SYNTHESIS AND CHARACTERIZATION OF NEW γ- LACTAMS USED TO DECREASE BLOOD CHOLESTEROL LEVEL

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This study is concerned with the synthesis and characterization derivatives of the mono/bis, syn and anti-γ-lactams **2a-2i.** These compounds were synthesized by reacting phenylsuccinic anhydride with the appropriate Schiff base (imines) **1a-1i** in moderate yields (50-92 %). The structures of these γ-lactams were established on the basis of the spectral data like IR, ^{1}H-NMR,^{13}C-NMR, HSQC ^{1}H-^{13}C-NMR, MS.

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Introduction

Five-membered ring lactams, which are known as γ-lactams or 2-oxopyrrolidines, are important structural motifs in biologically active natural products that are also found in medicinal leads and approved drugs. Heliotropamide[1,2] and bisavenanthramide[3,4] are examples of ferrulic acid amides that undergo biosynthetic dimerization to produce γ-lactams, whereas lactacystin[5] and salinosporamide[6] emanate from more complex bio syntheses. Although these compounds share the γ-lactam core, an important difference emerges in the substitution at nitrogen, in that the latter examples are sometimes described as "N-H lactams." A few of the recently reported examples of γ-lactam derivatives exhibiting promising bioactivity are Piracetam as nootropic[7] and Epolactaene[8] as inhibitors of collagen-induced thrombocyte aggregation for treatment of inflammation (Figure 1).

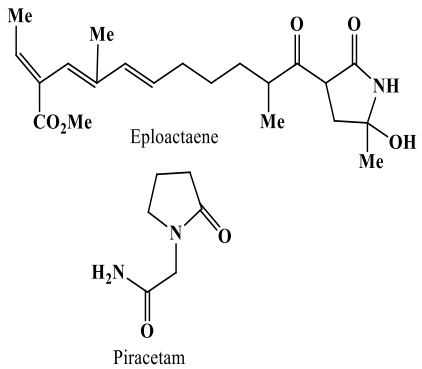

Figure 1. Some biologically important γ-lactam.

Experimental

Wherever necessary, the solvents were distilled/dried prior use by standard methods. All solvent extracts were dried over anhydrous sodium sulphate unless other wise specified. The ^{1}H-NMR spectra were recorded, using VARIAN spectrophotometer (300 MHz). The ^{13}C-NMR spectra were recorded, using VARIAN spectrophotometer (75 MHz). HSQC ^{1}H-^{13}C-NMR spectra were recorded, using VARIAN spectrophotometer (600 MHz, 150 MHz), the above measurements were recorded in National Hellenic Research Foundation, Institute of Biology Medicinal Chemistry and Biotechnology, Molecular analysis Group, Athens, Greece. The chemical shift values are expressed in δ (ppm), using tetramethylsilane (TMS) as internal standard and using DMSO-d_6 as solvent. The Mass spectra were recorded at 3 kV and 4 kV were using VARIAN spectrophotometer. IR spectra were recorded using Shimadzu FT-IR affinity spectrophotometer as KBr disks. Only principal absorption bonds of interest are reported and are expressed in cm^{-1}.

General Procedure for the preparation of imines 1a-1i

Preparation of mono-imines 1a-1d.

In general, the mono-imines **1a-1d** were prepared[9,10] by refluxing 0.01 mol amine, 0.01 mol aldehyde and 4-6 drops of acetic acid in chloroform (20 mL) at 55-60 ˚C for 2-20 h with stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the solvent evaporated and the product was recrystallized from a suitable solvent. The physical data of mono-imines **1a-1d** and the reactants are given below.

N-(2-Fluorobenzylidene)naphthalene-1-amine (**1a**) was prepared by reacting naphthalene-1-amine (0.01 mol, 1.34 g) with 2-fluorobenzaldehyde (0.01 mol, 1.24 g, 1.05 mL). Yield = 60 %, m.p. = 79-80 ^{0}C. IR (ν, cm^{-1}, KBr disk): 1620 (C=N).

N-(2-Chlorobenzylidene)naphthalene-1-amine (**1b**) was prepared by reacting naphthalene-1-amine (0.01 mol, 1.34 g) with 2-chlorobenzaldehyde (0.01 mol, 1.40 g, 1.12 mL). Yield = 66 %, m.p. = 89-90 ^{0}C. IR (ν, cm^{-1}, KBr disk):1612 (C=N).

N-(2-Bromobenzylidene)naphthalene-1-amine (**1c**) was prepared by reacting naphthalene-1-amine (0.01 mol, 1.34 g) with 2-bromobenzylidene (0.01 mol, 1.85 g, 1.16 mL). Yield = 83 %, m.p. = 99-100 ^{0}C. IR (ν, cm^{-1}, KBr disk):1612 (C=N).

4-Bromo-N-(2-fluorobenzylidene)aniline (**1d**) was prepared by reacting 4-bromoaniline (0.01 mol, 1.72 g) with 2-fluorobenzaldehyde (0.01 mole, 1.24 g, 1.05 mL). Yield = 85 %, m.p. = 61-62 ^{0}C. IR (ν, cm^{-1}, KBr disk):1620 (C=N).

Table 1. Physical properties of imines **1a-1d**

Imines, 1a-1i	m.p °C	Yield %	Colour
1a	79-80	60	green
1b	89-90	66	green
1c	99-100	83	yellow
1d	61-62	85	yellowish

Preparation of bis-imines 1e-1i.

In general, the bis-imines **1e-1i** were prepared by refluxing, 0.01 mol amine, 0.02 mol aldehyde and 4-6 drops of acetic acid in chloroform (20 mL) at 55-60 ˚C for 2-20 h with stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the solvent was evaporated and the product was recrystallized from a suitable solvent. The physical data of bis-imines **1e-1i** and the reactants are given below.

Bis(2-bromobenzylidene)naphthalene-1,5-diamine (**1e**) was prepared by reacting naphthalene-1,5-diamine (0.01 mol, 1.58 g) with 2-bromobenzaldehyde (0.02 mol, 3.7 g, 2.33 mL). Yield = 93 %, m.p. = 191-193 ^{0}C. IR (ν, cm^{-1}, KBr disk): 1612 (C=N).

Bis(2-fluorobenzylidene)naphthalene-1,5-diamine (**1f**) was prepared by reacting naphthalene-1,5-diamine (0.01 mol, 1.58 g) with 2-fluorobenzaldehyde (0.02 mol, 2.48 g, 2.1 mL). Yield = 86 %, m.p. = 113-115 ^{0}C. IR (ῡ, cm^{-1}, KBr disk): 1616 (C=N).

Bis(2-bromobenzylidene)benzene-1,4-diamine (**1g**) was prepared by reacting benzene-1,4-diamine (0.01 mol, 1.08 g) with 2-bromobenzaldehyde (0.02 mol, 3.7 g 2.33 mL). Yield = 86 %, m.p. = 164-165 ^{0}C. IR (ν, cm^{-1}, KBr disk): 1608 (C=N).

1,3-Bis(2-fluorobenzylidene)amino)propan-2-ol (**1h**) was prepared by reacting 1,3-diaminopropane-2-ol (0.01 mol, 0.9 g) with 2-fluorobenzaldehyde (0.02 mol, 2.48 g, 2.1 mL). Yield = 86 %, m.p. = 102-103 ^{0}C. IR (ν, cm^{-1}, KBr disk): 1643 (C=N).

Bis(2-bromobenzylidene)butane-1,4-diamine (**1i**) was prepared by reacting butane-1,4-diamine (0.01 mol, 0.881 g, 1.01 mL) with 2-bromobenzaldehyde (0.02 mol, 3.7 g, 2.33 mL). Yield = 93 %, m.p = 65-66 ^{0}C. IR (ν, cm^{-1}, KBr disk):1635 (C=N).

Table 2. Physical properties of imines, **1e-1i**

Imines, 1e-1i	m.p °C	Yield %	Colour
1e	191-193	93	Pale green
1f	113-115	86	Pale green
1g	164-165	86	green
1h	101-103	86	White
1i	65-66	93	yellow

General procedure of mono and bis(E,Z)-γ-lactams, 2a-2i

Preparation of mono(*E,Z*)-γ-lactams 2a-2d. In general the mono(*E,Z*)-γ-lactam **2a-2d** were prepared[11,12] by refluxing, at 55-60 ˚C, 0.01 mol mono-imine **1a-1d** and 0.01 mol of phenylsuccinic anhydride in 20 mL of chloroform for 12-17 h with stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the solvent was evaporated and the product was recrystallized from a suitable solvent. The physical data of the mono(*E,Z*)-γ-lactam **2a-2d** and the reactants are given below.

(*E,Z*)-2-(2-Fluorophenyl)-1-(naphthalene-1-yl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (**2a**) was prepared by reacting (**1a**) (0.01 mol, 2.49 g) and (0.01 mol, 1.76 g) of phenylsuccinic anhydride. Yield =57 %, m.p. = 245-247 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1689 (–N–C=O), 1651 (HO–C=O). For major isomer (*Z*-isomer): Yield = 70 %. ^{1}H-NMR: 2.86-2.94 (*dd, J* = 6, 9 Hz, 1H, C_4-H), (3.21-3.29) (*dd, J* = 9, 9 Hz, 1H, C_4-H), (4.06-4.12) (*dd* , *J* = 9, 6 Hz, 1H, C_2-H), (7.30-7.92) (*m*,16H), 9.95 (*s*, 1H, COOH). **^{13}C**-NMR: 39.12 (C_4-H_2), 47.69 (C_2-H), (122.15, 123.30, 125.70, 126.132, 127.59, 128.35, 129.03, 133.95, 134.10, 139.44, 140.28), 172.12, 170.23 (-N-C=O), 169.27 (COOH). For minor isomer (E-isomer): Yield 30 %, ^{1}H-NMR: (2.63-2.70) (*dd, J* = 3, 6 Hz, 1H, C_4-H), (3.11-3.17) (*t, J* = 6Hz, 1H, C_4-H), (4.36-4.41) (*dd, J* = 3, 6 Hz, 1H, C_2-H), (7.30-7.92) (*m*,16H), 10.16 (*s*,1H,COO-H). ^{13}C-NMR: 37.85 (C_4-H_2), 47.82 (C_2-H), (122.15, 123.30, 125.70, 126.132, 127.59, 128.35, 129.03, 133.95, 134.10, 139.44, 140.28), 174.69 (-N-C=O), 173.37, 172.74 (COOH).

(*E,Z*)-2-(2-Chlorophenyl)-1-(naphthalene-1-yl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (**2b**) was prepared by reacting (**1b**) (0.01 mol, 2.65 g) and phenylsuccinic anhydride (0.01 mol, 1.76 g). Yield = 61 %, m.p. = 198-199 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1693 (–N–C=O), 1651 (HO–C=O). For major isomer (*Z*-isomer): Yield = 71 %. ^{1}H-NMR: (2.86-2.93) (*dd, J* = 6, 6 Hz, 1H, C_4-H), (3.20-3.29) (*dd, J* = 9, 9 Hz 1H, C_4-H), (4.06-4.11) (*dd, J* = 6, 6 Hz 1H, C_2-H), (7.29-7.92) (m, 16H), 9.95 (*s*, 1H, COOH). ^{13}C-NMR: 39.22 (C_4-H_2), 47.24 (C_2-H), (121.70, 122.73, 122.85, 125.25, 125.40, 127.03, 128.09, 133.45, 138.96, 139.81), 171.67 (-N-C=O), 169.78 (COOH). For minor isomer (*E*-isomer): Yield = 29 %. ^{1}H-NMR: (2.63-2.70) (*dd, J* = 3, 6 Hz, 1H, C_4-H), (3.11-3.16) (*t, J* = 6Hz, 1H, C_4-H), (4.36-4.41) (*dd, J* = 6,6Hz, 1H,C_2-H), (7.29-7.92) (*m*, 16H), 10.15 (s, 1H, COO-H). ^{13}C-NMR: 37.39 (C_4-H_2), 47.37 (C_2-H), (121.70, 122.73, 122.85, 125.25, 125.40, 127.03, 128.09, 133.45, 138.96, 139.81), 174.23 (-N-C=O), 172.92 (COOH).

(*E,Z*)-2-(2-Bromophenyl)-1-(naphthalene-1-yl)-5-oxo-3–phenylpyrrolidine-3-carboxylic acid (**2c**) was prepared by reacting (**1c**) (0.01 mol, 3.1 g) and phenylsuccinic anhydride (0.01 mol, 1.76 g). Yield = 71 %, m.p. = 179-180 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1689 (–N–C=O), 1651 (HO–C=O). For major isomer (*Z*-isomer): Yield = 72 %. ^{1}H-NMR: (2.85-2.92) (*dd*, *J* = 6, 6 Hz, 1H, C_4-H), (3.19-3.28) (*dd*, *J* = 12,9Hz, 1H,C_4-H); δ (4.05 - 4.10) ppm; (*dd*, *J* = 6, 6 Hz, 1H, C_2-H); (7.28-7.92) (*m*,16H), 9.94 (*s*,1H,COO-H). ^{13}C-NMR: 39.03 (C_4-H_2); 47.16 (C_2-H), (120.47, 121.48, 123.96, 124.19, 125.71, 126.30, 127.18, 132.06,137.45, 138.28), 171.67 (-N-C=O), 169.78 (COOH). For minor isomer (*E*-isomer): Yield = 28 %. ^{1}H-NMR: (2.62-2.69) (*dd*, *J* = 3, 6 Hz, 1H, C_4-H), (3.10-3.15) (*t*, *J* = 6Hz, 1H, C_4-H), (4.35-4.40) (*dd*, *J* = 3, 6 Hz, 1H, C_2-H), (7.28-7.92) (*m*, 16H), 10.14 (*s*, 1H, COOH). ^{13}C-NMR: 37.48 (C_4-H_2), 47.30 (C_2-H), (120.47, 121.48, 123.96, 124.19, 125.71, 126.30, 127.18, 132.06,137.45, 138.28), 174.23 (-N-C=O), 172.92 (COOH).

(*E,Z*)-1-(4-Bromophenyl)-2-(2-fluorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (**2d**) was prepared by reacting (**1d**) (0.01 mol, 2.78 g) and phenylsuccinic anhydride (0.01 mol, 1.76 g). Yield =78 %, m.p. = 120-122 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1701 (–N–C=O), 1662 (HO–C=O). For major isomer (*Z*-isomer): Yield = 51 %. ^{1}H-NMR: (2.65-2.72) (*dd*, *J* = 6, 6 Hz, 1H, C_4-H), (3.04-3.13) (*dd*, *J* = 9, 12 Hz, 2H, C_4-H); (4.00 - 4.05) (*dd*, *J* = 3, 6 Hz, 1H, C_2-H), (7.22-7.57) (*m*, 13H), 10.12 (*s*, 1H, COO-H). ^{13}C-NMR: 39.24 (C_4-H_2), 46.75 (C_2-H) (114.50, 120.80, 127.10, 128.55, 131.48, 138.46, 139.29), 171.05 (-N-C= O), 169.29. For minor isomer (*E*-isomer): Yield = 49 %. ^{1}H-NMR: (2.55-2.63) (*dd*, *J* = 6, 6 Hz, 1H, C_4-H), (3.04-3.13) (*dd*, *J* = 9, 12 Hz, 1H, C_4-H), (4.00-4.05) (*dd*, *J* = 3, 6 Hz, 1H, C_2-H), (7.22-7.57) (*m*, 13H), 10.12 (s, 1H, COO-H). ^{13}CNMR: 37.32 (C_4-H_2), 47.98 (C_2-H), (114.50, 120.80, 127.10, 128.55, 131.48, 138.46, 139.29), 174.11 (-N-C=O), 172.74 (COOH).

Table 3. Physical properties of γ-lactams **2a-2d**.

γ-Lactams, 2a-2d	m.p °C	Yield %	Colour
2a	245-247	57	White
2b	198-199	61	White
2c	179-180	71	White
2d	120-122	78	White

Preparation of bis(*E,Z*)-γ-lactams 2e-2i.

In general the bis(*E,Z*)-γ-lactams **2e-2i** were prepared by refluxing 0.01 mol of bis-imine **1e-1i** and 0.02 mol of phenylsuccinic anhydride in 20 mL of chloroform at 55-60 ˚C for 12-17 h with stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the solvent was evaporated and the product was recrystallized from a suitable solvent. The physical data of the bis (*E,Z*)-γ-lactams **2e-2i** and the reactants are given below.

(*E,Z*)-1-1'-(Naphthalene-1,5-diyl)bis(2-(2-bromophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylicacid) (**2e**) prepared by reacting **1e** (0.01 mol, 5.19 g) and phenylsuccinic anhydride (0.02 mol, 3.52 g). Yield = 86 %, m.p. = 275-273 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1706 (–N–C=O), 1654 (HO–C=O). For major isomer (*Z*-isomer): Yield = 78 %, ^{1}H-NMR: 2.84-2.91 (*dd*, *J* = 3, 6 Hz, 2H, C_4-H), 3.18-3.27 (*dd*, *J* = 6,12Hz, 2H, C_4-H), 4.05 - 4.10 (*dd*, *J* = 6Hz, 2H, C_2-H), (7.30-7.76) (*m*, 24H), 9.96 (*s*, 2H, COO-H). ^{13}C-NMR: 39.24 (C_4-H_2), 47.28 ($2C_2$-H), (120.32, 122.03, 125.17, 127.05, 128.54, 133.64, 139.01, 139.79),171.69 (2-N-C=O), 169.80 (2COOH). For minor isomer (*E*-isomer): Yield = 22 %, ^{1}H-NMR: (2.62-2.69) (*dd*, *J* = 3, 6Hz, 2H, C_4-H), (3.10-3.15) (*t*, *J* = 9Hz, 2H,C_4-H), δ (4.34-4.39) (*dd*, *J* = 3, 6 Hz, 2H, C_2-H), (7.30-7.76) (*m*, 24H), 10.16 (*s*, 2H, COO-H). ^{13}C-NMR: 37.42 ($2C_4$-H_2), 47.37 ($2C_2$-H), δ (120.32, 122.03, 125.17, 127.05, 128.54, 133.64, 139.01, 139.79), 174.24 ((2-N-C=O), 172.93 (2COOH).

(*E,Z*)-1-1'-(Naphthalene-1,5-diyl)bis(2-(2-fluorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid) (**2f**) prepared by reacting **1f** (0.01 mol, 5.19 g) and phenylsuccinic anhydride (0.02 mol, 3.52 g). Yield = 85 %, m.p. = 244-245 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1708 (–N–C=O), 1654 (HO–C=O). For major isomer (*Z*-isomer): Yield = 55 %. ^{1}H-NMR: (2.86-2.91) (*dd*, *J* = 3, 6 Hz, 2H, C_4-H); (3.19-3.27) (*dd*, *J* = 6, 9 Hz, 2H, C_4-H), (4.05-4.10) (*t*, *J* = 6 Hz, 2H , C_2-H), (7.09-7.91) (*m*, 24H); 9.96 (*s*, 2H, COO-H). ^{13}C NMR: 39.13 ($2C_4$-H_2), 47.73 ($2C_2$-H), (108.07, 122.46, 123.31, 125.60, 127.35, 128.09, 129.02, 134.08, 139.46, 140.24, 145.34), (*m*, 34C), 171.13 (2-N-C=O), 170.24 (2COOH). For minor isomer (*E*-isomer): Yield = 15.30 %. ^{1}H-NMR: (2.62-2.69) (*dd*, *J* = 3, 6 Hz, 2H, C_4-H), (3.10-3.15) (*t*, *J* = 9 Hz, 2H, C_4-H), (4.34-4.39) (*dd*, *J* = 3, 6 Hz, 2H, C_2-H), (7.09-7.91) (*m*,24H), (10.16-9.73) (*s*, 2H, COO-H). ^{13}C-NMR: 37.86 ($2C_4$-H_2), 47.83 ($2C_2$-H), (108.07, 122.46, 123.31, 125.60, 127.35, 128.09, 129.02, 134.08, 139.46, 140.24, 145.34), 174.69 (2-N-C=O), 173.73 (2COOH).

(*E,Z*)-1,1'-(1,4-phenylene)bis(2-(2-bromophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid) (**2g**) was prepared by reacting **1g** (0.01 mol, 4.42 g) and phenylsuccinic anhydride (0.02 mol, 3.52 g). Yield = 91 %, m.p. = 188-190 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1701 (–N–C=O), 1658 (HO–C=O). For major isomer (*Z*-isomer): Yield = 67 %, ^{1}H-NMR: (2.62-2.69) (*dd*, *J* = 6, 6 Hz, 2H, C_4-H), (3.02-3.08) (*dd*, *J* = 12, 3 Hz, 2H, C_4-H), (4.00 – 4. 05) (*dd*, with *J* = 6,6 Hz, 2H, C_2-H), (7.06-7.49) (*m*, 22H), 9.89 (*s*, 2H, COO-H). ^{13}C-NMR: 39.12 ($2C_4$-H_2), 47.27 ($2C_2$-H), (119.72, 128.16, 129.02, 134.88, 135.00, 139.37, 140.09), 171.13 (2-N-C=O), 170.24 (2COOH). For minor isomer (*E*-isomer): Yield = 33 %. ^{1}H-NMR: (2.56-2.61) (*dd*, *J* = 3, 6 Hz, 2H,C_4-H), (2.89-2.98) (*dd*, *J* = 6,12 Hz, 2H, C_4-H), (4.00-4. 05) (*dd*, *J* = 6, 6 Hz, 2H, C_2-H), (7.06-7.49) (*m*,22H), 10.09 (*s*, 2H, COO-H). ^{13}C-NMR: 37.77 ($2C_4$-H_2), 47.53 ($2C_2$-H), (119.72, 128.16, 129.02, 134.88, 135.00, 139.37, 140.09), 174.69 (2-N-C=O), 173.73 (2COOH).

(*E*)-1-(3-(3-carboxy-2-(2-fluorophenyl)-5-oxo-3-phenylpyrrolidin-1-yl)-2-hydroxypropyl)-2-(3-fluorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (**2h**) was prepared by reacting **1h** (0.01 mol, 3.02 g) and phenylsuccinic anhydride (0.02 mol, 3.52 g). Yield = 92 %, m.p. = 149-150 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1716 (–N–C=O), 1651 (HO–C=O). ^{1}H-NMR: (2.56-2.61) (*dd*, *J* = 6, 6 Hz, 2H, C_4-H), (2.92-3.01) (*dd*, *J* = 6, 9 Hz, 2H, C_4-H), (3.19-3.27) (*dd*, *J* = 6, 9 Hz, 2H, C_4-H), (4.01-4.08) (*dd*, *J* = 3,9Hz, 2H, C_2-H), 7.10-7.88 (*m*, 18H), 10.25 (*s*, 2H, COOH). ^{13}C-NMR: 37.88 ($2C_4$-H_2), 47.29 ($2C_2$-H) (127.59, 128.05, 129.02, 137.26, 138.51, 139.12), 174.41 (2-N-C=O), 173.05 (2COOH).

(*E*)-1,1-(Butane-1,4-diyl)bis(2-(2-bromo phenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid) (**2i**) was prepared by reacting **1i** (0.01 mol, 4.22 g) with phenylsuccinic anhydride (0.02 mol, 3.52g). Yield = 88 %, m.p. = 98-99 ^{0}C. IR (**ν**, cm^{-1}, KBr disk): 1732 (–N–C=O), 1639 (HO–C=O). ^{1}H-NMR: (2.60-2.66) (*dd*, *J* = 6, 6 Hz, 2 H, C_4-H), (2.96-3.05) (*dd*, *J* = 12, 9 Hz, 2H, C_4-H), 4.00-4.06 (*dd*, *J* = 6, 6 Hz, 2H, C_2-H), (7.02-7.98) (*m*, 18H), 10.23 (s, 2H, COOH). DEPT: (+)37.92 ($2C_4$-H_2), (+)47.18 ($2C_2$-H), (+)125.57-126.10), (-)127.60-130.68), (+)133.06-138.82) (*m*, 34C), (-) 174.23 (2-N-C=O), (-)174.23 (2COOH).

Table 4. Physical properties of bis(E,Z)-γ- lactams **3e-3i.**

γ-Lactams, 3e-3i	m.p °C	Yield %	Colour
3e	273-275	86%	White
3f	244-245	85%	White
3g	188-190	91%	White
2h	149-150	92%	White
3i	98-99	88%	White

Results and Discussion

γ-Lactams are widely found among natural products.[13-17] Biologically important lactams[18-21] are obtained from the reaction of imines with phenylsuccinic anhydride to give pure γ-lactams. Structures of some of these are shown in Figures 2-4. The key step in the synthesis mono and bicyclic γ-lactams **2a-2i** involved the treatment of the mono or diimines **1a-1i** with phenyl succinic anhydride in chloroform to afford γ-lactams **2a-2i**, as shown in Schemes 1 and 2.

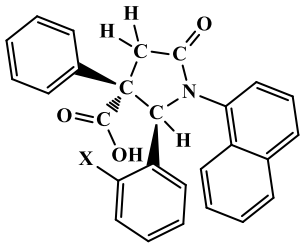

Figure 2. (2R,3S)-2-(2-halophenyl)-1-naphthalen-1-yl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acids, **2a-2c**

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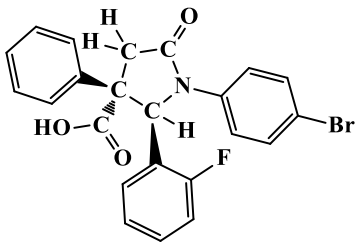


Figure 3. (2R,3S)-1-(4-Bromophenyl)-2-(2-fluorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (**2d**).

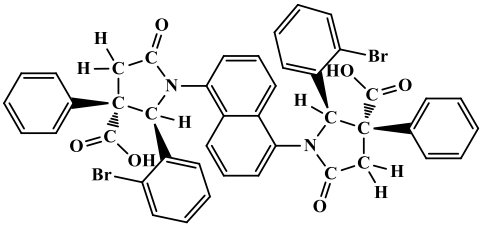
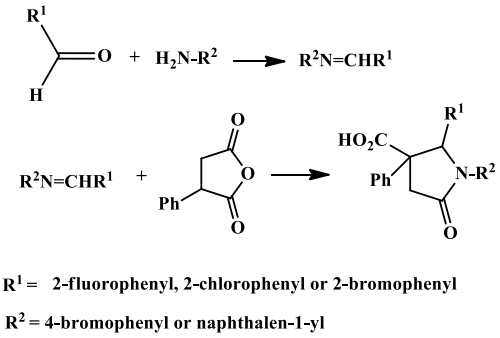
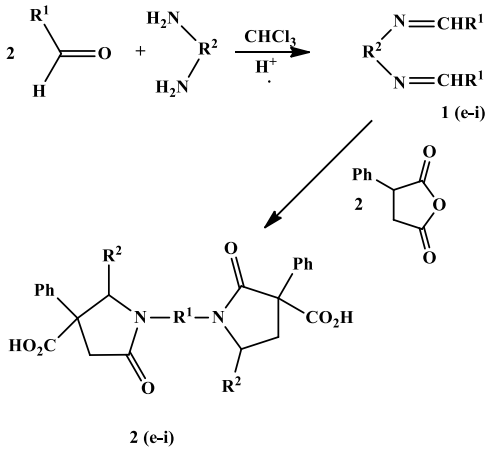


Figure 4. (2R,2'R,3S,3'S)-1,1-(naphthalene-1,5-diyl)bis(2-(2-bromophenyl)-5-oxo-3-phenylpyrrolidine-carboxylic acid) (**2e**).

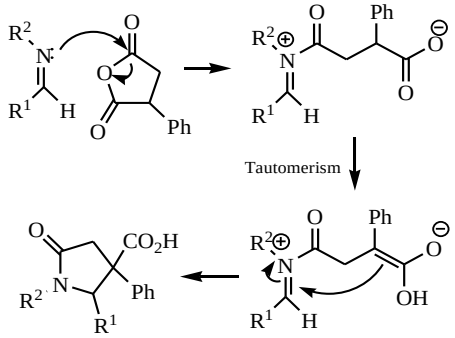


Scheme 1. Synthesis of (*E*,*Z*)-mono γ-lactams.



Scheme 2. Synthesis of (*E*,*Z*)-bis γ-lactams.

The general mechanism[22,23] of formation of both mono and bis-γ-lactams (Scheme3) involve formation of a zwitterionic enolate intermediate from phenylsuccinic anhydride. Formation of the enolate is favored by delocalization of negative charge by the aromatic ring if one is suitably positioned. The enolate zwitterions cyclise to form the lactam rings.



Scheme 3. Mechanism of formation of γ-lactams.

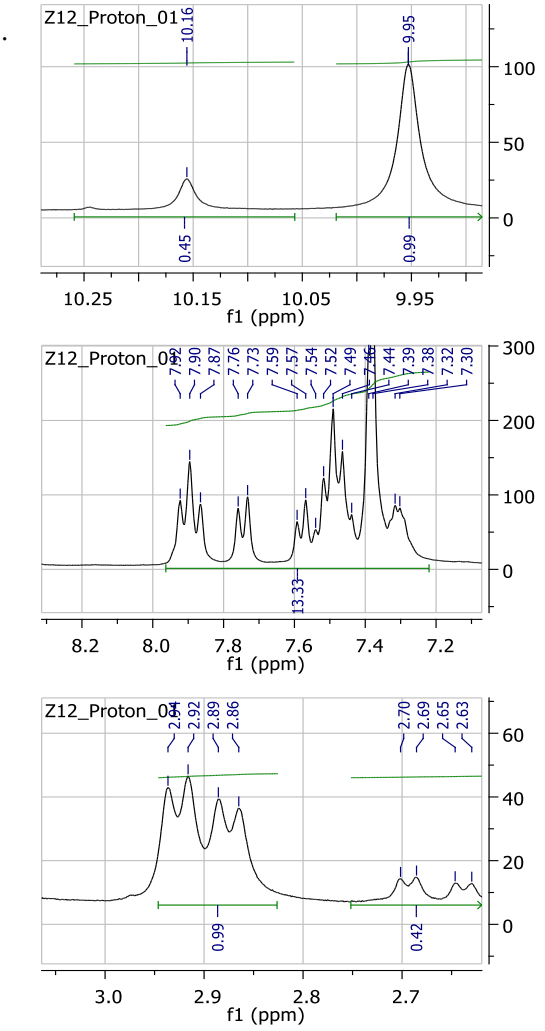
The structures of the mono and bicyclic γ-lactams were established on the basis of IR, ^{1}H-NMR,^{13}C-NMR, mass and HSQC ^{1}H-^{13}C-NMR spectral data.

IR spectral analysis

The IR spectra of the imines **1a-1i**, in KBr disc showed absorption bond at 1608-1643 cm^{-1} corresponding to the azomethine group of imine compounds. The IR spectra of γ-lactams **2a-2i** are characterized by the six bands corresponding to the stretching vibration of the aromatic C-H, aliphatic C-H, carbonyl amide group, carbonyl carboxylic group, aromatic C=C and substituted ring which occurs in the ranges 3062-3016, 2985-2830, 1732-1689, 1662-1639, 1604-1531 and 925-617 cm^{-1} respectively.

^{1}H-NMR spectral analysis

Some representative ^{1}H-NMR spectra of the γ-lactams are shown in Figure 5. The ^{1}H-NMR spectra of the major isomer of (**2a**) shows a double doublet signal at δ = 2.86-2.94 ppm with *J*= 6 Hz, 9 Hz, for one proton (*dd*, 1H, C$_4$-H) of the pyrrolidine-2-one ring. It also exhibited a double doublet signal at δ = 3.21-3.29 ppm with *J* = 9Hz, 9 Hz for one proton (*dd*, 1H, C$_4$-H). For the minor isomer, the pyrrolidine-2-one ring signal occurs at δ = 2.63-2.70 ppm with *J*= 3 Hz, 6 Hz for one proton (*dd*, 1H, C$_4$-H). A triplet signal at δ = 3.11-3.17 ppm with *J* = 6 Hz for one proton (*t*, 1H, C$_4$-H) is also exhibited.



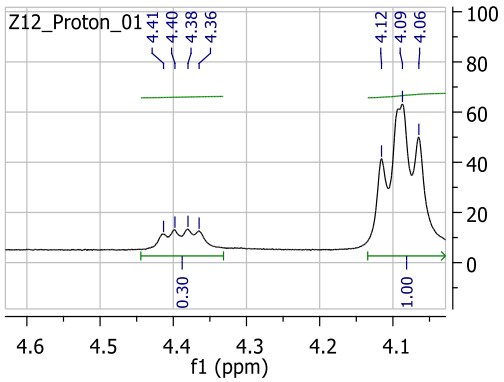


Figure 5. ^{1}H-NMR spectra of some of the compounds **2a-2i**.

^{13}C-NMR spectral analysis

The ^{13}C-NMR spectral data of the γ-lactams have described along with syntheses of these compounds in the experimental section. The major isomer of (**2a**) showed a signal at δ = 39.12 ppm for one carbon (C$_4$-H$_2$) of pyrrolidine-2-one ring, whereas the minor isomer showed the corresponding signal at δ = 37.85 ppm. A singlet signal occurs at δ = 47.69 ppm for one carbon (C$_2$-H) for the major isomer, the same for the minor isomer appears at δ = 47.82 ppm. For both the isomers the ^{13}C-NMR spectra showed signals of aromatic carbons at δ = 122.15-140-28 ppm. The signal for the (-N-C=O) carbon is exhibited at δ = 172.12 and 174.69 ppm for the major and minor isomers respectively. The signal for carboxylic (-COOH) carbon appears at δ = 170.23 and 173.37 ppm respectively.

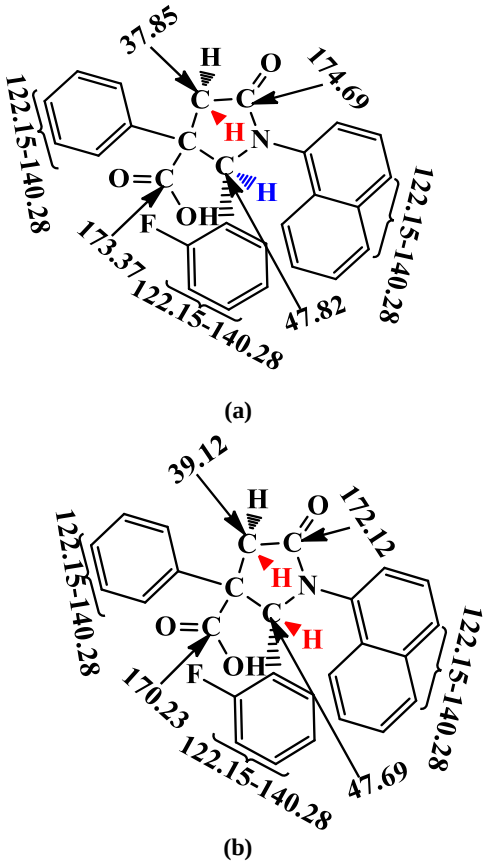


Figure 6. ^{13}C-NMR peaks γ-lactum (**2a**) (a) syn-isomer (b) anti-isomer.

HSQC ^{1}H-^{13}C - NMR spectral analysis

The HSQC^{1}H-^{13}C-NMR spectra of (**2b**)**,** showed the presence of a pyrrolidine-2-one ring. For major isomer, the correlation of protons signals for -CH_2- group at 2.91 and δ 3.25 ppm with carbon signal at 39.16 ppm for same group led to the assignment of this signal to methylene group. Correlation of the proton signal at 4.09 ppm for -CH- group with carbon signal of same group at 47.00 ppm led to the assignment of this signal to -CH- group. For the minor isomer, the correlation of protons signals for -CH_2- group at 2.65 ppm and 3.18 ppm with carbon signal at 37.12 of same group led to the assignment of this signal to methylene group and that of proton signal at 4.38 ppm for -CH- group with carbon signal of same group at 47.14 ppm , which led to the assignment of this signal to -CH- group (Figure).The HSQC 1H-13C-NMR spectra of (**2b**) showed, for both the major and minor isomers, the aromatic protons signals at 7.31 ,7.39 ,7.47 ,7.51 ,7.52 ,7.58, 7.74, 7.87 and 7.92 ppm in correlation with carbon aromatic signals at 121.50, 121.72, 122.54, 122.64, ,125.36, 125.75, 126.99, 127.78 and 128.14 ppm respectively Figure 7 .

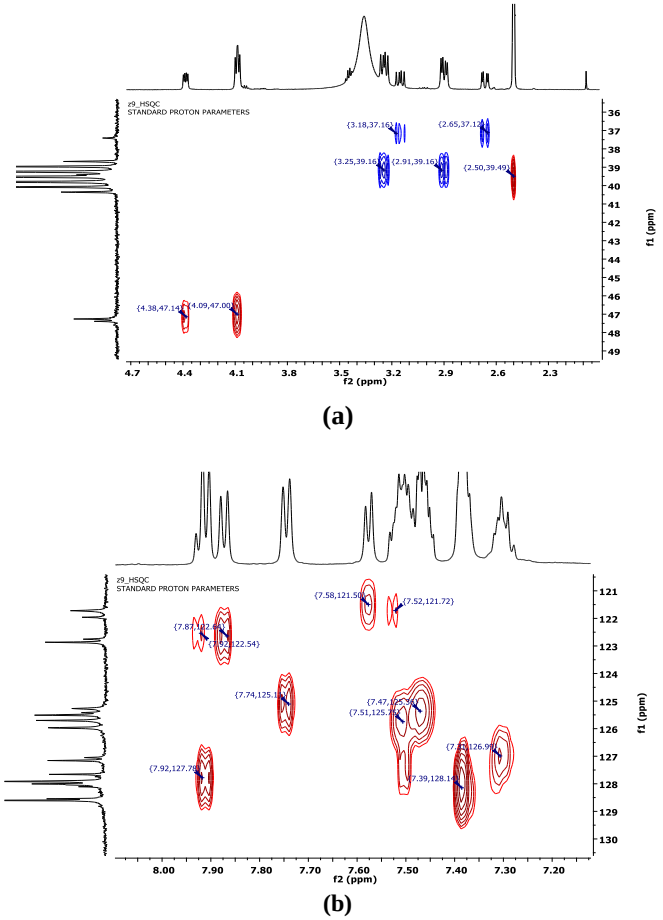


Figure 7. HSQC ^{1}H-^{13}C-NMR spectra of (**2b**), (a) major component (b) minor component.

Analysis of mass spectra

The mass spectrum of (**2a**) showed the molecular ion peak at m/z = 425 and the important fragmentation peaks at m/z = 359, 302, 313, 299, 250, 249, 232 and 143. The mass spectrum of (**2d**) showed the molecular ion peak at m/z = 453 and 455, and the important fragmentation peaks in m/z = 359, 393, 367, 348, 350, 343, 278, 260, 262, 243, 223, 171, 173 and 105.

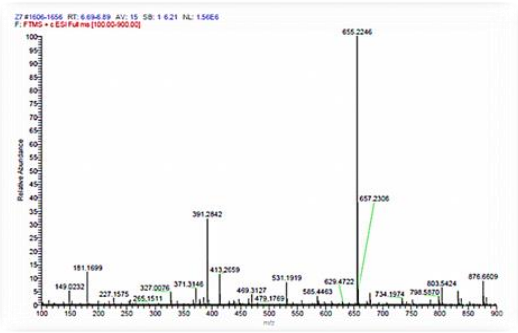


Figure 8. Mass spectrum of (**2h**).

The mass spectrum of (**2f**) showed the important fragmentation peaks at m/z = 664, 570, 528, 511, 468, 373, 349, 307, 293, 192 and 154. The mass spectrum of (**2g**) showed the molecular ion peak at m/z =792 and the important fragmentation peaks at 722, 610, 589, 536, 461, 359, 332, 282 and 163. The mass spectra of (**2h**) showed the molecular ion peak $[M+H]^{+}$, at m/z = 655 and the important fragmentation peaks at 585, 531, 469, 413, 391, 327, 181 and 149 as shown in Figure 8.

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