Supporting Information
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Supporting Information

Tetramic acids as scaffolds: synthesis, tautomeric and antibacterial behaviour

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Figure 4. $^{13}$C NMR spectra (125 MHz, A) and $^1$H NMR (500 MHz, D) of 1e in CD$_3$OD. The insets show the carbon peak on C(3) in CD$_3$OD (B) and acetone-d6 (C).

Experimental Section

1. General

1.1. Synthesis and calculation
Melting points were determined with a Stuart Scientific SMP1 melting point device and are uncorrected. The $^1$H NMR spectra were obtained using a Bruker AVB500 (500 MHz), Avance AV400 (400 MHz), DPX400 (400 MHz), and $^{13}$C NMR spectra were obtained using a Bruker AVB500 (126 MHz), Avance AV400 (101 MHz), DPX400 (101 MHz) with residual solvent peaks or tetramethylsilane as the internal reference. Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained with Micro Mass LCT and GCT spectrometers under the conditions of electrospray ionization (ESI) and chemical ionization (CI) respectively, and values were reported as a ratio of mass to charge in Daltons. Optical rotations were read on a Perkin Elmer 241 polarimeter
using the sodium D line (589 nm) and $[\alpha]_D$ were given in units of $10^{-1}$ deg dm$^2$g$^{-1}$. The energy was calculated in equilibrium geometry at ground state with Density Functional B3LYP (6-31G*) in Spartan 02.

1.2. Biological test

The compounds were dissolved in 70 % DMSO in water, and then serially diluted, normally 2-fold, in water for desired concentration (1.0 mg/ml, 0.8 mg/ml, 0.4 mg/ml, 0.2 mg/ml, 0.1 mg/ml). 100 µl of each concentration of the compounds to be tested were placed in 1 cm diameter holes in the agar plate containing an adequate dilution of the test organism and incubated overnight at 37 °C. The diameters of the resultant inhibition zones were measured, and amounts of product were estimated by reference to standards prepared with Cephalosporin C.

2. Synthesis

2.1. Synthesis of tetramic acids by Dieckmann condensation

2.1.1. Synthesis of pyrrolidine-2,4-dione (1a)

![Structure of 1a](image)

Pyrrolidine-2,4-dione (1a) as a solid was prepared from glycine ethyl ester hydrochloride (2a) and mono-ethyl malonate as the literature procedure.$^{3b}$

Keto: enol = 58: 42 in DMSO.

$^1$H NMR (400 MHz, DMSO); 11.34 (brs, 1H of enol, OH), 8.26 (s, 1H, NH of keto), 7.13 (s, 1H, NH of enol), 4.76 (s, 1H, H3 of enol), 3.77 (s, 2H, H5 of keto), 3.74 (s, 2H, H5 of enol), 2.93 (s, 2H, H3 of keto).

$^{13}$C NMR (100 MHz, DMSO); 208.79 (C4 of keto), 176.16 (C4 of enol), 175.16 (C2 of enol), 172.34 (C2 of keto), 95.04 (C3 of enol), 54.19 (C3 of keto), 47.39 (C5 of enol), 41.85 (C5 of keto).

2.1.2. Synthesis of ethyl 2-(hexylamino)acetate (2d)

![Structure of 2d](image)

To a glycine ethyl ester hydrochloride 2a (20.0 g, 144 mmol) in EtOH (400 ml) was added Et$_3$N (58.0 g, 577 mmol) and 1-bromohexane (12.0 g, 72.2 mmol). The mixture was refluxed for 24 hr. Concentration in vacuo followed by flash column chromatography gave the compound 2d (6.76 g, 36.1 mmol, 50 % yield) as a liquid.

$^1$H NMR (400 MHz, CDCl$_3$); 4.18 (q, 2H, $J = 7.2$ Hz, H3), 3.38 (s, 2H, H1), 2.58 (t, 2H, $J = 7.2$ Hz, H5), 1.63 (brs, 1H, NH), 1.49-1.44 (m, 2H, H6), 1.32-1.25 (m, 9H, H4, H7-H9), 0.87 (t, 3H, $J = 7.2$ Hz, H8).
Hz, H10). $^{13}$C NMR (100 MHz, CDCl$_3$); 172.62 (C2), 60.69 (C3), 51.04 (C1), 49.68 (C5), 31.74 (C8), 30.04 (C6), 26.93 (C7), 22.62 (C9), 14.24 (C4), 14.07 (C10). MS (ES$^+$); 188.5, HRMS (M+H); calcd for C$_{10}$H$_{22}$N$_1$O$_2$; 188.1645; found; 188.1645.

2.1.3. Synthesis of ethyl 3-((2-ethoxy-2-oxoethyl)(hexyl)amino)-3-oxopropanoate (2e)

To a stirred solution of compound 2d (3.9 g, 20.8 mmol), 4-dimethylaminopyridine (0.25 g, 2.1 mmol) and dicyclohexylcarbodiimide (4.5 g, 21.9 mmol) in CH$_2$Cl$_2$ (150 ml) was added mono-ethyl malonate (2.9 g, 21.9 mmol). The mixture was stirred for overnight at room temperature. The mixture was filtered and concentrated with DCM. Concentration in vacuo followed by flash column chromatography gave compound 2e (5.2 g, 17.3 mmol, 80% yield) as a liquid.

$^1$H NMR (400 MHz, CDCl$_3$, mixture of rotamers, a; major, b; minor); 4.09-4.00 (m, 4H, H3, H8), 3.93 (s, 2H, H1b), 3.92 (s, 2H, H6a), 3.26-3.22 (m, 4H, H6b, H10b), 3.19 (t, 2H, J = 8.0 Hz, H10a), 1.45-1.42 (m, 2H, H11a), 1.38-1.34 (m, 2H, H11b), 1.17-1.10 (m, 12H, H4, H9, H11-H14), 0.76-0.70 (m, 3H, H15). $^{13}$C NMR (100 MHz, CDCl$_3$, mixture of rotamers, a; major, b; minor); 169.02 (quart Cb), 168.78 (quart Ca), 167.30 (quart Cb), 167.19 (quart Ca), 166.30 (quart Ca), 166.19 (quart Cb), 61.57 (OCbH2CH3), 61.27 (OCH2CH3), 50.01 (C1b), 49.69 (C1a), 47.49 (C10), 41.31 (C6b), 40.74 (C6a), 31.42 (C13b), 31.34 (C13a), 28.37 (C11b), 27.07 (C11a), 26.26 (C12), 22.42 (C14), 14.00 (C4, C9), 13.84 (C15). MS (ES$^+$); 302.3, HRMS (M+Na); calcd for C$_{15}$H$_{27}$N$_1$NaO$_5$; 324.1782; found; 324.1781.

2.1.4. Synthesis of 1-hexyl-3-ethyl ester pyrrolidine-2,4-dione (2f)

To the solution of compound 2e (4.2 g, 14.0 mmol) in the mixture solution of benzene (100 ml) and ethanol (10 ml) was added sodium methoxide (0.83 g, 15.4 mmol) and the mixture was refluxed for 4 hour. After completion of reaction, the mixture was cooled and diluted with water (20 ml) and the two phases were separated. The aqueous layer was carefully acidified with conc. hydrochloric acid under 0°C and 2f (3.4 g, 13.2 mmol, 94%) was precipitated as a white powder.

M.P.; 103°C. $^1$H NMR (400 MHz, CD$_2$OD); 4.31 (q, 2H, J = 7.2 Hz, H13), 4.06 (s, 2H, H5), 3.41 (t, 2H, J = 7.2 Hz, H6), 1.61-1.54 (m, 2H, H7), 1.50-1.32 (m, 9H, H8-10, H14), 0.92 (t, 3H, J = 7.2 Hz,
H11). $^{13}$C NMR (100 MHz, CD$_3$OD); 183.10 (C4), 170.36 (C2), 165.63 (C12), 99.29 (C3), 61.52 (C13), 51.07 (C5), 42.59 (C6), 32.73 (C9), 29.27 (C7), 27.65 (C8), 23.78 (C10), 14.83 (C14), 14.52 (C11). MS (ES$^-$); 254.4, MS (ES$^+$); 256.4, HRMS (M-H); calcd for C$_{13}$H$_{20}$N$_2$O$_4$; 254.1399; found; 254.1398.

2.1.5. Synthesis of 1-hexyl-pyrrolidine-2,4-dione (1b)

Compound 2f (1.0 g, 3.9 mmol) was dissolved in dry CH$_3$CN (400 ml) and 2-drop of water was added. The mixture was refluxed for 2 hour. After completion of reaction, the solvent was removed and 1b (0.70 g, 3.8 mmol, 98 %) was obtained.

$^1$H NMR (400 MHz, CDCl$_3$, keto-form); 3.82 (s, 2H, H5), 3.39 (t, 2H, $J = 7.2$ Hz, H6), 2.99 (s, 2H, H3), 1.54-1.46 (m, 2H, H7), 1.28-1.20 (m, 6H, H8-10), 0.82 (t, 3H, $J = 7.2$ Hz, H11). $^{13}$C NMR (100 MHz, CDCl$_3$, keto-form); 203.88 (C4), 168.71 (C2), 57.17 (C5), 42.04 (C3), 41.69 (C6), 31.37 (C9), 26.94 (C7), 26.40 (C8), 22.48 (C10), 13.97 (C11). MS (ES$^-$); 182.1, MS (ES$^+$); 184.1, HRMS (M+Na); calcd for C$_{10}$H$_{17}$N$_1$O$_2$; 206.1151; found; 206.1151.

2.1.6. Synthesis of 1,1'-dihexyl-4-hydroxy-3,3'-bi(1H-pyrrole)-2,5'(5H,5'H)-dione (1c)

Compound 2f (1.0 g, 3.9 mmol) was dissolved in the mixture of CH$_3$CN (300 ml) and water (60 ml) and the mixture was refluxed for 2 hour. After completion of reaction, the solvent was removed and 1c (0.66 g, 1.9 mmol, 98 %) was obtained as a solid.

M.P.: 171°C (decomp.). $^1$H NMR (400 MHz, CDCl$_3$); 6.52 (s, 1H, H3'), 4.55 (s, 2H, H5), 4.00 (s, 2H, H5'), 3.48 (t, 2H, $J = 7.2$ Hz, H6), 3.37 (t, 2H, $J = 7.2$ Hz, H6'), 1.62-1.51 (m, 4H, H7,H7'), 1.35-1.20 (m, 12H, H8-10, H8'-10'), 0.86 (t, 6H, $J = 6.8$ Hz, H11, H11'). $^{13}$C NMR (100 MHz, CDCl$_3$); 174.32 (quart C), 173.73 (quart C), 170.80 (quart C), 149.30 (C3'), 115.59 (C4'), 99.65 (C4), 54.18 (C5), 50.42 (C5'), 42.33 (C6), 41.52 (C6'), 31.53 (C9), 31.40 (C9'), 28.51 (C7,C7'), 26.51 (C8), 26.42 (C8'), 22.56 (C10, C10'), 14.03 (C11,C11'). MS (ES$^-$); 347.6; MS (ES$^+$); 349.4; HRMS (M+Na); calcd for C$_{20}$H$_{32}$N$_2$Na$_1$O$_3$; 371.2295; found; 371.2305.

2.2. Synthesis of tetramic acids by using Meldrum’s acid
2.2.1. Synthesis of ethyl 2-heptanamidoacetate (3a)

![Chemical Structure](image)

Triethyl amine (5.58 g, 55.2 mmol) was added in dichloromethane (200 ml) solution of glycine ethyl ester hydrochloride (2a, 7.00 g, 50.2 mmol) and the mixture was stirred for 1hr at room temperature. DCC (12.4 g, 60.2 mmol) and heptanoic acid (7.83 g, 60.2 mmol) were added in this solution and the mixture was stirred for over night at room temperature. The crude reaction mixture was filtered with DCM. Concentration in vacuo followed by flash column chromatography gave the 3a (8.03 g, 37.3 mmol, 74 % yield) as colorless liquid.

$^1$H NMR (400 MHz, CDCl$_3$); 6.32 (brs, 1H, NH), 4.15 (q, 2H, $J = 6.8$ Hz, H10), 3.97 (d, 2H, $J = 5.2$ Hz, H8), 2.19 (t, 2H, $J = 7.6$ Hz, H6), 1.621-1.548 (m, 2H, H5), 1.31-1.21 (m, 9H, H2-4, H11), 0.824 (t, 3H, $J = 5.6$ Hz, H1). $^{13}$C NMR (100 MHz, CDCl$_3$); 173.49 (C7), 170.14 (C9), 61.39 (C10), 41.28 (C8), 36.31 (C6), 31.51 (C3), 28.89 (C4), 25.54 (C5), 22.46 (2C), 14.10 (C1). MS (ES$^-$); 214.1; MS (ES$^+$); 216.1; HRMS (M+Na); calcd for C$_{11}$H$_{21}$N$_1$O$_3$; 238.1414; found; 238.1413.

2.2.2. Synthesis of 2-heptanamidoacetic acid (3b)

![Chemical Structure](image)

Lithium hydroxide (2.67 g, 111 mmol) in water (40 mL) was slowly added in THF (80 mL) solution of 3a (8.00 g, 37.2 mmol) at 0°C and the mixture was stirred for 2hr at 0°C. After completion reaction, THF was removed in vacuo, and wash with dichloromethane and water. The aqueous lay was acidified with HCl and extracted with dichloromethane. 3b (6.83 g, 36.5 mmol, 98 % yield) was obtained as white solid after solvent evaporation.

M.P.; 98 °C. $^1$H NMR (400 MHz, CD$_3$OD); 4.96 (brs, 2H, NH & OH), 3.90 (s, 2H, H8), 2.26 (t, 2H, $J = 7.6$ Hz, H6), 1.67-1.60 (m, 2H, H5), 1.40-1.29 (m, 6H, H2-4), 0.92 (t, 3H, $J = 7.2$ Hz, H1). $^{13}$C NMR (100 MHz, CD$_3$OD); 175.8 (quart C), 172.08 (quart C), 40.72 (C8), 35.82 (C6), 31.74 (C3), 28.96 (C4), 25.85 (C5), 22.63 (C2), 13.42 (C1). MS (ES$^-$); 186.1; MS (ES$^+$); 188.1; HRMS (M+Na); calcd for; C$_9$H$_{17}$N$_1$O$_3$; 210.1101; found; 210.1102.

2.2.3. Synthesis of N-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-2-hydroxyethyl)heptanamide (4a)
To a solution of compound 3b (6.83 g, 36.5 mmol) in dichloromethane (200 mL) we added Meldrum's acid (5.52 g, 38.3 mmol), DMAP (6.69 g, 54.7 mmol) and DCC (8.28 g, 40.1 mmol), and stirred 4 hr at room temperature. The mixture was filtered and the solution was washed with 5% aqueous KHSO₄ and saturated NaCl. The organic layer was evaporated to give a solid mass. The residue was dissolved in acetone and filtered for removing impurity and the solution was evaporated. The product 4a (4.58 g, 14.6 mmol, 40%) was obtained as a solid from precipitation in ethyl acetate and petrol solution.

M.P.: 74 °C. ¹H NMR (400 MHz, CDCl₃); 6.26 (t, 1H, J = 5.6 Hz, NH), 4.75 (d, 2H, J = 5.6 Hz, H₈), 2.26 (t, 2H, J = 7.2 Hz, H₆), 1.75 (s, 6H, H₁₄), 1.68-1.60 (m, 2H, H₅), 1.35-1.26 (m, 6H, H₂-₄), 0.87 (t, 3H, J = 6.8 Hz, H₁). ¹³C NMR (100 MHz, CDCl₃); 192.59 (C₉), 173.83 (C₇, C₁₁, C₁₃), 105.94 (C₁₂), 90.78 (C₁₀), 43.48 (C₈), 36.34 (C₆), 31.51 (C₃), 28.88 (C₄), 26.86 (C₁₄), 25.56 (C₅), 22.50 (C₂), 14.05 (C₁). MS (ES⁻); 312.2; MS (ES⁺); 314.2; HRMS (M+Na); calcd for C₁₅H₂₃N₁O₆Na; 336.1418; found; 336.1419.

2.2.4. Synthesis of 1-heptanoylpyrrolidine-2,4-dione (1d)

A solution of compound 4a (530 mg, 1.7 mmol) in acetonitrile (150 ml) was refluxed for 1 hr. The solution was evaporated to give 1d (360 mg, 1.7 mmol, 99%) as a white solid.

Enol: Keto = 63: 37 in CDCl₃, only keto-form in CD₃OD,

M.P.; 95 °C. ¹H NMR (400 MHz, CD₃OD, only enol form); 4.94 (brs, 2H of H₃, OH), 4.24 (s, 2H, H₅), 2.90 (t, 2H, J = 7.6 Hz, H₇), 1.68-1.60 (m, 2H, H₈), 1.37-1.34 (m, 6H, H₉-₁₁), 0.92 (t, 3H, J = 6.8 Hz, H₁₂). ¹H NMR (400 MHz, CDCl₃); 5.11 (s, 1H of enol H₃), 4.29 (s, 2H of enol & keto H₅), 3.34 (s, 2H of keto H₃), 2.98 (t, 2H of keto H₇, J = 7.6 Hz), 2.93 (t, 2H of enol H₇, J = 7.6 Hz), 1.68-1.61 (m, 2H of enol & keto H₈), 1.37-1.27 (m, 6H of enol & keto H₉-₁₁), 0.90-0.86 (m, 3H of enol & keto H₁₂). ¹³C NMR (100 MHz, CDCl₃); 200.39 (keto C₄), 176.35 (enol C₄), 173.97 (quart C), 173.81 (quart C), 172.49 (quart C), 168.62 (quart C), 95.51 (enol C₃), 56.44 (keto C₅), 49.09 (enol C₅), 44.20 (keto C₃), 37.91 (keto C₇), 36.63 (enol C₇), 31.55 (enol & keto C₁₀), 28.91 (enol C₉), 28.78 (keto C₉), 24.46 (enol C₈), 24.02 (keto C₈), 22.51 (enol & keto C₁₁), 14.05 (enol & keto C₁₂). MS (ES⁻); 210.1; HRMS (M+Na); calcd for C₁₁H₁₇N₁NaO₃; 234.1101; found; 234.1098.
2.2.5. Synthesis of \((E)\)-ethyl 2-hex-2-enamidoacetate \((3c)\)

Compound \(3c\) (5.5 g, 27.6 mmol, 63 %) as a white solid was obtained from compound \(2a\) (6.0 g, 43.8 mmol) and \textit{trans}-2-hexenoic acid (5.0 g, 43.8 mmol) as the same method with synthesis of \(3a\).

**M.P.**; 35 °C. \(^1\)H NMR (400 MHz, CD\(_2\)OD); 6.90-6.83 (m, 1H, H4), 6.11 (brs, 1H, NH), 5.84 (d, 1H, \(J = 15.6\) Hz, H5), 4.22 (q, 2H, \(J = 7.2\) Hz, H9), 4.09 (d, 2H, \(J = 5.2\) Hz, H7), 2.16 (q, 2H, \(J = 7.6\) Hz, H3), 1.52-1.43 (m, 2H, H2), 1.29 (t, 3H, \(J = 7.2\) Hz, H10), 0.92 (t, 3H, \(J = 7.2\) Hz, H1). \(^13\)C NMR (100 MHz, CDCl\(_3\)); 170.19 (quart C), 166.10 (quart C), 145.57 (C4), 122.98 (C5), 61.50 (C8), 41.39 (C7), 34.09 (C3), 21.43 (C2), 14.15 (C10), 13.68 (C1). MS (ES\(^-\)); 198.1, MS (ES\(^+\)); 200.1; HRMS (M+Na); calcd for C\(_{10}\)H\(_{17}\)N\(_1\)O\(_3\); 222.1101; found; 222.1101.

2.2.6. Synthesis of \((E)\)-2-hex-2-enamidoacetic acid \((3d)\)

Compound \(3d\) (4.2 g, 24.5 mmol, 90 %) as a white solid was obtained from compound \(3c\) (5.4 g, 27.1 mmol) as the same method with synthesis of \(3b\).

**M.P.**; 114 °C. \(^1\)H NMR (400 MHz, CD\(_2\)OD); 6.86-6.79 (m, 1H, H4), 6.01 (d, 1H, \(J = 13.6\) Hz, H5), 5.14 (brs, 1H, NH), 3.98 (s, 2H, H7), 2.20 (q, 2H, \(J = 6.8\) Hz, H3), 1.55-1.46 (m, 2H, H2), 0.96 (t, 3H, \(J = 7.2\) Hz, H1). \(^13\)C NMR (100 MHz, CD\(_2\)OD); 172.08 (quart C), 168.05 quart C), 145.32 (C4), 123.41 (C5), 40.85 (C7), 34.15 (C3), 21.64 (C2), 13.10 (C1). MS (ES\(^+\)); 170.1; HRMS (M+Na); calcd for C\(_8\)H\(_{13}\)N\(_1\)O\(_3\); 194.0788; found; 194.0796.

2.2.7. Synthesis of \((E)\)-\(\textit{N}\)-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-2-hydroxyethyl)hex-2-enamide \((4b)\)

Compound \(4b\) (2.1 g, 7.0 mmol, 60 %) was obtained as a solid from compound \(3d\) (2.0 g, 11.7 mmol) as the same method with synthesis of \(4a\).

**M.P.**; 88 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)); 6.92-6.85 (m, 1H, H4), 6.36 (brs, 1H, NH), 5.86 (d, 1H, \(J = 15.6\) Hz, H5), 4.22 (q, 2H, \(J = 7.2\) Hz, H9), 4.09 (d, 2H, \(J = 5.2\) Hz, H7), 2.16 (q, 2H, \(J = 7.6\) Hz, H3), 1.52-1.43 (m, 2H, H2), 1.29 (t, 3H, \(J = 7.2\) Hz, H10), 0.92 (t, 3H, \(J = 7.2\) Hz, H1). \(^13\)C NMR (100 MHz, CDCl\(_3\)); 170.19 (quart C), 166.10 (quart C), 145.57 (C4), 122.98 (C5), 61.50 (C8), 41.39 (C7), 34.09 (C3), 21.43 (C2), 14.15 (C10), 13.68 (C1). MS (ES\(^+\)); 170.1; HRMS (M+Na); calcd for C\(_{10}\)H\(_{17}\)N\(_1\)O\(_3\); 222.1101; found; 222.1101.
2.2.8. Synthesis of (E)-1-hex-2-enoylpyrrolidine-2,4-dione (1e)

Tetramic acid 1e (0.69 g, 3.5 mmol, 99 %) as a solid was obtained from compound 4b (1.1 g, 3.5 mmol) as the same method with synthesis of 1d.

Only keto-form in CDCl$_3$, only enol-form in MeOD, Enol: Keto = 85: 15 in acetone,
M.P.; 156 °C. $^1$H NMR (400 MHz, CDCl$_3$, keto-form); 7.29-7.22 (m, 2H, H7,8), 4.36 (s, 2H, H5), 3.36 (s, 2H, H3), 2.30 (q, 2H, J = 5.2 Hz, H9), 1.58-1.52 (m, 2H, H10), 0.97 (t, 3H, J = 7.2 Hz, H11). $^1$H NMR (500 MHz, methanol-d$_4$, enol-form); 7.33 (d, 1H, J = 15.5 Hz, H7), 7.09-7.03 (m, 1H, H8), 4.88 (brs, 2H, H3 & OH), 4.27 (s, 2H, H5), 2.25 (q, 2H, J = 7.0 Hz, H9), 1.56-1.49 (m, 2H, H10), 0.97 (t, 3H, J = 8.0 Hz, H11). $^1$H NMR (500 MHz, acetone-d$_6$, mixture of enol & keto form); 7.37 (d, 1H of enol, J = 15.5 Hz, H7), 7.30 (d, 1H of keto, J = 15.5 Hz, H7), 7.12-6.99 (m, 1H of enol & keto, H8), 5.01 (s, 1H of enol, H3), 4.27 (s, 2H of enol, H5), 4.24 (s, 2H of keto, H5), 3.41 (s, 2H of keto, H3), 2.28-2.21 (m, 2H of enol & keto, H9), 1.54-1.47 (m, 2H of enol & keto, H10), 0.94 (t, 3H of enol & keto, J = 7.5 Hz, H11). $^{13}$C NMR (100 MHz, CDCl$_3$, keto-form); 200.37 (C4), 168.69 (C2), 165.38 (C6), 152.81 (C8), 122.30 (C7), 56.57 (C5), 44.34 (C3), 34.75 (C9), 21.32 (C10), 13.69 (C11). $^{13}$C NMR (125 MHz, methanol-d$_4$, enol-form); 178.13 (C4), 173.74 (C2), 166.42 (C6), 150.69 (C8), 124.05 (C7), 95.72 (C3 with H), 95.50 (triplet, C3 with D), 50.10 (C5), 35.74 (C9), 22.64 (C10), 14.15 (C11). $^{13}$C NMR (125 MHz, acetone-d$_6$, mixture of enol & keto form); 202.24 (keto C4), 176.01 (enol C4), 171.48 (enol C2), 171.01 (keto C2), 165.71 (keto C6), 164.63 (enol C6), 150.85 (keto C8), 148.95 (enol C8), 124.11 (enol & keto C7), 96.22 (enol C3), 57.25 (keto C5), 49.41 (enol C5), 45.03 (keto C3), 35.14 (enol & keto C9), 22.29 (enol C10), 22.16 (keto C10), 14.01 (enol & keto C11). MS (ES); 194.1; HRMS (M+Na); calcd for C$_{10}$H$_{13}$N$_2$NaO$_3$; 222.0788; found; 222.0788.

2.2.9. Synthesis of tert-butyl 2,4-dioxopyrrolidine-1-carboxylate (1f)
To a solution of compound 3e (5.00 g, 28.5 mmol) in dichloromethane (150 mL) were added Meldrum’s acid (4.32 g, 30.0 mmol), DMAP (4.53 g, 37.1 mmol) and DCC (6.48 g, 31.4 mmol), and stirred for over night at room temperature. The mixture was filtered and the solution was washed with 5 % aqueous KHSO₄ and saturated NaCl. The organic layer was evaporated to give a brown oil. This brown oil was refluxed for 30 min until completion of reaction checking with TLC and the solution was evaporated. Tetramic acid 1f (2.25 g, 11.3 mmol, 40 %) as a solid was afforded from precipitation in ethyl acetate and petrol solution.

Keto: enol = 53: 47 in CDCl₃, only enol-form in MeOD,

M.P.; 169 °C (decomp.). ¹H NMR (400 MHz, CDCl₃); 5.12 (s, 1H, H3 of enol), 4.25 (s, 2H, H5 of keto), 4.24 (s, 2H, H5 of enol), 3.25 (s, 2H, H3 of keto), 1.55 (s, 9H, H8-10 of keto), 1.53 (s, 9H, H8-10 of enol). ¹H NMR (400 MHz, methanol-d₄, only enol-form); 5.10 (brs, 2H, H3, OH), 4.23 (s, 2H, H5), 1.55 (s, 9H, H8-10).

¹H NMR (400 MHz, mixture of CDCl₃ and methanol-d₄, only enol-form), 4.85 (s, 1H, H3), 4.01 (s, 2H, H5), 1.35 (s, 9H, H8-H10). ¹³C NMR (100 MHz, CDCl₃); 200.56 (C4 of keto), 175.35 (C4 of enol), 173.18 (C2 of keto), 167.46 (C2 of enol), 148.87 (C6 of enol, keto), 95.72 (C4 of enol), 84.46 (C7 of keto), 83.07 (C7 of enol), 57.08 (C5 of keto), 50.31 (C5 of enol), 43.57 (C3 of keto), 28.05 (C8-10 of enol), 27.91 (C8-10 of keto).

¹³C NMR (100 MHz, methanol-d₄, only enol-form), 176.95 (C4), 173.75 (C2), 150.88 (C6), 95.67 (C3 with H), 95.43 (triplet, C3 with D), 83.65 (C7), 51.18 (C5), 28.46 (C8-10). ¹³C NMR (100 MHz, mixture of CDCl₃ and methanol-d₄, only enol-form); 175.25 (C4), 172.87 (C2), 149.79 (C6), 95.48 (C4), 83.08 (C7), 50.31 (C5), 28.26 (C8-10). MS (ES⁻); 198.1; HRMS (M+Na); calcd for C₉H₁₃N₃NaO₄; 222.0737; found; 222.0737.

2.2.10. Deprotection of tert-butyl 2,4-dioxopyrrolidine-1-carboxylate (1f)

Tetramic acid 1f (700 mg, 3.51 mmol) was dissolved in mixture of CH₂Cl₂ (20 ml) and TFA (3 ml). The mixture was stirred for 30 minutes. After completion of reaction, the solution was extracted with CH₂Cl₂ and 5 % aqueous HCl. The organic layer was dried with MgSO₄ and concentrated to afford 1a (345 mg, 3.49 mmol, 99 %).

2.3. Synthesis of tetramic acid 1g

2.3.1. Synthesis of (E)-2-decenoic acid

Lithium hydroxide (1.63 g, 68.1 mmol) in water (20 mL) was slowly added in the mixture of THF (40 mL) and methanol (20 ml) solution of (E)-2-decenoic acid ethyl ester (4.5 g, 22.7 mmol) at 0 °C and the mixture was stirred for over night at room temperature. After completion reaction, the solution was extracted with CH₂Cl₂ and 5 % aqueous HCl. The organic layer was dried with MgSO₄ and
concentrated to afford (E)-2-decenoic acid (3.80 g, 22.3 mmol, 98 % yield) as a liquid.

\[^{1}\text{H} \text{NMR (400 MHz, CDCl}_3\); 7.13-7.06 (m, 1H, H8), 5.82 (d, 1H, \(J = 15.6 \text{ Hz, H9})\), 2.23 (q, 2H, \(J = 6.4 \text{ Hz, H7})\), 1.43-1.43 (m, 2H, H6), 1.35-1.26 (m, 8H, H2-5), 0.89 (t, 3H, \(J = 6.8 \text{ Hz, H1})\). \[^{13}\text{C NMR (100 MHz, CDCl}_3\); 172.40 (C10), 152.65 (C8), 120.58 (C9), 32.34, 31.74, 29.12, 29.05, 27.88, 22.64, 14.10 (C1). MS (ES\^-); 169.1; HRMS (M-H); calcd for C\(_{10}\)H\(_{17}\)N\(_1\)O\(_2\); 169.1234; found; 169.1239.\]

2.3.2. Synthesis of \(D\)-Leucine methyl ester hydrochloride (3g)

\[
\begin{align*}
\text{ClHH}_2\text{N} & \quad \text{O} \\
\text{5} & \quad \text{7} \\
\text{3} & \\
\end{align*}
\]

To methanol (30 ml) at 0°C was added thionyl chloride (3.06 ml, 41.9 mmol) dropwise for 5 minutes followed by portion wise addition of \(D\)-leucine (3f) (5.0 g, 38.1 mmol) and mixture was stirred for over night at 40°C. Solvent was evaporated in vacuo to give \(D\)-leucine methyl ester hydrochloride 3g (6.89 g, 37.9 mmol, 99 %) as a solid.

\([\alpha]_D^{25} = -12.3 \ (c = 3.0 \text{ CH}_3\text{OH}), \text{M.P.; } 148 \degree \text{C.} \quad {^{1}\text{H NMR (400 MHz, CDCl}_3\}; 8.79 \ (bs, 3H, NH}_2\text{HCl), 4.11 \ (t, 1H, J = 5.2 \text{ Hz, H5}), 3.79 \ (s, 3H, H7), 2.01-1.93 \ (m, 2H, H4), 1.88-1.80 \ (m, 1H, H3), 0.97 \ (d, 6H, J = 6.0 \text{ Hz, H1,2}). \quad {^{13}\text{C NMR (100 MHz, CDCl}_3\); 170.24 (C6), 53.07 (C7), 51.80 (C5), 39.45 (C4), 24.43 (C3), 22.32 (C2), 22.04 (C1).}\]

2.3.3. Synthesis of (\(R,E\))-methyl 2-dec-2-enamido-4-methylpentanoate (3h)

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{11} & \quad \text{13} \\
\text{9} & \\
\text{15} & \\
\text{17} & \\
\end{align*}
\]

Compound 3h (3.1 g, 10.4 mmol, 51 %) as a liquid was obtained from compound 3g (3.7 g, 20.3 mmol) and (E)-2-decenoic acid (3.8 g, 22.3 mmol) as the same method with synthesis of compound 3a.

\([\alpha]_D^{25} = -1.8 \ (c = 3.0, \text{CHCl}_3). \quad {^{1}\text{H NMR (400 MHz, CDCl}_3\}; 6.86-6.79 \ (m, 1H, H8), 6.21 \ (brs, 1H, NH), 5.80 \ (d, 1H, J = 15.2 \text{ Hz, H9}), 4.72-4.66 \ (m, 1H, H11), 3.70 \ (s, 3H, H13), 2.12 \ (q, 2H, J = 7.2 \text{ Hz, H7}), 1.68-1.59 \ (m, 2H, H14), 1.55-1.50 \ (m, 1H, H15), 1.41-1.38 \ (m, 2H, H6), 1.28-1.22 \ (m, 8H, H2-5), 0.91 \ (t, 6H, J = 5.6 \text{ Hz, H16,17), 0.84 \ (t, 3H, J = 5.6 \text{ Hz, H1).} \quad {^{13}\text{C NMR (100 MHz, CDCl}_3\); 173.88 \ (quart C), 165.79 \ (quart C), 145.79 \ (C8), 122.93 \ (C9), 52.25 \ (C13), 50.55 \ (C11), 41.69 \ (C14), 32.07, 31.74, 29.15, 29.07, 28.18, 24.83 \ (C15), 22.81 \ (C16), 22.62 \ (C2), 21.89 \ (C17), 14.07 \ (C1). MS (ES\^-); 296.2, MS (ES\^-); 298.2; HRMS (M+H); calcd for C\(_{17}\)H\(_{32}\)N\(_1\)O\(_3\); 298.2377; found; 298.2373.\]
2.3.4. Synthesis of \((R,E)-2\text{-dec-2-enamido-4-methylpentanoic acid (3i)}\)

Compound 3i (2.1 g, 7.4 mmol, 96 %) as a liquid was obtained from compound 3h (2.3 g, 7.7 mmol) as the same method with synthesis of compound 3b.

\[ \alpha \]D \text{25} = + 14.6 (c = 6.0, CHCl}_3. \ H NMR (400 MHz, CDCl\text{3}); 9.72 (brs, 1H, OH), 6.91-6.84 (m, 1H, H8), 6.35 (d, 1H, \text{J} = 8.0 \text{ Hz}, \text{NH}), 5.84 (d, 1H, \text{J} = 15.2 \text{ Hz}, H9), 4.70-4.65 (m, 1H, H11), 2.17 (q, 2H, \text{J} = 7.2 \text{ Hz}, H7), 1.77-1.68 (m, 2H, H13), 1.63-1.59 (m, 1H, H14), 1.44-1.39 (m, 2H, H6), 1.30-1.21 (m, 8H, H2-5), 0.94 (d, 6H, \text{J} = 6.0 \text{ Hz}, H15,16), 0.87 (t, 3H, \text{J} = 6.4 \text{ Hz}, H1). \ 13C NMR (100 MHz, CDCl\text{3}); 176.35 (quart C), 166.76 (quart C), 146.81 (C8), 122.55 (C9), 51.01 (C11), 41.26 (C13), 32.18, 31.75, 29.20, 29.10, 28.16, 24.86 (C14), 22.86 (C15), 22.64, 21.91 (C16), 14.10 (C1). MS (ES\text{-}); 282.2, MS (ES\text{+}); 284.2; HRMS (M+Na); calcd for C_{16}H_{29}N_{1}O_{3}; 306.2040; found; 306.2034.

2.3.5. Synthesis of \((E)-N-(1-(2,2\text{-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1\text{-hydroxy-4-methylpentan-2-yl})\text{dec-2-enamide (4d)}\)

Compound 4d (1.5 g, 3.66 mmol, 52 %) as a solid was obtained from compound 3i (2.0 g, 7.06 mmol) as the same method with synthesis of compound 4a.

M.P; 97 °C. \ H NMR (400 MHz, CDCl\text{3}); 15.48 (brs, 1H, OH), 6.88-6.81 (m, 1H, H8), 6.19 (d, 1H, \text{J} = 6.4 \text{ Hz}, \text{NH}), 5.82 (d, 1H, \text{J} = 15.2 \text{ Hz}, H9), 5.78-5.74 (m, 1H, H11), 2.16 (q, 2H, \text{J} = 6.8 \text{ Hz}, H7), 1.77-1.71 (m, 7H, H17,18, H20), 1.62 (t, 2H, \text{J} = 7.2 \text{ Hz}, H19), 1.43-1.40 (m, 2H, H6), 1.29-1.19 (m, 8H, H2-5), 1.01 (d, 3H, \text{J} = 6.8 \text{ Hz}, H21), 0.95 (d, 3H, \text{J} = 6.8 \text{ Hz}, H22), 0.85 (t, 3H, \text{J} = 6.8 \text{ Hz}, H1). \ 13C NMR (100 MHz, CDCl\text{3}); 196.04 (quart C), 166.05 (quart C), 146.43 (C8), 122.50 (C9), 105.51 (C15), 90.73 (C13), 50.91 (C11), 40.90, 32.12, 31.74, 29.15, 29.07, 28.16, 25.27 (C20), 23.45 (C17,18), 22.62 (C2), 20.92 (C21,22), 14.08 (C1). MS (ES\text{+}); 408.2; HRMS (M+Na); calcd for C_{22}H_{35}N_{1}O_{6}; 432.2357; found; 432.2355.

2.3.6. Synthesis of \((E)-1\text{-dec-2-enoyl-5-isobutylpyrrolidine-2,4-dione (1g)}\)
Tetramic acid 1g (0.975 g, 3.17 mmol, 99 %) as a liquid was obtained from compound 4d (1.30 g, 3.17 mmol) as the same method with synthesis of 1d.

Enol: keto = 45: 55. \(^1\)H NMR (400 MHz, CDCl\(_3\)); 7.27-7.04 (m, 2H of enol & keto, H11,12), 5.04 (s, 1H of enol, H3), 4.71 (t, 1H of enol, \(J = 6.0\) Hz, H5), 4.65-4.63 (m, 1H of keto, H5), 3.38 (dd, 1H of keto, \(J_1 = 22.4\) Hz, \(J_2 = 1.2\) Hz, H3), 3.24 (d, 1H of keto, \(J = 22.4\) Hz, H3), 2.31-2.24 (m, 2H of enol & keto, H13), 1.89-1.70 (m, 3H of enol & keto, H6,7), 1.50-1.43 (m, 2H of enol & keto, H14), 1.30-1.26 (m, 8H of enol & keto, H15-18), 0.96-0.84 (m, 9H of enol & keto, H8,9, H19). \(^13\)C NMR (100 MHz, CDCl\(_3\)); 203.82 (C4 of keto), 181.08 (C4 of enol), 173.10 (quart C), 169.21 (quart C), 165.57 (quart C), 165.33 (quart C), 152.65 (C12), 150.74 (C12), 122.83 (C11), 122.79 (C11), 94.46 (C3 of enol), 65.60 (C5 of keto), 59.15 (C5 of enol), 43.26 (C3 of keto), 39.80, 38.82, 32.80, 32.77, 31.75, 29.20, 29.16, 29.07, 28.18, 28.07, 24.46 (C7), 24.16 (C7), 23.67 (C9), 23.35 (C9), 22.89 (C8), 22.64 (C20 of enol & keto), 21.78 (C8), 14.10 (C19 of enol & keto). MS (ES-); 306.3; HRMS (M+Na); calcd for C\(_{18}\)H\(_{29}\)N\(_1\)NaO\(_3\); 330.2040; found; 330.2036.