SYNTHESIS AND CHARACTERIZATION OF SOME NEW γ-LACTAM COMPOUNDS

S. Awadh Gatea[a] and M. Shakir Magtoof [a]*

Keywords: γ-lactams, cycloaddition, imines, NMR.

This study is concerned with the synthesis and characterization of γ-lactams **3a-3h**. These compounds were prepared by reacting phenylsuccinic anhydride with the appropriate Schiff bases (imines) **2a-2h** by heating at 51-61 ˚C in chloroform with moderate yields (70-92 **%)**. The structures of these γ-lactams were established on the basis of the spectral studies using IR, ^{1}H-NMR,^{13}C-NMR, HSQC ^{1}H-^{13}C-NMR, and MS.

*Corresponding Authors
Tel: 009647813199256
E-Mail: Mahmood672000@yahoo.com
[a] Department of Chemistry, Science, College, Thiqar University, Thiqar, Nashyria, Iraq.

Introduction

Five-membered ring lactams, which are known as γ-lactams or 2-oxopyrrolidines (Figure 1), are important structural motifs in biologically active natural products and are used in medicines and approved drugs.[1]

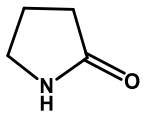


Figure 1. γ-Lactam ring

γ -Lactams have attracted great attention in recent years because they are valuable building blocks in synthesis, and due to the presence of a γ-lactam core are present in the structure of several biologically active molecules.[2] Substituted γ-lactams, in particular, have potential application in drug synthesis, but the development of stereoselective synthesis of chiral γ-lactams remains a challenge.[3,4]

Developing effective and simple synthetic methods is important so that the drug candidates can be screened. A stereoselective addition to a γ-lactam skeleton provides a direct and efficient method for synthesizing various γ-lactam derivatives. However, the most commonly used methods for synthesizing chiral γ-lactams are based on the cyclization or cycloaddition of N-containing precursors, which are synthesized stereoselectively, and there are limited studies on the stereoselective additions to γ-lactam skeletons.[5-7]

Experimental part

All solvents were distilled/dried prior to use, whenever this seemed necessary, 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), and the HSQC ^{1}H-^{13}C-NMR spectra were recorded using VARIAN spectrophotometer (600 MHz, 150 MHz). The chemical shift values are expressed in δ (ppm), using tetramethylsilane (TMS) as internal standard and d_6-DMSO as solvent. The mass spectra were recorded at (3 kV) and (4 kV) using HPLC-LCQ Fleet/Thermo Scientific spectrophotometer. The IR spectra were recorded using Shimadzu FT-IR affinity spectrophotometers as KBr disks. Only principal absorption bands of interest are reported and expressed in cm^{-1}.

General Procedure for the preparation of imines 2a-2h [27-29]

Preparation of mono-imines 2a-2d.

In general, the mono-imines **2a-2d** were prepared by reacting the mixture of 0.01 mol amine with 0.01 mol aldehyde in 20 ml of chloroform and 4-6 drops of glacial acetic acid under heating in water bath at 51-61 ˚C. The reaction mixture was refluxed for 2-20 h with stirring. The progress of the reaction was followed by TLC. After completion, the solvent was evaporated and the residue was recrystallized from a suitable solvent.

N-(2-Chlorobenzylidene)-4-chloro-aniline 2a

The compound was prepared by reacting 1.27 g (0.01 mol) of 4-chloroaniline and 1.40 g (0.01 mol) of 2-chloro-benzaldehyde. Yield = 77 %, m.p. = 64-65 ˚C, IR (KBr disk) 1620 cm^{-1} (C=N).

N-(2-Bromobenzylidene)-4-chloro-aniline, 2b

The compound was prepared by reacting 1.27 g (0.01 mol) of 4-chloroaniline with 1.85 g (0.01 mol) of 2-bromobenzaldehyde. Yield = 83 %, m.p. = 74-75 °C, IR (KBr disk): 1616 cm^{-1} (C=N).

N-(2-Bromobenzylidene)-4-methyl-aniline, 2c

The compound was prepared by reacting 1.07 g, (0.01 mol) of 4-methylaniline with 1.85 g (0.01 mol) of 2-bromobenzaldehyde. Yield = 80 %, m.p. = 43-44 °C, IR (KBr disk): 1616 cm^{-1} (C=N).

N-(2-Fluorobenzylidene)-4-methyl-aniline, 2d

The compound was prepared by reacting 1.07 g (0.01 mol) of 4-methylaniline with 1.24 g (0.01 mol) of 2-fluorobenzaldehyde. Yield = 90 %, m.p = 44-45 °C, IR (KBr disk): 1624 cm^{-1} (C=N).

Preparation of bis-imines, 2e-2h .

In general, the bis-imines **2e-2h** were prepared by reacting the mixture of 0.01 mol amine with 0.02 mol of aldehyde in 20 mL of chloroform and 4-6 drops of glacial acetic acid under heating in water bath at 51-61°C, The reaction mixture was refluxed for 2-20 h with stirring. The progress of the reaction was followed by TLC. After completion, the solvent was evaporated and the residue was recrystallized from a suitable solvent.

N^1,N^4-Bis(2-chlorobenzylidene)benzene-1,4-diamine, 2e

The compound was prepared by reacting 1.08 g (0.01 mol) of *p*-phenylenediamine with 2.80 g (0.02 mol) of 2-chlorobenzaldehyde. Yield = 88 %, m.p = 150-151 °C, IR (KBr disk): 1612 cm^{-1} (C=N).

N^1,N^4-Bis(2-fluorobenzylidene)benzene-1,4-diamine, 2f

The compound was prepared by reacting 1.08 g (0.01 mol) of *p*-phenylenediamine with 2.48 g (0.02 mol) of 2-fluorobenzaldehyde. Yield = 60 %, m.p = 94-96 °C, IR (KBr): 1612 cm^{-1} (C=N).

N^1,N^5-Bis(2-chlorobenzylidene)naphthalene-1,5-diamine, 2g

The compound was prepared by reacting 1.58 g (0.01 mol) of 1,5-diaminonaphthalene with 2.80 g (0.02 mol) of 2-chlorobenzaldehyde. Yield = 89 %, m. p. =240-241 °C, IR (KBr disk): 1612 cm^{-1} (C=N).

N^1,N^5-Bis(4-methoxybenzylidene)naphthalene-1,5-diamine, 2h

The compound was prepared by reacting 1.58 g (0.01 mol) of 1,5-diaminonaphthalene with 2.72 g (0.02 mol) of 4-methoxybenzaldehyde. Yield = 85 %, m.p =180-182 °C, IR (KBr disk): 1620 cm^{-1} (C=N).

General procedure for the preparation of γ-lactams 3a-3h [30,31]

Preparation of mono-γ-lactams 3a-d

In general, the mono-γ- lactams **3a-3d** were prepared by reacting the mixture of 0.01 mol of mono-imine **2a-2d** with 0.01 mol of phenylsuccinic anhydride in 20 ml of chloroform and heating the mixture in water bath at 51-61 °C. The reaction mixture was refluxed for 12-16 h with stirring. The progress of the reaction was followed by TLC. After completion, the solvent was evaporated, and the residue was recrystallized from a suitable solvent.

(*E*,*Z*)-2-(2-Chlorophenyl)-1-(4-chlorophenyl)-5-oxo-3-phenyl-pyrrolidine-3-carboxylic acid, 3a

The compound was prepared by reacting 2.50 g (0.01 mol) of N-(2-chlorobenzylidene) 4-chloroaniline (**2a)** with 1.76 g (0.01 mol) of phenylsuccinic anhydride. Yield = 78 %, m.p = 153-154 ºC, IR (KBr): 1658 cm^{-1} (HO–C=O), 1705 cm^{-1} (–N–C=O). **For major isomer (*Z*-isomer):** yield = 55 %, ^{1}H-NMR (300 MHz, DMSO) data: δ 2.64-2.72 ppm (*dd*, *J* = 6, 6 Hz, 1H), 3.04-3.13 ppm (*dd*, *J* = 9, 12 Hz, 2H), 4.00-4.05 ppm (*dd*, *J* = 6, 6 Hz, 1H), 7.61-7.24 ppm (*m*, 13H), 10.11 ppm (*s*, 1H), ^{13}C-NMR (75 MHz, DMSO) data : δ. 39.60 ppm, 46.77 ppm, 120.42 ppm, 120.47 ppm, 126.51 ppm, 126.64 ppm, 127.10 ppm, 127.11 ppm, 127.53 ppm, 127.70 ppm, 128.56 ppm, 128.59 ppm, 138.05 ppm, 138.93 ppm, 139.32 ppm , 169.27 ppm, 174.12 ppm. **For minor isomer (*E*-isomer):** yield = 45 %; ^{1}H-NMR (300 MHz, DMSO) data, δ: 2.55-2.62 ppm (*dd*, *J* =3, 6 Hz, 1H), 3.04-3.13 ppm (*dd*, *J*=9, 12Hz, 2H), 4.07-4.12 ppm (*dd*, *J*=3, 6 Hz, 1H), 7.24-7.61 ppm (*m*, 13H); 10.29 ppm (*s*, 1H), ^{13}C-NMR (75 MHz, DMSO) data: δ: 37.33 ppm, 47.97 ppm, 120.42 ppm, 120.47 ppm, 126.51 ppm, 126.64 ppm, 127.10 ppm, 127.11 ppm, 127.53 ppm, 127.70 ppm, 128.56 ppm, 128.59 ppm, 138.05 ppm, 138.93 ppm, 139.32 ppm, 171.03 ppm, 172.74 ppm.

(*E*,*Z*)-2-(2-Bromophenyl)-1-(4-chlorophenyl)-5-oxo-3-phenyl-pyrrolidine-3-carboxylic acid, 3b

The compound was prepared by reacting 2.94 g (0.01 mol) of N-(2-bromobenzylidene)-4-chloroaniline (**2b)** with 1.76 g (0.01 mol) of phenylsuccinic anhydride. Yield = 70 %, m.p. = 160-161 ºC, IR (KBr disk): 1658 cm^{-1} (HO–C=O), 1705 cm^{-1} (–N–C=O). For **major isomer (*Z*-isomer)**: Yield = 66 %, ^{1}H-NMR (300 MHz, DMSO) : δ 2.64-2.71 ppm (*dd*, *J* = 6, 6 Hz, 1H), 3.04-3.13 ppm (*dd*, *J* = 9, 12 Hz, 2H); 3.99-4.05 ppm (*dd*, *J* = 6, 6 Hz, 1H; 7.61-7.24 ppm (*m*, 13H), 10.12 ppm (*s*, 1H); ^{13}C-NMR (75 MHz, DMSO) data: δ: 39.60 ppm, 46.78 ppm, 120.41 ppm, 120.46 ppm, 126.50 ppm, 126.63 ppm, 127.11 ppm, 127.53 ppm, 127.70 ppm, 128.58 ppm, 138.05 ppm, 138.18 ppm, 138.94 ppm, 139.32 ppm, 169.27 ppm, 174.11 ppm. For **minor isomer (*E*-isomer):** yield = 34 %, ^{1}H-NMR (300 MHz, DMSO): δ: 2.55- 2.62 ppm (*dd*, *J* = 3, 6 Hz, 1H), 3.04-3.13 ppm (*dd*, *J* = 9, 12 Hz, 2H), 4.06-4.11 ppm (*dd*, *J*=6, 3 Hz, 1H); 7.24-7.61 ppm (*m*, 13H); 10.29 ppm (*s*, 1H), ^{13}C-NMR (75 MHz, DMSO): δ 37.33 ppm; 47.97 ppm; 120.41 ppm, 120.46 ppm, 126.50 ppm, 126.63 ppm, 127.11 ppm, 127.53 ppm, 127.70 ppm, 128.58 ppm, 138.05 ppm, 138.18 ppm, 138.94 ppm, 139.32 ppm, 172.74 ppm, 171.02 ppm.

(*E*)-2-(2-Bromophenyl)-5-oxo-3-phenyl-1-(p-tolyl)pyrrolidine-3-carboxylic acid, 3c

The compound was prepared by reacting 2.74 g (0.01 mol) N-(2-bromobenzylidene)-4-methylaniline (**2c**) with 1.76 g (0.01 mol) phenylsuccinic anhydride. Yield = 88 %, m.p = 159-160ºC, IR (KBr disk): 1651 cm^{-1} (HO–C=O), 1701 cm^{-1} (–N–C=O). ^{1}H-NMR (300 MHz, DMSO) data: δ: 2.22 ppm (*s*, 3H), 2.54-2.61 ppm (*dd*, *J* = 6, 3 Hz, 1H); 3.04-3.13 ppm (dd, J= 9, 12 Hz, 2H), 4.07-4.12 ppm (*dd*, *J* = 3, 6 Hz, 1H), (7.05–7.46) ppm, (*m*, 13H), 10.05 ppm (*s*, 1H), ^{13}C-NMR (75 MHz, DMSO) data : δ^{13}C 20.20 ppm, 37.15 ppm, 47.67 ppm, 118.73 ppm, 126.80 ppm, 127.34 ppm, 128.30 ppm, 128.82 ppm, 131.77 ppm, 136.59 ppm, 139.48 ppm, 170.36 ppm, 172.57 ppm.

(*E*)-2-(2-Fluorophenyl)-5-oxo-3-phenyl-1-(p-tolyl)pyrrolidine-3-carboxylic acid, 3d

The compound was prepared by reacting 2.13 g (0.01 mol) N-(2-fluorobenzylidene)-4-methylaniline (**2d**) with 1.76 g (0.01 mol) of phenylsuccinic anhydride. Yield = 90 %, m.p = 204-205 ºC, IR (KBr disk): 1651 cm^{-1} (HO-C=O), 1701 cm^{-1} (–N–C=O). ^{1}H-NMR (300 MHz, DMSO) data : δ 2.22 ppm (*s*, 3H), 2.54-2.61 ppm (*dd*, *J*=6, 3 Hz, 1H), 3.03-3.12 ppm (*dd*, J = 9, 12 Hz, 2H), 4.06-4.11 ppm (*dd*, *J*=3, 6 Hz, 1H), 6.82-7.46 ppm (m, 13H), 10.04 ppm (s, 1H), ^{13}C-NMR (75 MHz, DMSO) data : δ: 20.22 ppm, 37.15 ppm, 47.68 ppm, 118.74 ppm, 126.80 ppm, 127.35 ppm, 128.30 ppm, 128.82 ppm, 131.77 ppm, 136.59 ppm, 139.48 ppm, 170.36 ppm; 172.56 ppm.

Preparation of bis-γ-lactams 3e-3h

In general, the bis-γ-lactams **3e-3h** were prepared by reacting 0.01 mol bis-imines **2e-2h** with 0.02 mol of phenylsuccinic anhydride in 20 ml of chloroform under heating in water bath at 51-61 ˚C. The reaction mixture was refluxed for 12-16 h with stirring. The progress of the reaction was followed by TLC. After completion, the solvent was evaporated and the residue was recrystallized from a suitable solvent.

(*E,Z*)-1-(4-(3-Carboxy-2-(2-chlorophenyl)-5-oxo-3-phenylpyrrolidin-1-yl)phenyl)-2-(2-chlorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid, 3e

The compound was prepared by reacting 3.53 g (0.01 mol) N^1,N^4-bis(2-fluorobenzylidene)benzene-1,4-diamine (**2e)** with 3.52 g, (0.02 mol) of phenylsuccinic anhydride. Yield = 71 %, m.p = 180-181 ºC, IR (KBr): 1658 cm^{-1} (HO–C=O), 1701 cm^{-1} (–N–C=O). **For major isomer (*Z*-isomer):** yield = 69 **%**, ^{1}H-NMR (300 MHz, DMSO) data: δ 2.61-2.69 ppm (*dd*, *J* = 6, 6 Hz, 2H); 3.02-3.10 ppm (*dd*, *J* = 9, 12 Hz, 4H); 3.99-4.04 ppm (*dd*, *J* = 6, 6 Hz, 2H), 7.23-7.49 ppm (*m*, 22H), 9.90 ppm (*s*, 2H), ^{13}C-NMR (75 MHz , DMSO) data: δ 39.65 ppm; 46.86 ppm, 119.18 ppm, 119.24 ppm, 126.95 ppm, 127.03 ppm, 127.50 ppm, 127.69 ppm, 128.45 ppm, 134.40 ppm, 134.49 ppm, 134.52 ppm, 139.05 ppm, 139.64 ppm, 168.69 ppm, 174.15 ppm. **For minor isomer (*E*-isomer):** yield 31 %, ^{1}H-NMR (300 MHz, DMSO) data : δ: 2.54-2.61 ppm (*dd*, *J* = 3, 6 Hz, 2H), 3.02-3.10 ppm (*dd*, *J* = 9, 12 Hz, 4H), 4.05-4.11 ppm (*dd*, *J* = 6, 3 Hz, 2H), 7.23-7.49 ppm (*m*, 22H), 10.08 ppm (*s*, 2H), ^{13}C-NMR (75 MHz, DMSO) data : δ: 37.33 ppm, 47.81 ppm, 119.18 ppm, 119.24 ppm, 126.95 ppm, 127.03 ppm, 127.50 ppm, 127.69 ppm, 128.45 ppm, 134.40 ppm, 134.49 ppm, 134.52 ppm, 139.05 ppm, 170.43 ppm, 172.75 ppm.

(*E,Z*)-1-(4-(3-Carboxy-2-(2-fluorophenyl)-5-oxo-3-phenylpyrrolidin-1-yl)phenyl)-2-(2-fluorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid, 3f

The compound was prepared by reacting 3.20 g (0.01 mol) N^1,N^4-bis(2-fluorobenzylidene)benzene-1,4-diamine (**2f)** with 3.52 g (0.02 mol) phenylsuccinic anhydride. Yield = 90 %, m.p = 185-186º C, IR (KBr disk): 1658 cm^{-1} (HO–C=O), 1701 cm^{-1} (–N–C=O). **For major isomer (*Z*-isomer):** yield = 76%, ^{1}H-NMR (300 MHz, DMSO) data : δ 2.61-2.68 ppm (*dd*, *J* = 6, 6 Hz, 2H); 3.01-3.10 ppm (*dd*, *J*=9, 12 Hz, 4H); 3.99-4.04 ppm (*dd*, *J* = 6, 6 Hz, 2H); 7.23-7.64 ppm (*m*, 22H), 9.90 ppm (*s*, 2H), ^{13}C-NMR (75 MHz, DMSO) data : δ: 39.69 ppm, 46.90 ppm, 119.26 ppm, 126.97 ppm, 127.05 ppm, 127.53 ppm, 127.71 ppm, 128.48 ppm, 128.55 ppm, 134.43 ppm, 134.51 ppm, 139.08 ppm, 139.67 ppm, 168.72 ppm, 174.18 ppm. HSQC ^{1}H-^{13}C NMR (600 MHz, 150 MHz, DMSO) data: (2.67, 39.40) ppm, (3.06, 39.40) ppm, (4.02, 46.61) ppm, {(7.26, 126.83), (7.27, 128.24), (7.32, 128.10), (7.34, 128.30), (7.38, 127.33), (7.43, 118.94), (7.45, 119.00), (7.46, 119.01)} ppm. **For minor isomer (*E*-isomer):** yield 24 %, ^{1}H-NMR (300 MHz, DMSO) data δ: 2.53-2.61 ppm (*dd*, *J* = 3, 6 Hz, 2H), 3.01-3.10 ppm (*dd*, *J* = 9, 12 Hz, 4H), 4.05-4.10 ppm (*dd*, *J* = 6, 3 Hz, 2H), 7.23-7.64 ppm (*m*, 22H), 10.08 ppm (*s*, 2H), ^{13}C-NMR (75 MHz, DMSO) data: δ 37.37 ppm, 47.84 ppm,119.26 ppm, 126.97 ppm, 127.05 ppm, 127.53 ppm, 127.71 ppm, 128.48 ppm, 128.55 ppm, 134.43 ppm, 134.51 ppm, 139.08 ppm, 139.67 ppm, 170.46 ppm, 172.77 ppm. HSQC ^{1}H-^{13}C NMR (600 MHz, 150 MHz, DMSO) data: (2.56, 37.08) ppm, (3.07, 37.09) ppm, (4.08, 47.55) ppm, {(7.26, 126.83), (7.27, 128.24), (7.32, 128.10), (7.34, 128.30), (7.38, 127.33), (7.43, 118.94), (7.45, 119.00), (7.46, 119.01)} ppm.

(*E,Z*)-1-(5-(-3-Carboxy-2-(2-chlorophenyl)-5-oxo-3-phenylpyrrolidin-1-yl)naphthalene-1-yl)-2-(2-chlorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid, 3g

The compound was prepared by reacting (4.03 g, 0.01 mol) N^1,N^5-bis(2-chlorobenzylidene)-1,5-diaminonaphthalene (**2g**) with (3.52 g, 0.02 mol) of phenylsuccinic anhydride. Yield = 84 %, m.p = 244-245 ºC, IR (KBr disk) 1654 cm^{-1} (HO–C=O), 1705 cm^{-1} (–N–C=O). ^{1}H-NMR (300 MHz, DMSO) data: **For major isomer (*Z*-isomer):** yield=81 %; δ 2.84-2.92 ppm (*dd*, *J* = 6, 6 Hz, 2H); 3.18-3.27 ppm (*dd*, *J* = 12, 9 Hz, 4H), 4.05 -4.10 ppm (*t*, *J* = 6, 9 Hz, 2H), 7.08-8.38 ppm (*m*, 24H), 9.96 ppm (*s*, 2H), ^{13}C-NMR (75 MHz, DMSO) data : δ: 39.36 ppm; 47.20 ppm; 120.27 ppm, 121.97 ppm, 125.11 ppm, 127.09 ppm, 127.58 ppm, 127.84 ppm, 128.53 ppm, 128.67 ppm, 128.91 ppm, 133.57 ppm, 138.93 ppm, 169.62 ppm, 174.17 ppm. **For minor isomer (*E*-isomer):** yield=19 %, δ: 2.62- 2.69 ppm (*dd*, *J* = 3, 6 Hz, 2H); 3.18-3.27 ppm (*dd*, *J* = 12, 9 Hz, 4H), 4.34-4.39 ppm (*dd*, *J* = 3, 6 Hz, 2H), 7.08-8.38 ppm (*m*,

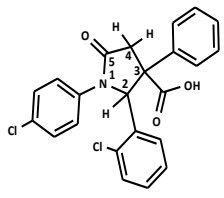
24H); 10.16 ppm (*s*, 2H), ^{13}C-NMR (75 MHz, DMSO) data : δ: 37.33 ppm, 47.31 ppm, 119.18 ppm, 119.24 ppm, 126.95 ppm, 127.03 ppm, 127.50 ppm, 127.69 ppm, 128.45 ppm, 134.40 ppm, 134.49 ppm, 134.52 ppm, 139.05 ppm, 139.64 ppm, 171.62 ppm, 172.86 ppm.

(*E,Z*)-1-(5-(-3-Carboxy-2-(4-methoxyphenyl)-5-oxo-3-phenyl-pyrrolidin-1-yl)naphthalene-1-yl)-2-(4-methoxyphenyl)-5-oxo-3-phenyl-pyrrolidine-3-carboxylic acid, 3h

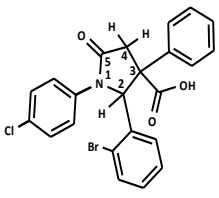
The compound was prepared by reacting 3.94 g (0.01 mol) N^1,N^5-bis(4-methoxybenzylidene)-1,5-diamino-naphthalene **(2h)** with 3.52 g (0.02 mol) phenylsuccinic anhydride. Yield = 85 %, m.p = 214-216 ºC, IR (KBr disk): 1654 cm^{-1} (HO–C=O), 1708 cm^{-1} (–N–C=O). **For major isomer (*Z*-isomer):** yield = 70 %, ^{1}H-NMR (300 MHz, DMSO) data: δ: 2.85-2.94 ppm (*q*, *J* = 6, 6, 9, 6 Hz, 2H); 3.10-3.29 ppm (*m*, *J* = 9, 12, 9, 6 Hz, 4H); 3.86 ppm (*s*, 6H); 4.05-4.12 ppm (*dd*, *J* = 6, 6 Hz, 2H); 7.11-8.61 ppm (*m*, 24H); 9.95 ppm (*s*, 2H), ^{13}C-NMR (75 MHz, DMSO) data: δ: 39.34 ppm, 47.18 ppm, 55.45 ppm, 114.42 ppm, 114.54 ppm, 120.20 ppm, 121.99 ppm, 122.24 ppm, 125.13 ppm, 127.11 ppm, 127.60 ppm, 127.85 ppm, 128.49 ppm, 128.55 ppm, 128.93 ppm, 129.04 ppm, 129.09 ppm, 130.69 ppm, 131.76 ppm, 133.36 ppm, 133.59 ppm, 138.91 ppm, 139.74 ppm, 144.38 ppm, 169.73 ppm, 174.17 ppm. **For minor isomer (*E*-isome**r): yield=30 %, 1H-NMR (300 MHz , DMSO) data: δ 2.62- 2.69 ppm (*dd*, *J* = 3, 3 Hz, 2H), 3.10-3.29 ppm (*m*, *J* = 9, 12, 9, 6 Hz, 4H); 3.86 ppm (*s*, 6H), 4.34-4.39 ppm (*dd*, *J* = 6, 6 Hz, 2H), 7.11-8.61 ppm (*m*, 24H), 10.16 ppm (*s*, 2H); ^{13}C -NMR (75 MHz, DMSO) data: δ: 37.33 ppm; 47.32 ppm, 55.65 ppm, 114.42 ppm, 114.54 ppm, 120.20 ppm, 121.99 ppm, 122.24 ppm, 125.13 ppm, 127.11 ppm, 127.60 ppm, 127.85 ppm, 128.49 ppm, 128.55 ppm, 128.93 ppm, 129.04 ppm, 129.09 ppm, 130.69 ppm, 131.76 ppm, 133.36 ppm, 133.59 ppm, 138.91 ppm, 139.74 ppm, 144.38 ppm, 171.63 ppm, 172.85 ppm.

RESULTS AND DISCUSSION

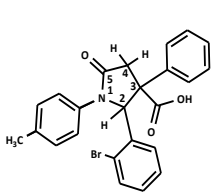
γ-Lactams represent important substructures for the synthesis of natural products,[8-12] and biologically important compounds in drug discovery [13-16]. The prevalence of these structures has resulted in the development of many efficient syntheses [17–22], which have led to the production of diverse libraries of small molecules for biological evaluation [16,23,24]. γ-lactams **3a-3h** are obtained from reaction of imines with phenylsuccinic anhydride.



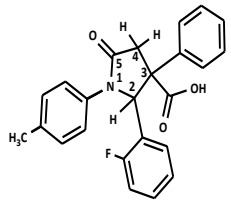
3a



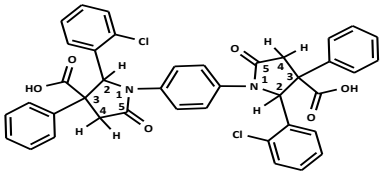
3b



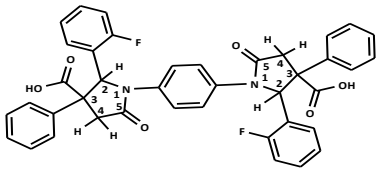
3c



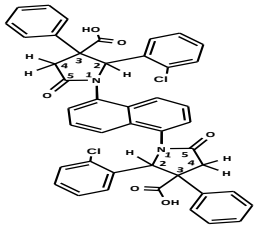
3d

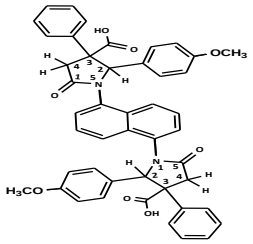


3e



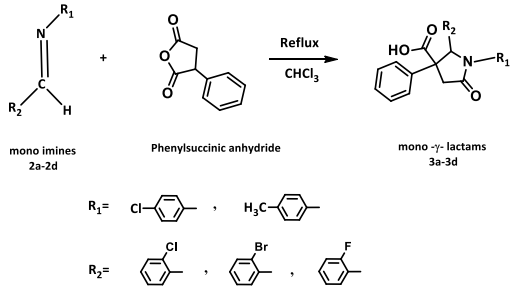
3f





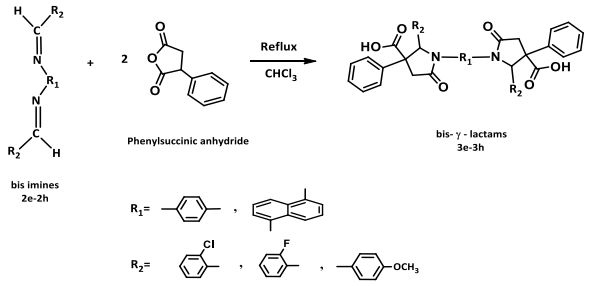
3g **3h**

The general reaction of mono-γ-lactams **3a-3d** is outlined in Scheme 1. It is the reaction between phenylsuccinic anhydride with mono-imines **2a-2d** in chloroform solvent to yield the products mono-γ-lactams **3a-3d**, and these are shown in Table 1.



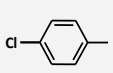
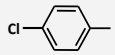
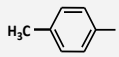
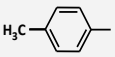
Scheme 1.

The general reaction of bis-γ-lactams **3e-3h** is outlined in Scheme 2. It is the reaction between phenylsuccinic anhydride with bis-imines **2e-2h** in chloroform solvent to yield the products bis-γ-lactams **3e-3h** as shown in Table 2**.**



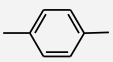
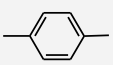
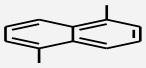
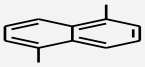
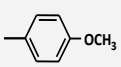
Scheme 2.

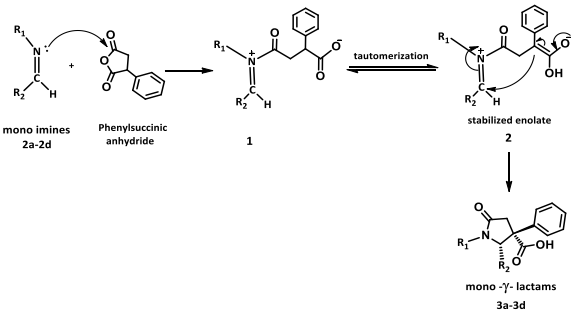
Table 1. Mono-γ-lactam **3a-3d** compounds and its imines **2a-2d**

Imines	Mono-γ-lactams	R^1	R^2
2a	**3a**		
2b	**3b**		
2c	**3c**		
2d	**3d**		

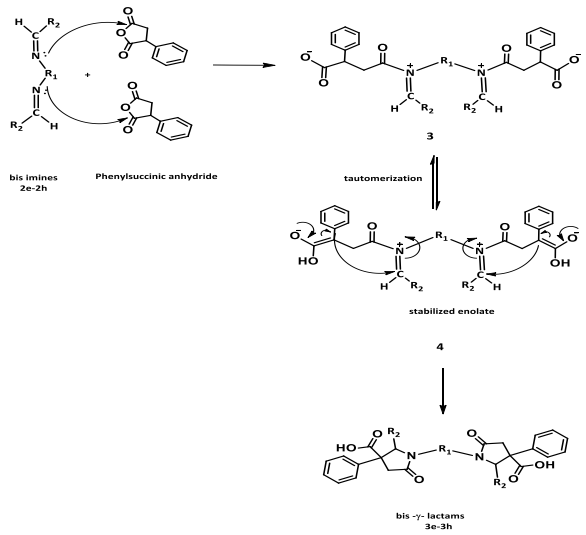
The general mechanism [25,26] of these reactions involve formation of a zwitterionic enolate intermediate **1,3** from a phenylsuccinic anhydride, and the formation of enolate **2,4** is favored by delocalization of negative charge into the electron deficient aromatic ring if one is suitably positioned. This is how the lactam ring is formed.

Table 2 . bis-γ-lactam **3e-3h** compounds and its imines **2e-2h**

Imines	Bis-γ-lactams	R^1	R^2
2e	**3e**		
2f	**3f**		
2g	**3g**		
2h	**3h**		



Scheme 3.



Scheme 4

Infrared (IR) spectral analysis

The **IR** spectra of mono-γ-lactam **3a-3d)** and bis-γ-lactam **3e-3h)** are characterized by the six bands corresponding to the stretching vibration of the aromatic C-H, aliphatic C-H, carbonyl carboxylic group, carbonyl amide group, aromatic C=C and substituted ring which occurs within the ranges 3025-3082, 2735-2958, 1651-1658, 1701-1708, 1512-1612 and 817-983 cm^{-1} respectively.

^{1}H-NMR spectral analysis

The ^{1}H-NMR spectra of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid **3a**, shows the presence of **syn (Z) isomer (major isomer)**: in pyrrolidine-2-one ring double doublet signal at δ (2.64-2.72) ppm with J = 6 Hz, 6 Hz for one proton (*dd*, 1H, C_4-H), and for **anti (E) isomer (minor isomer)** : in pyrrolidine-2-one ring double doublet signal at δ (2.55-2.62) ppm with J = 6 Hz, 3 Hz for one proton (*dd*, 1H, C_4-H), Fig. 2. and double doublet signal at δ (3.04-3.13) ppm with J = 9 Hz, 12 Hz for two protons (dd, 2H, C_4-H) of **syn isomer** and **anti isomer**, Fig. 3.

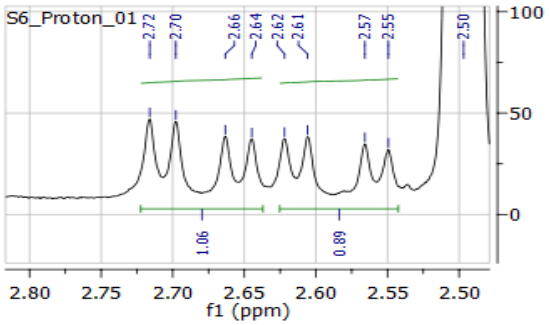


Figure 2. Selected ^{1}H NMR signals of the **syn-3a** isomer

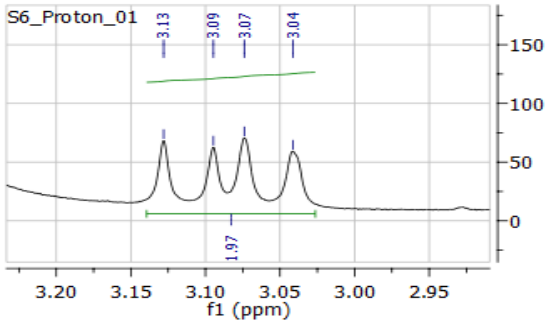


Figure 3. Selected ^{1}H NMR signals of the **anti-3a** isomer

A double doublet signal at δ 4.00-4.05 ppm with J = 6 Hz, 6 Hz for one protons (*dd* , H, C_2-H) of **syn isomer**, and a double doublet signal at δ 4.07-4.12 ppm with J = 3 Hz, 6 Hz for one proton (*dd*, 2H, C_2-H) of **anti isomer can be seen in** Fig 4.

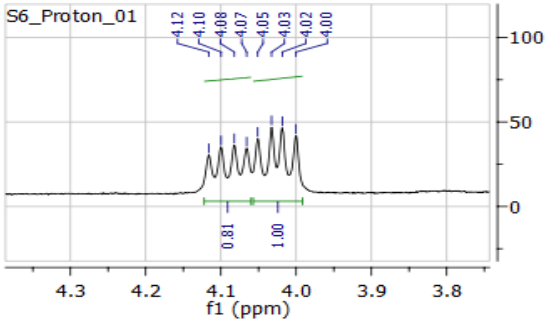


Figure 4. Selected ^{1}H NMR signals of the **anti-3a** and the **syn-3a** isomers

The ^{1}H-NMR spectra of **3a** shows multiplet signal at δ 7.4-7.61 ppm for thirteen aromatic protons (*m*, 13H, aromatic protons) of **syn isomer** and **anti isomer** can be seen in Fig. 5.

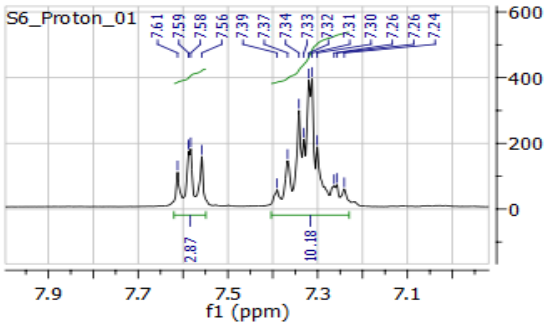


Figure 5. Aromatic ^{1}H NMR signals of the **syn-3a** and the **anti-3a** isomers

A singlet signal at δ 10.11 ppm for one proton of carboxylic group (*s*, 1H, COO-H) of **syn** isomer and the singlet signal at δ 10.29 ppm is for one proton of carboxylic group (*s*, H, COO-H) of **anti** isomer as is shown in Fig. 6.

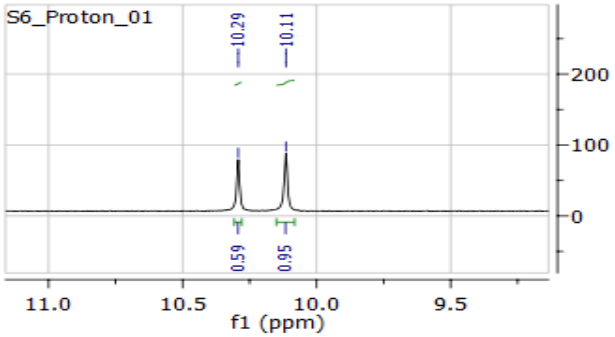
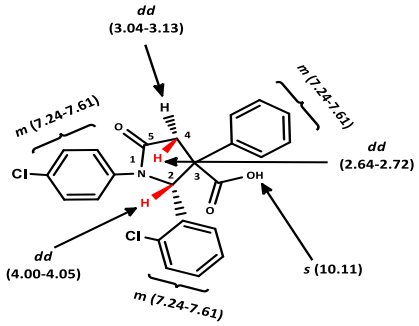
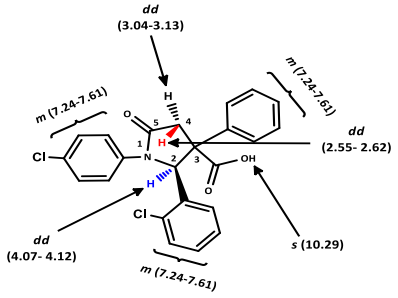


Figure 6. Carboxylic ^{1}H NMR signals of **the syn-3a** and the **anti-3a** isomers



Syn isomer (Major)



Anti isomer (Minor)

^{13}C-NMR spectral analysis

The ^{13}C-NMR spectra of the 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid **3a**, are shown in pyrrolidine-2-one ring: for syn (Z) isomer (major isomer) singlet signal at δ 39.60 ppm of one carbon (C_4-H_2), and for anti (E) isomer (minor isomer) singlet signal at δ 37.33 ppm of one carbon (C_4-H_2), Figure 7.

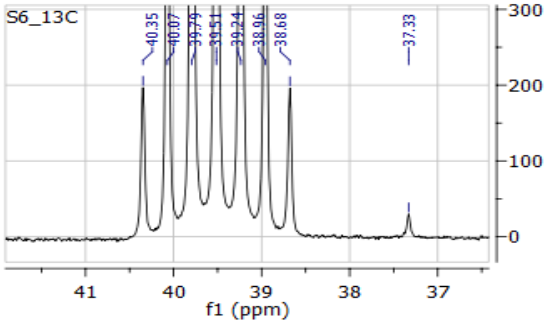


Figure 7. Pyrrolidine-2-one ring ^{13}C NMR signals of the **syn-3a** and **the anti-3a**

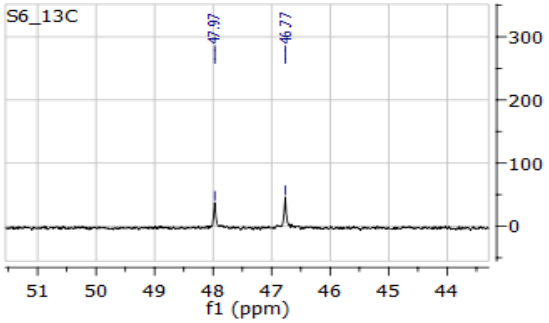


Figure 8. C_2-H type ^{13}C NMR signals of the **syn-3a** and **the anti-3a**

A singlet signal at δ 46.77 ppm is for one carbon (C_2-H) for **syn isomer**, and singlet signal at δ 47.97 ppm of one carbon (C_2-H) is for the anti isomer. The spectrum can be seen in Figure 8.

The ^{13}C-NMR spectra of the **3a** shows signals of aromatic carbons at δ 120.42, 120.47, 127.10, 127.11, 127.53, 127.70, 128.56, 128.59, 138.05, 138.19, 138.93 and 139.32 ppm for the **syn isomer** and the **anti isomer**. The spectrum can be seen in Figure 9.

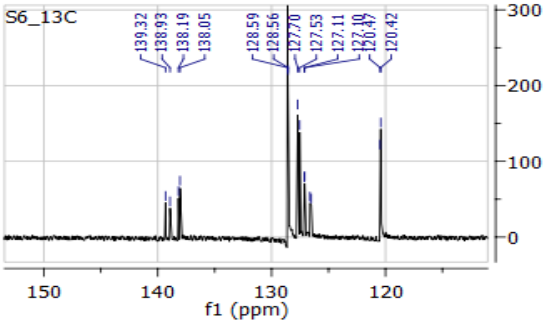


Figure 9. Aromatic ^{13}C NMR signals of the **syn-3a** and **the anti-3a**

Table 3 . ^{1}H-NMR spectral analysis of the mono-γ-lactams **3a-3d**

Mono-γ-lactams	**C_4-H,ring, *J* Hz**	**C_2-H, ring, *J* Hz**	**COOH**	**C_4-H ring, *J* Hz**	**C_2-H,ring, *J* Hz**	**COOH**
$C_{23}H_{17}Cl_2NO_3$	(syn isomer) Major(55 % yield)			(anti isomer) Minor (45 % yield)		
3a	2.64-2.72 (*dd*), *J*=6, 6, 1H	4.00-4.05, (*dd*), *J*=6, 6, 1H	10.11 (*s*), 1H	2.55-2.62, (*dd*), *J* =6, 3, 1H	4.07-4.12, (*dd*), *J*=3, 6, 1H	10.29 (*s*), 1H
$C_{23}H_{17}BrClNO_3$	(syn isomer) Major (66 % yield)			(anti isomer) Minor (34 % yield)		
3b	2.64-2.71, (*dd*), *J*=6, 6, 1H	3.99-4.05, (*dd*), *J*=6, 6, 1H	10.12 (*s*), 1H	2.55-2.62, (*dd*), *J* =3, 6, 1H	4.06-4.11, (*dd*), *J*=6, 3, 1H	10.29 (*s*), 1H
Mono-γ-lactams	**C_4-H_2 ring, *J* Hz**		**C_2-H ring, *J* Hz**		**COOH**	
$C_{24}H_{20}BrNO_3$ **anti-3c**	2.54-2.61 (*dd*), *J* = 6, 3, 1H		4.07-4.12 (*dd*), *J*=3, 6, 1H		10.05 (*s*)1H	
$C_{24}H_{20}FNO_3$ **anti-3d**	2.54-2.61 (*dd*), *J*=6, 3, 1H		4.06-4.11 (*dd*), *J*=3, 6, 1H		10.04 (*s*)1H	

Table 4. ^{1}H-NMR spectral analysis of the bis-γ-lactams **3e-3h**

Bis-γ-lactams	**C_4-H ring, *J* Hz**	**C_2-H ring, *J* Hz**	**COOH**	**C_4-H ring, *J* Hz**	**C_2-H ring, *J* Hz**	**COOH**
$C_{40}H_{30}Cl_2N_2O_6$	(syn isomer) Major (69% yield)			(anti isomer) Minor (31% yield)		
3e	2.61-2.69 (*dd*), *J*=6, 6(2H)	3.99-4.05 (*dd*), *J*=6, 6 (2H)	9.90 (*s*) 2H	2.54-2.61 (*dd*), *J* =3, 6(2H)	4.05-4.10 (*dd*) *J*=6, 3 2H	10.08 (*s*), 2H
$C_{40}H_{30}F_2N_2O_6$	(syn isomer) Major(76% yield)			(anti isomer) Minor(24% yield)		
3f	2.61-2.68 (*dd*), *J*=6, 6 (2H)	3.99-4.04 (*dd*) *J*=6, 6 (2H)	9.90 (*s*), 2H	2.53-2.61 (*dd*), *J* =3, 6 (2H)	4.07-4.10 (*t*), *J*=6, 3 (2H)	10.08 (*s*), 2H
$C_{44}H_{32}Cl_2N_2O_6$	(syn isomer) Major (81% yield)			(anti isomer) Minor(19% yield)		
3g	2.84-2.92 (*dd*), *J*=6, 6 (2H)	4.05-4.10 (*dd*), *J*=6, 9 (2H)	9.96(*s*), 2H	2.62-2.62 (*dd*), *J* = 3, 6 (2H)	4.07-4.12 (*dd*), *J*=3, 6 (2H)	10.16 (*s*), 2H
$C_{46}H_{38}N_2O_8$	(syn isomer) Major (70% yield)			(anti isomer) Minor (30% yield)		
3h	2.85-2.94, *q*, *J*=6, 6, 9, 9 (2H)	4.05-4.12, (*dd*), *J*=6, 6 (2H)	9.95(*s*), 2H	2.62-2.69, (*dd*), *J* =3, 3 (2H)	4.34-4.39, (*dd*), *J*=6, 6 (2H)	10.16, (*s*), 2H

Table 5. ^{13}C-NMR spectral analysis of the mono-γ-lactams **3a-3d**

Mono-γ-lactams	**C_4-ring, ppm**	**C_2-ring, ppm**	**HOC=O, ppm**	**-N-C=O, ppm**	**C_4-ring, ppm**	**C_2-ring, ppm**	**HOC=O, ppm**	**-N-C=O, ppm**
$C_{23}H_{17}Cl_2NO_3$	(syn isomer) Major (69 % yield)				(anti isomer) Minor (31 % yield)			
3a	39.60	46.77	169.27	171.03	37.33	47.97	172.74	174.12
$C_{23}H_{17}BrClNO_3$	(syn isomer) Major (66 % yield)				(anti isomer) Minor (34 % yield)			
3b	39.60	46.78	169.27	171.02	37.33	47.97	172.74	174.11
Mono-γ-lactams	**C_4- ring, ppm**		**C_2-ring, ppm**		**HO-C=O, ppm**		**-N-C=O, ppm**	
Anti, 3c	37.15		47.67		170.36		172.57	
$C_{24}H_{20}BrNO_3$								
Anti, 3d	37.15		47.68		170.36		172.56	
$C_{24}H_{20}FNO_3$								

Table 6. ^{13}C-NMR spectral analysis of the bis- γ-lactams **3e-3h**

Bis-γ-lactams	**C_4-ring, ppm**	**C_2-ring, ppm**	**HOC=O,ppm**	**-N-C=O, ppm**	**C_4-ring, Ppm**	**C_2-ring, ppm**	**HOC=O, ppm**	**-N-C=O, ppm**
$C_{40}H_{30}Cl_2N_2O_6$	syn isomer (69 % yield)				anti isomer (31 % yield)			
3e	39.65	46.86	168.69	170.75	37.33	47.81	172.75	174.15
$C_{40}H_{30}F_2N_2O_6$	syn isomer (76 % yield)				anti isomer (24 % yield)			
3f	39.69	46.90	168.72	170.46	37.33	47.84	172.77	174.18
$C_{44}H_{32}Cl_2N_2O_6$	syn isomer (81 % yield)				anti isomer (19 % yield)			
3g	39.36	47.20	169.73	171.62	37.33	47.31	172.86	174.17
$C_{46}H_{38}N_2O_8$	syn isomer (70 % yield)				anti isomer (30 % yield)			
3h	39.34	47.18	169.73	171.63	37.33	47.32	172.85	174.17

The spectrum shows a singlet signal of the carboxylic carbonyl group at δ 169.27 ppm**,** and an other singlet signal of the amide carbonyl group for the **syn isomer** at 171.03 ppm and a singlet signal of the carboxylic carbonyl group at δ 172.74 ppm, and an other singlet signal of the amidecarbonyl group carbon at 174.12 ppm (equivalent carbon).

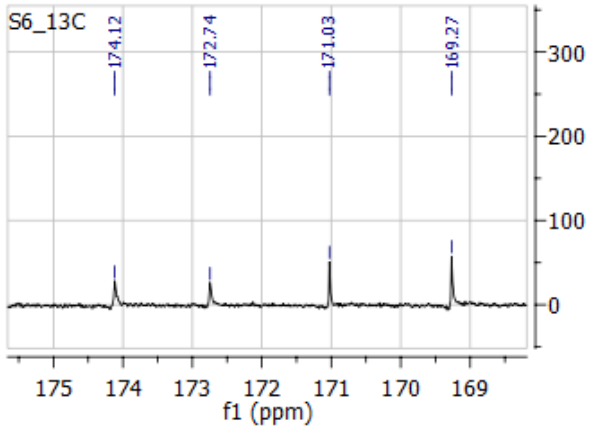


Figure 10. Selected ^{13}C NMR signals of syn-3a and anti-3a

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

The **HSQC ^{1}H-^{13}C-NMR** spectra of **3f**, showed pyrrolidine-2-one ring: for syn (Z) isomer (major isomer), the correlation of protons signals for -CH_2- group at δ 2.67 ppm and δ 3.06 ppm with carbon signal at δ 39.40 ppm of same group led to the assignment of this signal to methylene group, and proton signal 4.02 ppm for -CH- group with carbon signal of same group at 46.61 ppm, which lead to the assignment of this signal to -CH- group, and in pyrrolidine-2-one ring for anti *(E)* isomer (minor isomer): the correlation of protons signals for -CH_2- group,.and showed in pyrrolidine-2-one ring for anti *(E)* isomer (minor isomer): the correlation of protons signals for -CH_2- group at δ 2.56 ppm and δ 3.07 ppm with carbon signal at δ 37.08 ppm of same group which lead to the assignment of this signal to methylene group, and proton signal 4.08 ppm for -CH- group with carbon signal of same group at 47.55 ppm, which led to the assignment of this signal to -CH- group, (Digure 11). The HSQC ^{1}H-^{13}C-NMR spectra of the **3f** showed for syn isomer and anti isomer, the aromatic protons signals at δ 7.26, 7.27, 7.32, 7.34, 7.38, 7.43, 7.45 and 7.46 ppm correlation with carbon aromatic signals at 126.83, 128.24, 128.10, 128.30, 127.33, 118.94, 119.00 and 119.01 ppm respectively, (Figure 12).

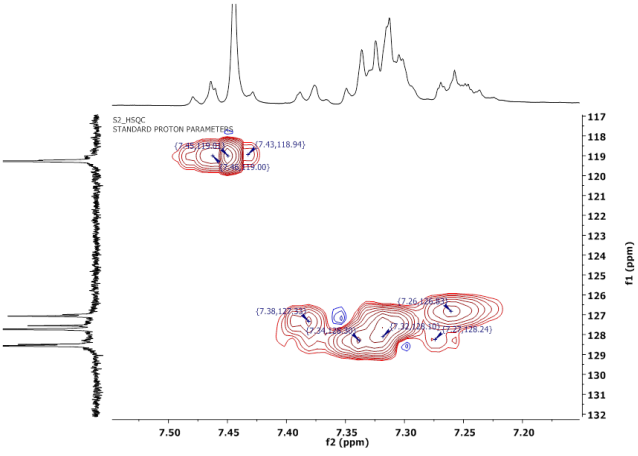


Figure 11. Selected **HSQC ^{1}H-^{13}C-NMR** spectra of the **3f**

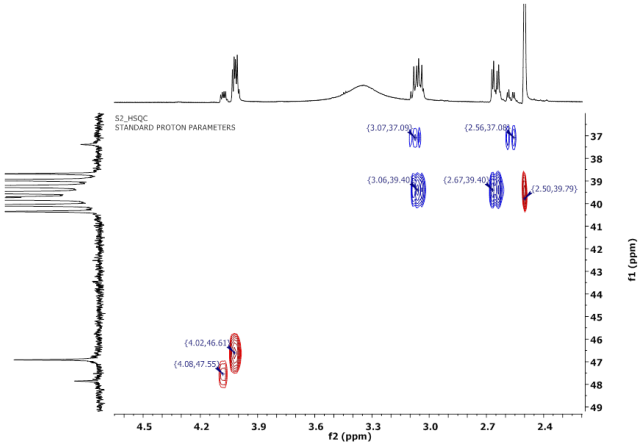


Figure 12. Aromatic HSQC ^{1}H-^{13}C-NMR spectra of the **3f**

Mass spectral analysis

The Mass spectra of 3b, showed the molecular ion peak $[M+H]^+$ = 470, $[2M+H]^+$ = 939 and showed the important fragmentation peaks in m/z = 304 m/z = 386, m/z = 393, m/z =326, m/z =315, m/z =474, m/z = 486, m/z =607, m/z =645, m/z = 629.

The Mass spectra of 3c, showed the molecular ion peak $[M+H]^+$ =685, $[M+Na]^+$ = 450, $[2M+H]^+$ = 899, and showed the important fragmentation peaks in m/z = 284 , m/z = 266, m/z = 238, m/z = 567, m/z = 477, m/z = 589, m/z = 605.

The Mass spectra of 3d (fig. 9) and (fig. 10), showed the molecular ion peak $[M+H]^+$ = 390, $[2M+H]^+$ = 779, and showed the important fragmentation peaks in m/z = 255, m/z = 371, m/z = 629, m/z = 585, m/z = 429, m/z = 412.

The Mass spectra of 3e, showed the molecular ion peak $[M+H]^+$ = 705, and showed the important fragmentation peaks in m/z = 285, m/z = 300, m/z = 341, m/z = 383, m/z = 391, m/z = 443, m/z = 461, m/z = 579.

The Mass spectra of 3h, showed the molecular ion peak $[M+H]^+$ = 747, $[2M+H]^+$ = 1493, and showed the important fragmentation peaks in m/z = 453, m/z = 533, m/z =689, m/z = 453, m/z = 905, m/z = 985, m/z = 963, m/z = 845, m/z = 809.

Acknowledgements

NMR and MS measurements were done at National Hellenic Research Foundation, Institute of Biology Medicinal Chemistry and Biotechnology, Molecular analysis Group, Athens, Greece.

References

[1]Younai, A., Chin, G. F., Fettinger, J. C. and Shaw, J. T., *J. Org. Chem*., **2010,** *75*, 8337.
[2]Nöth, J., Frankowski, K. J., Neuenswander, B., Aubé, J. and Reiser, O., *J. Comb. Chem.*, **2008,** *10*, 456.
[3]Zhao, X., DiRocco, D. A. and Rovis, T., *J. Am. Chem. Soc.*, **2011,** *133*, 12466-12469.
[4]Comesse, S., Sanselme, M. and Daïch, A., *J. Org. Chem*., **2008,** *73*, 5566-5569.
[5]Zhang,Y., Shao, Y. -L., Xu, H. -S. and Wang, W., *J. Org. Chem*., **2011,** *76*, 1472-1474.
[6]Shao, C., Yu, H. -J., Wu, N. -Y., Tian, P., Wang, R., Feng, C. -G. and Lin, G. -Q., *Org. Lett*., **2011,** *13*, 788-791.
[7]Lin, L., Zhang, J., Ma, X., Fu, X. and Wang, R., *Org .Lett*., **2011,** *13*, 6410-6413.
[8]Mori,T., Takahashi, K., Kashiwabara, M., Uemura, D., Katayama, C., Iwadare, S., Shizuri,Y., Mitomo, R., Nakano, F. and Matsuzaki, A., *Tetrahedron. Lett*., **1985,** *26*, 1073-1076.
[9]Feling, R. H., Buchanan, G. O., Mincer, T. J., Kauffman, C.A., Jensen, P. R. and Fenical, W., *Angew. Chem. Int. Ed*., **2003,** *42*, 355-357.
[10]Guntern, A., Ioset, J. R., Queiroz, E. F., Sandor, P., Foggin, C. M. and Hostettmann, K., *J. Nat. Prod*., **2003,** *66*, 1550-1553.
[11]Manam, R. R., Teisan, S., White, D. J., Nicholson, B., Grodberg, J., Neuteboom, S. T. C., Lam, K. S., Mosca, D. A., Lloyd, G. K. and Potts, B. C. M., *J. Nat. Prod*., **2005,** *68*, 240-243.
[12]Okazaki,Y., Ishizuka, A., Ishihara, A., Nishioka ,T. and Iwamura ,H., *J. Org. Chem*., **2007,** *72*, 3830-3839.
[13]Stuk, T. L., Assink, B. K., Bates, R. C., Erdman, D. T., Fedij, V., Jennings, S. M., Lassig, J. A., Smith, R. J. and Smith, T. L., *Org. Proces. Res. Dev*,. **2003,** *7*, 851-855.
[14]Masse, C. E., Morgan ,A. J., Adams, J. and Panek, J. S., *Eur. J Org. Chem*., **2000,** 2513-2528.
[15]Fenical, W., Jensen, P. R., Palladino, M. A., Lam, K. S., Lloyd, G. K. and Potts, B.C., *Bioorg. Med. Chem.*, **2009,** *17*, 2175-2180.
[16]Ng, P. Y., Tang,Y., Knosp, W. M., Stadler, H. S. and Shaw, J. T., *Angew. Chem. Int. Ed.*, **2007,** *46*, 5352-5355.
[17]Ng, P. Y., Masse, C. E. and Shaw, J. T., *Org Lett*. **2006,** *8*, 3999-4002.
[18]Wei, J. Q. and Shaw, J. T., Org. Lett., **2007,** *9*, 4077-4080.
[19]Tan, D. Q., Martin, K. S., Fettinger, J. C. and Shaw, J. T., *Proc Natl. Acad. Sci. USA*., **2011,** *108*, 6781-6786.
[20]Lettan, R. B., Galliford, C.V., Woodward, C. C. and Scheidt, K. A., *J. Am. Chem. Soc*., **2009,** *131*, 8805-8814.
[21]Raup, D. E. A., Cardinal-David, B., Holte, D. and Scheidt, K. A., *Nat. Chem*. **2010,** *2*, 766-771.
[22]Zhao, X., DiRocco, D. A. and Rovis, T., *J. Am. Chem. Soc*., **2011,** *133*, 12466-12469.
[23]Galliford, C. V. and Scheidt, K. A., *Angew. Chem. Int. Ed*. **2007,** *46*, 8748-8758.
[24]Marti, C. and Carreira, E. M., *Eur. J. Org. Chem*., **2003,** 2209-2219.
[25]Lopez, M. G. and Shaw, J. T., *Chem. Rev*., **2009,** *109*, 164-189.
[26]Masse, C. E., Ng, P. Y., Fukase,Y., Sanachez-Rosello, M. and Shaw, J. T., *J. Comb. Chem.*, **2006**, *8*, 293-296.
[27]Hello, K .M ., *Iraqi. J. Chem*., **2000**, *24*, 266.

[28]Krishnaswamy, D., *Tetrahedron.*, **2002,** *34*, 4567.
[29]Abdulrhman, Y. K., Mahmood, S. M., *Best Journal.*, **2014,** *2, (5)*, 37-48.
[30]Burdzhiev, N. T. and Stanoeva, E. R., *Z. Naturforsch.*, **2008,** *63b*, 313-320.
[31]Majeed, N. N., Esaa, A. H. and Turki, A. A., *Pharm. Chem.*, **2014,** *6(2)*, 288-293.

Received: 30.12.2014.
Accepted: 21.04.2015.