4.78; N, 33.24. Found: C, 28.40; H, 4.55; N, 33.17.

***N*'^{2},*N*'^{6}-Bis(4,5-dihydro-1*H*-imidazol-2-yl)pyridine-2,6-dicarbohydrazide Hydrobromide • Hydrochloride (Cb)**

A solution of pyridine-2,6-dicarbonyl dichloride (0.50 g, 2.45 mmol) and 2-hydrazinoimidazoline hydrobromide (1.06 g, 5.86 mmol) in DMF (1 mL) was stirred at 130 °C for 3 min under an N_2 stream. After cooling, precipitated material was washed with AcOEt and dissolved in water (1 mL). Addition of EtOH (1 mL) and isoPrOH (2 mL) to the solution gave **Cb** (0.62 g, 53.9%). Mp >240 °C. IR (KBr) cm^{-1}: 3165, 1702, 1655, 1604. FAB-MS (positive) *m/z*: 332 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) *δ:* 3.70 (8H, br s, imidazole H-4, H-5), 8.29 (3H, s, Pyridine H-3, H-4, H-5), 8.7 (4H, br, imidazole -NH-C=N^+H-), 10.67 (2H, br s, CONHNH), 11.57 (2H, s, CONHNH), ^{13}C-NMR (DMSO-d_6) *δ:* 42.8 (imidazole C-4, C-5), 125.5 (pyridine C-3, -5), 139.8 (Pyridine C-4), 147.2 (Pyridine C-2, C-6), 160.8 (imidazole C-2), 162.8 (CO). *Anal*. Calcd for $C_{13}H_{17}N_9O_2 \cdot 1.5HBr \cdot 0.5HCl \cdot 1.5H_2O$: C, 31.36; H, 4.45; N, 25.32. Found: C, 31.32; H, 4.64; N, 25.05.

2, 2', 2"-(1,3,5-Cylohexanetricarbonyl)tris(carboximidamide) Trihydrochloride (Da)

A mixture of 1,3,5-*cis*-cyclohexanetricarbonyl chloride[9] (0.50 g, 1.84 mmol) and aminoguanidine hydrochloride (0.73 g, 6.60 mol) in a round-bottomed flask was heated slowly up to 165 °C in an oil bath

and kept for 5 min. After cooling, the precipitated solid material was washed with MeOH/EtOH to give **Da** (0.53 g, 58.5%). Mp 248–250 °C (dec). IR (KBr) cm^{-1}: 3363, 3141, 1662. FAB-MS (positive) *m/z*: 385 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.40–1.48 (3H, dd, J = 15.5, 12.5 Hz, Cyclehexane H_A-2, H_A-4, H_A-6), 2.12 (3H, d, J =12.5 Hz, Cyclehexane H_B-2, H_B-4, H_B-6), 2.50–2.51 (3H, m, Cyclohexane H-1, H-3, H-5), 7.58–7.69 {12H, br, C=(N^+H_2)NH_2}, 9.58 (3H, s, CONHNH), 10.21 (3H, s, CONHNH), ^{13}C-NMR (DMSO-d_6) δ: 30.0 (Cyclohexane C-2, C-4, C-6), 40.4 (Cyclohexane C-1, C-3, C-5), 158.6 {NHC(=NH)NH}, 174.1 (CO). *Anal*. Calcd for $C_{12}H_{24}N_{12}O_3$ • 3 HCl • H_2O: C, 28.16; H, 5.71; N, 32.84. Found: C, 28.25; H, 5.71; N, 32.86.

***N*'^{1},*N*'^{3},*N*'^{5}-Tris(4,5-dihydro-1*H*-imidazol-2-yl)cyclohexane-1,3,5-tricarbohydrazide Trihydrobromide (Db)**

A mixture of 1,3,5-*cis*-cyclohexanetricarbonyl chloride[9] (0.30 g, 1.10 mmol) and 2-hydrazinoimidazoline hydrobromide (0.66 g, 3.65 mmol) in a round-bottomed flask was heated slowly up to 180 °C in an oil bath and kept for 10 min. After cooling, the resulting mixture was washed with EtOH/isoPrOH to give **Db** (0.31 g, 39.8%). Mp >250 °C. IR (KBr) cm^{-1}: 3179, 1712, 1645. FAB-MS (positive) *m/z*: 463 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.41–1.49 (3H, m, Cyclehexane ring H_A-2, H_A-4, H_A-6), 2.12–2.14 (3H, m, Cyclehexane ring H_B-2, H_B-4, H_B-6), 2.31–2.37 (3H, m, Cyclehexane ring H-1, H-3, H-5), 3.64 (12H, s, imidazole H-4, H-5), 8.50 (6H, br, imidazole -NH-C=N^+H-), 10.26 (3H, s, CONHNH), 10.40 (3H, s, CONHNH), ^{13}C-NMR (DMSO-d_6) δ: 30.0 (Cyclehexane ring C-2, C-4, C-6), 40.4 (Cyclehexane ring C-1, C-3, C-5), 42.7 (imidazole C-4, C-5), 160.7 (imidazole C-2), 173.9 (CO). *Anal*. Calcd for $C_{18}H_{30}N_{12}O_3$ • 3 HBr: C, 30.66; H, 4.72; N, 23.83. Found: C, 30.82; H, 4.87; N, 23.90.

REFERENCES AND NOTES

1. G. V. Oshovsky, D. N. Reinhoudt, and W. Verboom, *Angew. Chem. Int. Ed.,* 2007, **46**, 2366; M. Mazik and H. Cavga, *J. Org. Chem.*, 2006, **71**, 2957; P. B. Palde, P. C. Gareiss, and B. L. Miller, *J. Am. Chem. Soc.*, 2008, **130**, 9566.
2. A. Imberty and A. Varrot, *Curr. Opin. Struct. Biol.,* 2008, **18**, 567.
3. F. Fujisaki, K. Shoji, M. Shimodouzono, N. Kashige, F. Miake, and K. Sumoto, *Chem. Pharm. Bull*., 2010, **58**, 1123.
4. L. E. Browne, L. Cao, H. E. Broomhead, L. Bragg, W. J. Wilkinson, and R. A. North, *Nat. Neurosci.,* 2011, **14**, 17; A. I. Sobolevsky, M. P. Rosconi, and E. Gouaux, *Nature,* 2009, **462**, 745; I. J. Balzarini, *Antiviral Res.,* 2006, **71**, 237 and related references cited therein.
5. G. W. Camille, 'The Practice of Medicinal Chemistry" 3rd ed., Academic Press, San Diego, 2008.
6. V. M. Krishnamurthy, L. A. Estroff, and G. M. Whitesides, "Multivalency in Ligand Design", in

Fragment-based Approaches in Drug Discovery, ed. by W. Jahnke, D. A. Erlanson, and R. Mannhold, Wiley-VCH, Weinheim, 2006, pp. 11-53.

7. R. Nagai, T. Araki, C. M. Hayashi, F. Hayase, and S. Horiuchi, *J. Chromatogr. B,* 2003, **788**, 75.
8. A. Varki, 'Essentials of Glycobiology' 2nd ed. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y, 2009, pp. 719-732.
9. We prepared 1,3,5-*cis*-cyclohexanetricarbonyl chloride from the reaction of 1,3,5-*cis*-cyclohexanetricarboxylic acid with $SOCl_2$ *in situ* and used it without further purification. Thus, a mixture of 1,3,5-*cis*-cyclohexanetricarbxylic acid (13 g, 60.2 mmol) and $SOCl_2$ (50 g, 420 mmol) was heated at 65–82 °C for 30 h. Removal of excess $SOCl_2$ gave 1,3,5-*cis*-cyclohexanetricarbonyl chloride in quantitative yield. (see H. H. Weyland, E. E. Hamel, Division of U. S.3,551,469 (*Chem. Abstr*., 74, 64954z).
10. The report of the committee for antimicrobial susceptibility measurement method, The Japanese Society of Chemotherapy (1989). *Chemotherapy*, 1990, **38**, 102.
11. The report of the committee for antimicrobial susceptibility measurement method, The Japanese Society of Chemotherapy (1992). *Chemotherapy*, 1993, **41**, 184.