SYNTHESIS AND CHARACTERIZATION OF γ-LACTAMS THROUGH IMINE INTERMEDIATES

Assala Salam Jebur[a] and Mahmood Shakir Magtoof[a]*

Keywords: γ- lactams, imines, NMR.

This study is concerned with the synthesis and characterization of γ-lactams (**3a-3h**). γ-Lactams were prepared by reacting phenylsuccinic anhydride with the appropriate Schiff bases (imines) by heating at 51-61 °C in chloroform with moderate yields (51-75 **%**). The structures of these compounds were established on the basis of the spectral studies using IR, ^{1}H-NMR, ^{13}C-NMR , ^{13}C- NMR DEPT and MS.

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

Introduction

2-Oxopyrrolidine γ-lactam is five-membered ring lactams (Figure 1). γ-Lactams exist in many natural products and biologically active compounds and are one of the most important classes of compounds for drug discovery.[1-3] Substituted γ-lactams, in particular, have potential application in drug synthesis, but the development of stereoselective synthesis of chiral γ-lactams remains a challenge.[4,5] Developing effective and simple synthetic methods is important so that the drug candidates can be screened.

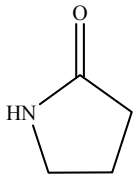


Figure 1. γ-Lactam ring

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. [6-8]

Experimental

The ^{1}H-NMR spectra were recorded using VARIAN spectrophotometer (500 MHz), the ^{13}C-NMR spectra were recorded using VARIAN spectrophotometer (75 MHz).The chemical shift values are expressed in δ (ppm), using tetramethylsilane (TMS) as internal standard and DMSO-d_6 as solvent. The mass spectra were recorded at 3 kV.

Preparation of mono-imines (2a-2d)

In general, the mono-imines (**2a-2d)** are prepared by the reaction of the mixture of 0.01 mole amine with 0.01 mol aldehyde in 25 mL of methanol or ethanol and 4-6 drops of glacial acetic acid, the reaction mixture is refluxed with stirring for 0.5-9 h, the progress of the reaction is followed by TLC using hexane : ethyl acetate (6:4) as eluent. After completion, the solvent evaporates and then recrystallizes from a suitable solvent.[9-11]

(E)-3-((4-Bromophenyl)imino)indolin-2-one (2a)

The compound was prepared by reacting 1.169 g (0.01 mol) of 4-bromoaniline and 1 g (0.01 mol) of indoline-2,3-dione. Yield 75 %, m.p. 273-275 ºC, colour orange, IR (KBr disk) 1608 cm^{-1} (C=N).

(E)-2-(((4-Bromophenyl)imino)methyl)-6-ethoxyphenol (2b)

The compound was prepared by reacting 1.036 g (0.01 mol) of 4-bromoaniline and 1.169 g (0.01 mol) of 3-ethoxy-2-hydroxybenzaldehyde. Yield 79 %, m.p. 89-90 ºC, colour orange, IR (KBr disk) 1681 cm^{-1} (C=N).

(E)-4-Bromo-2-(((4-nitrophenyl)imino)methyl)phenol (2c)

The compound was prepared by reacting 0.68g (0.01 mol) of 4-nitroaniline and 1 g (0.01 mol) of 5-bromo-2-hydroxybenzaldehyde. Yield 69 %, m.p. 178-180 ºC, colour yellowish, IR (KBr disk) 1618 cm^{-1} (C=N).

(E)-4-Bromo-2-((naphthalen-1-ylimino) methyl)phenol (2d)

The compound was prepared by reacting 0.71g (0.01 mol) of naphthalen-1-amine and 1 g (0.01 mol) of 5-bromo-2-hydroxybenzaldehyde. Yield 87.5 %, m.p. 105-106 ºC, colour maronite, IR (KBr disk) 1620 cm^{-1} (C=N).

Preparation of bis-imines (2e-2g)

In general, the bis-imines (**2e-2g**) are prepared by the reaction of 0.01 mole diamine with 0.02 mole of aldehyde

in 25 mL of methanol or ethanol and 4-6 drops of glacial acetic acid, the reaction mixture is refluxed for 1-9 h, the progress of the reaction is followed by TLC using hexane : ethyl acetate 6:4 as eluent. After completion, the solvent was evaporated and the product was then recrystallized from a suitable solvent.

6,6'-((1E,1'E)-((Methylenebis(4,1-phenylene)) bis(azanylidene)) bis(methanylylidene))bis(2-ethoxyphenol) (2e)

The compound was prepared by reacting 0.595 g (0.01 mol) of 4,4'-methylenedianiline with 1g (0.02 mol) of 3-ethoxy-2-hydroxybenzaldehyde. Yield 87.6 %, m.p.157-158 ºC, colour yellowish, IR (KBr disk)1624 cm^{-1} (C=N).

6,6'-((1E,1'E)-(Naphthalene-1,5-diylbis(azanylylidene))-bis(methan ylylidene))bis(2-ethoxyphenol) (2f)

The compound was prepared by reacting 0.452 g (0.01 mol) of 1,5-diaminonaphthalene with 0.95 g (0.02 mol) of 3-ethoxy-2-hydroxybenzaldehyde .Yield 96 %, m.p. 133-136ºC, colour chartreuse, IR (KBr disk)1618 cm^{-1} (C=N).

(N1E,N5E)-N1,N5-Bis(4-chlorobenzylidene)naphthalen-e-1,5-diamine (2g)

The compound was prepared by reacting 0.562 g (0.01 mol) of 1,5-diaminonaphthalene with1 g (0.02mol) of 4-chlorobenzaldehyde. Yield 96.5 %, m.p. 190-192ºC, colour green, IR (KBr disk) 1621 cm^{-1} (C=N).

General procedure for the preparation of γ-lactams 3a-3g

Preparation of mono-γ-lactams 3a-3d.

In general, the mono-γ- lactams (**3a-3d)** were prepared by reacting a mixture of 0.01 mol of monoimine (**2a-2d**) with 0.01 mol of phenylsuccinic anhydride in 25 mL of chloroform and heating the mixture in water bath at 51-61 °C. The reaction mixture was then refluxed for 12-30 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. [12-13]

1'-(4-Bromophenyl)-2,5'-dioxo-3'-phenylspiro[indoline-3, 2'-pyrrolidine]-3'-carboxylic acid (3a)

The compound was prepared by reacting 0.5 g (0.01 mol) of **2a** with 0.292 g (0.01 mol) of phenylsuccinic anhydride. Yield 51 %, m.p. 192-195 ºC, colour orange. IR (KBr): 1650 cm^{-1} (HO–C=O), 1721 cm^{-1} (–N–C=O).^{1}H-NMR (500 MHz, DMSO) δ = 3.3 (s, 2H, γ-Lactam ring), 7.2-8.21 (m, 13H, Ar-H), 9.4 (s, 1H, -NHC=O), 11.3 (s, 1H, OHC=O). ^{13}C-NMR (75 MHz, DMSO) δ = 48 (s, C_4H), 52(-C_2-), 58(s, C_3-H), 116-151 (m, C-Ar), 174 (s, CH_2-C=O), 175(s, HN-C=O), 179(s, HO-C=O).

1-(4-Bromophenyl)-2-(3-ethoxy-2-hydroxyphenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (3b)

The compound was prepared by reacting 0.8 g (0.01mol) of **2b** with 0.43 g (0.01 mol) of phenylsuccinic anhydride. Yield 74 %, m.p. 83-85 ºC, colour orange. IR (KBr): 1656 cm^{-1} (HO–C=O), 1722 cm^{-1} (–N–C=O). ^{1}H-NMR (500 MHz, DMSO) δ = 3.6 (s, 2H, C_4-H), 3.8 (s, 2H, CH_2-O), 1.78 (3H, -CH_3), 7.72 - 8.28 (m, 12H, Ar-H), 4.02 (s, 1H, C_2-H), 10.8 (s, 1H, OHC=O), 9.6 (s, 1H, Ar-OH). ^{13}C-NMR (75 MHz, DMSO) δ = 29 (s, -CH_3), 42 (s, -CH_2-), 44 (s, CH_2-O), 49 (s, -CH-), 59 (s, -COOH), 115-158 (m, C-Ar), 173 (s, CH_2-C=O), 180 (s, HO-C=O).

2-(5-Bromo-2-hydroxyphenyl)-1-(4-nitrophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (3c)

The compound was prepared by reacting 0.8 g (0.01mol) of **2c** with 0.438 g (0.01 mol) of phenylsuccinic anhydride. Yield 65 %, m.p. 110-112 ºC, colour yellow. IR (KBr): 1682 cm^{-1} (HO–C=O), 1725 cm^{-1} (–N–C=O). ^{1}H-NMR (500 MHz, DMSO) δ = 3.7 (s, 2H, C_4-H), 4.1 (s, 1H, C_2-H), 7.28-8.15 (m, 12H, Ar-H), 11.0 (s, 1H, OHC=O), 9.4 (s, 1H, Ar-OH).^{13} C-NMR (75 MHz, DMSO) δ = 44 (s, -CH_2-O), 46 (s, CH_2-), 52 (s, -CH-), 57 (s, COOH), 120-156 (m, C-Ar), 181 (s, HO-C=O), 178 (s, CH_2-C=O).

2-(5-Bromo-2-hydroxyphenyl)-1-(naphthalen-1-yl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (3d)

The compound was prepared by reacting 0.6 g (0.01 mol) of **2d** with 0.323g (0.01 mol) of phenylsuccinic anhydride. Yield 69 %, m.p. 190-192 ºC, colour brown. IR (KBr):1690 cm^{-1} (HO-C=O), 1721 cm^{-1} (–N–C=O). ^{1}H-NMR (500 MHz, DMSO) δ = 3.7 (s, 2H, C_4-H), 4.3 (s, 1H, C_2-H), 7.20-8.52 (m,15H, Ar-H), 10.9 (s, 1H, OHC=O), 9.6 (s, 1H, Ar-OH).^{13} C-NMR (75 MHz, DMSO) δ = 42 (s, -CH2-O), 45 (s ,-CH_2), 53(s, -CH-), 56 (s, -COOH), 112-154 (m, C-Ar), 175 (s, HO-C=O), 178(s, CH_2-C=O).

Preparation of bis-γ-lactams (3e-3g)

In general, the bis-γ-lactams (**3e-3g**) were prepared by reacting 0.01 mol bis-imines (**2e-2g**) with 0.02 mol of phenylsuccinic anhydride in 25 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.

1,1'-(Methylenebis(4,1-phenylene))bis(2-(3-ethoxy-2-hydroxyphenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid) (3e)

The compound was prepared by reacting 0.5 g (0.01 mol) of **2e** with 0.385 g (0.02 mol) of phenylsuccinic anhydride. Yield 73 %, m.p. 172-173 ºC, colour orange. IR (KBr): 1654 cm^{-1} (HO-C=O), 1733 cm^{-1} (–N–C=O).

^{1}H-NMR (500 MHz, DMSO) δ = 1.78 (s, 6H, -CH_3), 3.6 (s, 4H, C_4-H), 3.85 (s, 2H, -CH_2-), 4.1 (s, -CH_2-),7.2-8.58 (m, 24H, Ar-H), 9.4 (s, 2H, Ar-OH), 10.73 (s, 2H, OHC=O).[13] C-NMR (75 MHz, DMSO) δ = 41 (d, -CH_2-O), 29 (d, -CH_3),31 (s, Ar-CH_2-Ar), 42 (d, -CH_2-), 57 (d, -CH-), 55 (d, -COOH), 111-158 (m, C-Ar),171 (d, CH $_2$-C=O), 173 (d, HN-C=O),178 (d, HO-C=O).

1,1'-(Naphthalene-1,5-diyl)bis(2-(3-ethoxy-2-hydroxyphe-nyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid) (3f)

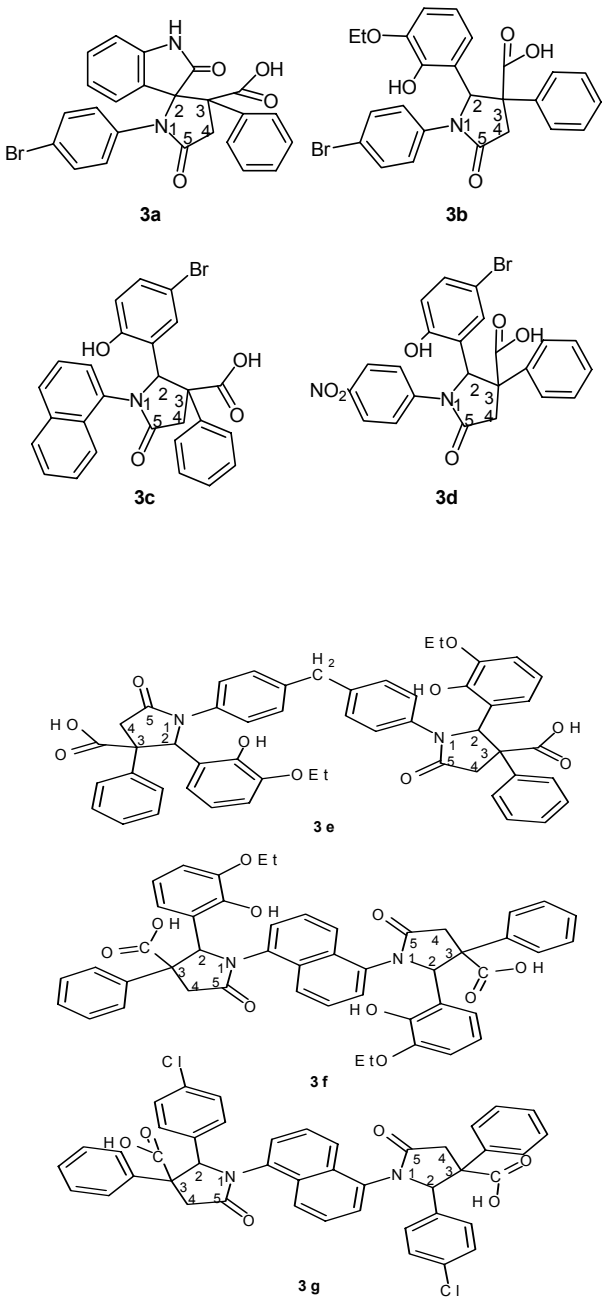


Figure 2. Structures of the compounds (**3a-3g**).

The compound was prepared by reacting 0.454 g (0.01mol) of **2f** with 0.352 g (0.02 mol) of phenylsuccinic anhydride. Yield 66 %, m.p. 146-147 ºC, colour orange. IR (KBr): 1636 cm^{-1} (HO-C=O), 1732 cm^{-1} (–N–C=O). ^{1}H-NMR (500 MHz, DMSO) δ = 1.86 (d, 6H, -CH_3), 3.7 (d, 4H, CH_2-O), 4.05 (d, 4H, C_4-H), 4.7 (d, 2H, -C_2-H), 7.4-8.5 (m, 24H, Ar-H), 9.5 (d, 2H, -OH), 10.7 (d, 2H, OHC=O).

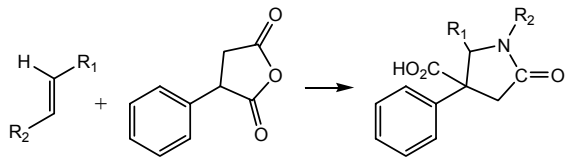
1,1'-(Naphthalene-1,5-diyl)bis(2-(4-chlorophenyl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid) (3g)

The compound was prepared by reacting 0.6 g (0.01 mol) of **2g** with 0.525 g (0.02 mol) of phenylsuccinic anhydride. Yield 75 %, m.p. 190-193 ºC, colour greenish. IR (KBr): 1656 cm^{-1} (HO-C=O), 1706 cm^{-1} (–N–C=O). ^{1}H-NMR (500 MHz, DMSO) δ = 3.5 (d, 4H, C_4-H), 4.45 (d, 2H, -C_2-H), 7.6-8.3 (m, 24H, Ar-H), 11.0 (d, 2H, OHC=O).

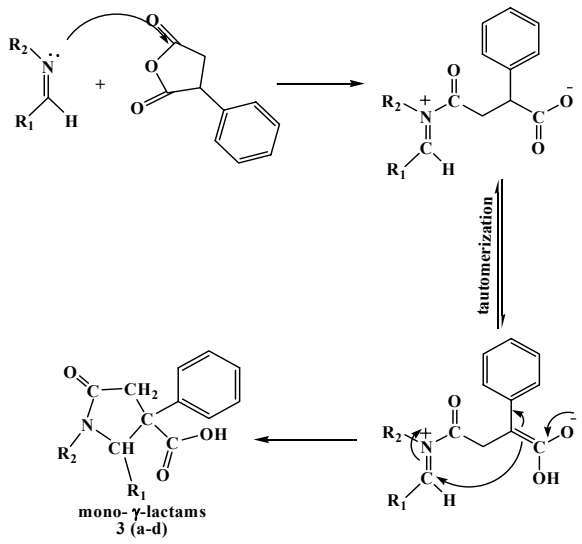
Results and discussion

The structural skeleton of chiral lactams are found in a broad range of natural and biologically active molecules, such as penicillins, cephalosporins, carbapenems, monobactams, salinosporamide A, rolipram and brivaracetam.

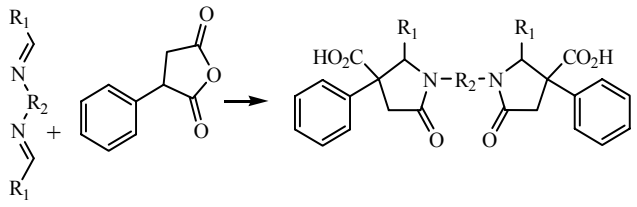
In the present investigation, γ-lactams are obtained by the reaction of imines with phenylsuccinic anhydride to in a suitable solvent (dioxane or chloroform). The structures of the compounds **3a–3g**, as established by spectral analysis, are given in Fig. 2. A probable mechanism for synthesis has been suggested (Schemes 1 - 4).



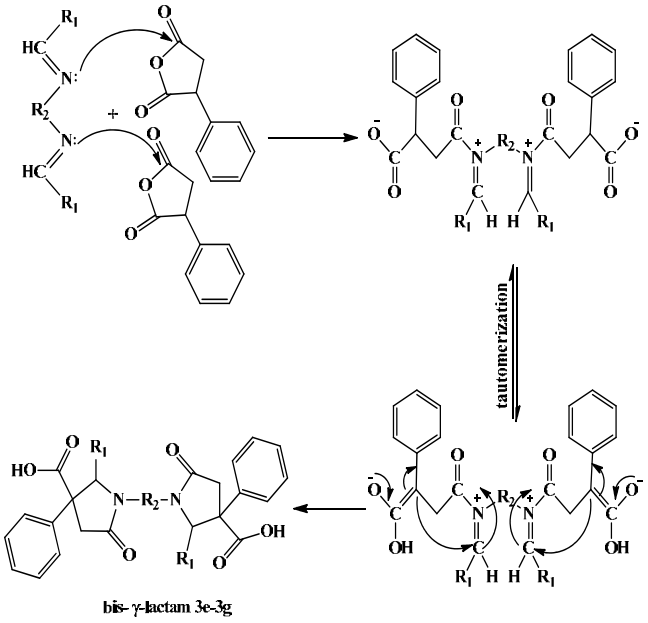
Scheme 1. Synthesis of mono γ-lactam



Scheme 2. Mechanism of formation of mono γ-lactam



Scheme 3. Synthesis of bis γ-lactam



Scheme 4. Probable mechanism of the formation of bis-γ-lactams.

Analysis of infrared spectra

The IR spectra of mono and bis γ-lactams (**3a-3g)** are characterized by the seven bands corresponding to the stretching vibration of the aromatic C-H, aliphatic C-H, carbonyl carboxylic group, carbonyl amide group, aromatic C=C, C-N band and the substituted ring which occurs within the ranges 3126-3030, 2990- 2878, 1733-1706, 1699-1636, 1603-1568, 1340-1325, and 925-617 cm^{-1} respectively.

Analysis of ^{1}H-NMR spectra

The ^{1}H-NMR spectra (Figure 3) of **3a** showed γ-lactam ring singlet signal at δ = 3.3 ppm for methylene group (CH_2), multiplet signal at δ = 7.2 - 8.21 ppm for aromatic protons (m, 13H, Ar-H), singlet signal for one proton in γ-lactam ring at δ= 9.4 ppm for NH, and finally showed singlet signal for proton carboxylic acid at δ = 11.3 ppm.

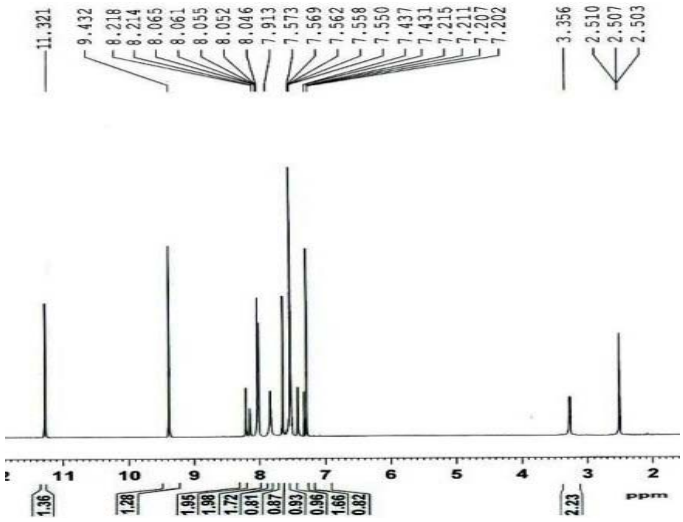


Figure 3. ^{1}H-NMR spectra of **3a**.

Analysis of ^{13}C-NMR spectra

The ^{13}C-NMR spectra (Figure 4) of **3a** showed in γ-lactam ring singlet signal at δ = 48 ppm for methylene group (C_4-H_2), at 52 ppm for C_2-ring, at 58 ppm for C_3-ring, at 174 ppm for O=C-ring, multiplet at 114-151 ppm for aromatic protons (m, C-Ar), at δ 175ppm for HN-C=O, and at 179 ppm for HO-C=O.

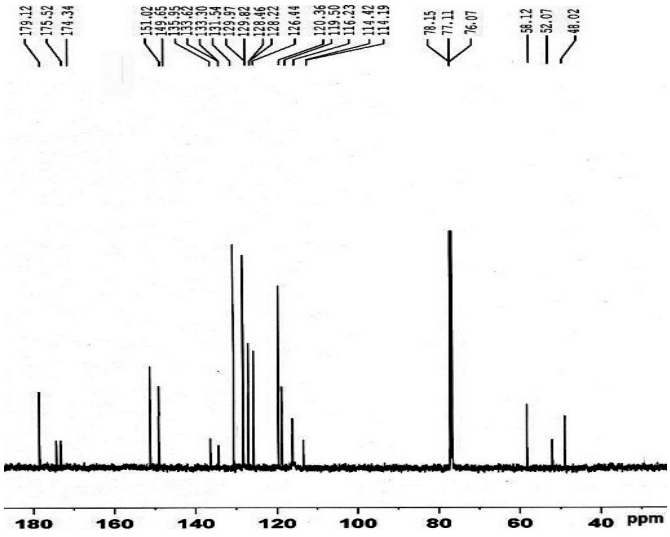


Figure 4. ^{13}C-NMR spectra of **3a**.

Analysis of mass spectra

The mass spectrum of **3a** shows the molecular ion peak corresponding to the particular compound at 477 m/z, and the fragmentation of **3a** showed the peaks at 346, 301, 198, 132, 104, 90 ,77,65 m/z which are attributed to the fragments of $C_{16}H_{12}BrNO_3^+$, $C_{15}H_{11}BrNO^+$, $C_7H_4BrNO^+$, $C_8H_6NO^+$, $C_7H_6N^+$, $C_7H_6^+$, $C_6H_5^+$ and $C_5H_5^+$ respectively.

The mass spectrum of **3b** shows the molecular ion peak corresponding to the compound at 496 m/z. The fragmentation of **3b** showed the peaks at 428, 467, 439, 422, 387, 329, 198, 131, 77 and 65 m/z which are attributed to the fragments of $C_{24}H_{20}BrNO_5^+$, $C_{23}H_{17}BrNO_5^+$, $C_{22}H_{17}BrNO_4^+$, $C_{22}H_{16}BrNO_3^+$, $C_{23}H_{17}NO_5^+$, $C_{16}H_{11}BrNO_2^+$, $C_7H_4BrNO^+$, $C_9H_7O^+$, $C_6H_5^+$, $C_5H_5^+$ respectively.

The mass spectrum of **3c** shows the molecular ion peak corresponding to the compound at 497 m/z. The fragmentation of **3c** showed the peaks at 312, 295, 267, 225, 174, 77 and 65 m/z which are attributed to the fragments of $C_{16}H_{12}N_2O_3^+$, $C_{16}H_{11}N_2O_4^+$, $C_{13}H_9N_2O_2^+$, $C_9H_9N_2O_2^+$, $C_6H_5^+$ and $C_5H_5^+$ respectively.

Analysis of ^{13}C-NMR DEPT spectra

^{13}C-NMR DEPT spectral of **3a** showed in γ-lactam ring singlet signal at δ = 48 (negative) ppm for methylene group (C_4-H_2), at 52 (positive) ppm for (C_2-ring), at 58 (positive) ppm for (C_3-ring), at 174 (positive) ppm for (O=C-ring) a multiplet signal at 116-151 (positive) ppm for aromatic protons (m, C-Ar), at 175 (positive) ppm for (HN-C=O) and a signal at 179 (positive) ppm for (HO-C=O).

^{13}C-NMR DEPTspectral of **3b** showed in γ-lactam ring singlet signal at δ = 42.11 (negative) ppm for methylene group (C_4-ring), at 49.17 (positive) ppm for C_2-ring, at 58.18 (positive) ppm for C_3-ring, at 173 (positive) ppm for O=C-ring, a multiplet at 115-158 (positive) ppm for aromatic protons (m, C-Ar), at 180 (positive) ppm for (HO-C=O), at 29 (positive) ppm for -CH_3 and a signal at 42 (negative) ppm for O-CH_2.

Acknowledgements

This work is sponsored by the university of Thi-Qar as a part of research development and higher studies projects.

References

[1]Catalani, M.., Alvaro, G., Bernasconi, G., Bettini, E., Bromidge, S. M., Heer, J., Tedesco, G., Tommasi, S., *Bioorg. Med. Chem. Lett.,* **2011,** *21,* 6899–6904.

[2]Lee, C., Choi, E., Cho, M., Lee, B., Oh, S. J., Park, S. K., Lee, K., Kim, H. M., Han, G., *Bioorg. Med. Chem. Lett.,* **2012,** *22,* 4189–4192.

[3]Cornut, D., Lemoine, H., Kanishchev, O., Okada, E., Albrieux, F., Beavogui, A. H., Bienvenu, A.-L., Picot, S., Bouillion, J.-P., Médebielle, M., *J. Med. Chem.,* **2013,** *56,* 73–83.

[4]Zhao, X., DiRocco, D. A., Rovis, T., *J. Am. Chem. Soc.,* **2011,** *133,*12466–12469.

[5]Comesse, S., Sanselme, M., Daïch, A., *J. Org. Chem.,* **2008,** *73,* 5566–5569.

[6]Zhang, Y., Shao, Y.-L., Xu, H.-S., Wang, W., *J. Org. Chem.,* **2011,** *76,* 1472–1474.

[7]Shao, C., Yu, H.-J., Wu, N.-Y., Tian, P., Wang, R., Feng, C.-G., Lin, G.-Q., *Org. Lett.,* **2011,** *13,* 788–791.

[8]Lin, L., Zhang, J., Ma, X., Fu, X., Wang, R., *Org. Lett.,* **2011,** *13,* 6410–6413.

[9]Hello, K. M., *Iraqi J. Chem*., **2000,** *24*, 266.

[10]Krishnaswamy, D., *Tetrahedron.*, **2002,** *34,* 4567.

[11]Abdulrhman, Y. K., Mahmood, S. M., *Best J.,* **2014,** *2(5)*, 37-48.

[12]Burdzhiev, N. T., Stanoeva, E. R., *Z. Naturforsch*., **2008,** *63b*, 313-320.

[13]Majeed, N. N., Esaa, A. H., Turki, A. A., *Pharm. Chem.,* **2014,** *6(2),* 288-293.

Received: 18.11.2016.
Accepted: 14.01.2017.