

SYNTHESIS AND CHARACTERIZATION OF MONO/BIS β - LACTAMS BY USING [2+2] CYCLOADDITION REACTION AND STUDY ANTIHYPERGLYCEMIC ACTIVITY

AYAD SHLAGA FUDALLA, MAHMOOD SHAKIR MAGTOOF & MOHAMED AJA AUDA

Department of Chemistry, Science College, Thiqr University, Thiqr, Nashyria, Iraq

ABSTRACT

This study is concerned with the synthesis of 3-phenylthio/3 phthalimido mono/bis azetidone compounds from (phenylthio acetic acid/phthalimido acetic acid with appropriate Schiff's bases using POCl_3 and Et_3N in CH_2Cl_2 under N_2 atmosphere and characterization of these compounds by IR, UV, Mass, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$. and study anti hyperglycemic activity for 2, 2'-(1, 1'-(1, 4-phenylene) bis (2-(4-(dimethylamino) phenyl) - 4 - oxoazetidone- 3, 1-diyl)) diisoindolin-1, 3-dione (**3d**). used rats (*Rattus norvegicus*) injected with Alloxan, Alloxane a beta-cytotoxin induces chemical diabetes through damage of insulin secreting cells. test compound (**3d**) significantly lowered the serum glucose levels indicating their anti-hyperglycemic activity.

KEYWORDS: Damage of Insulin Secreting Cells, Monobactams, Appropriate Aldehydes

INTRODUCTION

β -lactam (beta-lactam) ring, is a four-membered ring¹(figure1). It is named as such, because the nitrogen atom is attached to the β -carbon relative to the carbonyl. The simplest β -lactam possible is 2-azetidinone.

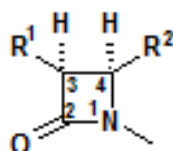


Figure 1

The β -lactam ring is part of the core structure of several antibiotic families, the principal ones being the penicillins, Cephalosporins, carbapenems, and monobactams, which are, therefore, also called β -lactam antibiotics. Nearly all of these antibiotics work by inhibiting bacterial cell wall biosynthesis. This has a lethal effect on bacteria. Bacteria do, however contain within their populations, in smaller quantities, bacteria that are resistant against β -lactam antibiotics. They do this by expressing one of many β -lactamase genes. More than 1,000 different β -lactamase enzymes have been documented in various species of bacteria.² These enzymes vary widely in their chemical structure and catalytic efficiencies.² When bacterial populations have these resistant subgroups, treatment with β -lactam can result in the resistant strain becoming more prevalent and therefore more virulent.

The first synthetic β -lactam was prepared by Hermann Staudinger in 1907 by reaction of the Schiffbase of aniline and benzaldehyde with diphenylketene^{3,4} in a [2+2] cycloaddition: (figure 2).

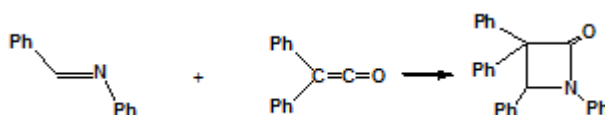


Figure 2

Up until 1970, most β -lactam research was concerned with the penicillin and cephalosporin groups⁵, (Figure 3).

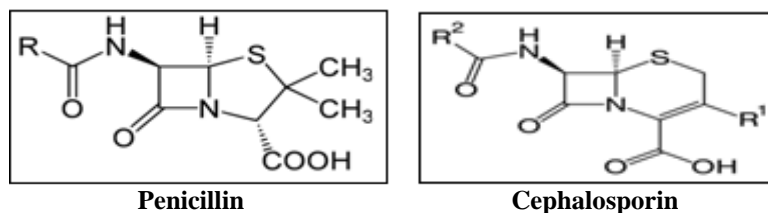


Figure 3

RESULTS AND DISCUSSIONS

Taking a lead from recent earlier studies,^{6,7} it was considered to utilize ketene-imine cyclization in the presence of triethylamine for the synthesis of 3- phthalimido/3-(phenylthio) substituted β -lactams **3** (a-d).

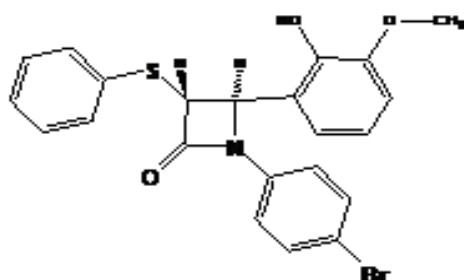


Figure 3a: 1-(4-Bromophenyl)-4-(2-Hydroxy-3-(2-Hydroxy-3-Methoxyphenyl)-3-(Phenylthio) Azetidino-2-one (**3a**)

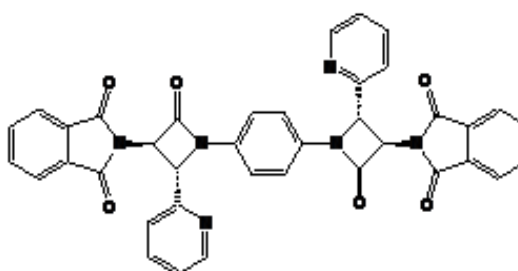


Figure 3b: 2,2'-(1,1'-(1,4-Phenylene)bis(2-oxo-4-(Pyridine-2-yl) Azetidino-3,1-Diyl)) Diisoindolin-1,3-Dione (**3b**)

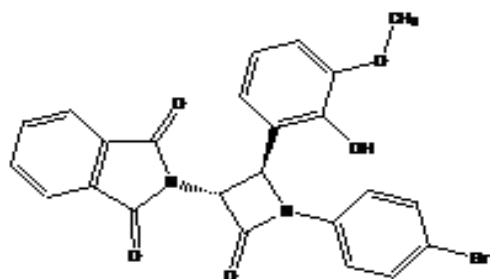


Figure 3c: 2-(1-(4-Bromophenyl)-2-(2-Hydroxy-3-Methoxy phenyl)-4- Oxoazetidino-3-yl)Isoindolin-1,3-Dione (**3c**)

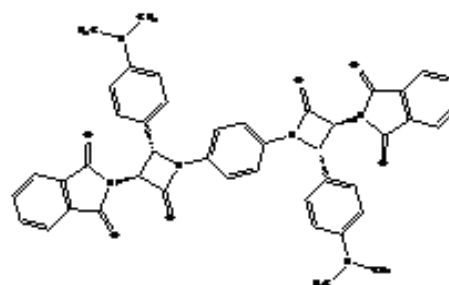


Figure 3d: 2,2'-(1,1'-(1,4-Phenylene)bis(2-(4-(Dimethyl Amino) Phenyl)-4- Oxoazetidino-3,1-diyl))Diisoindolin-1,3-Dione (**3d**)

In view of the associated biological activity and its utility in organic synthesis, the synthesis of 3-phthalimido/3-(henylthio) mono/Biscyclic azetidino-2- ones **3** (a-d) were performed. The key step involved the treatment of imine **2(a-c)** with N-phthaloglycine/phenylthio acetic acid by using triethylamine in the presence of phosphorus oxychloride in dry methylene chloride under nitrogen to afford *cis/trans* azetidino-2-one **3a**, **3c** as shown in (scheme 3), **3b**, **3d** (scheme 4).

Various schiff's bases **2(a-c)** were prepared from the appropriate aldehydes and amines in dry methylene chloride in the presence of molecular sieves (4A^o) or in hot ethanol. The structures of the imines were confirmed on the basis of their spectral data, FT. IR spectrophotometer. Scheme1, Scheme 2.

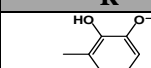
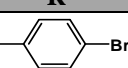
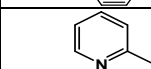
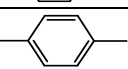
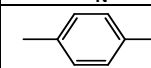
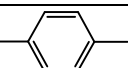


Scheme 1

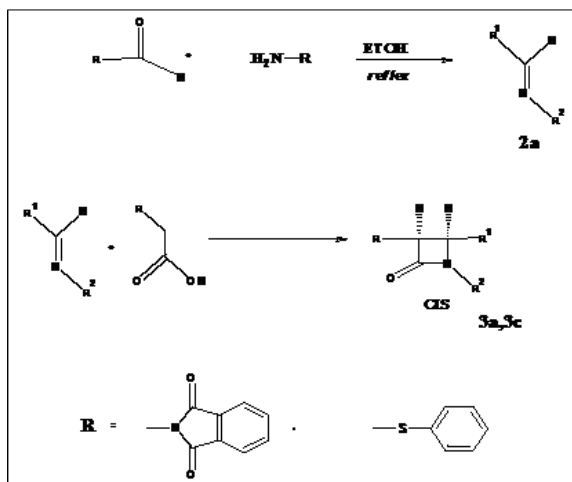


Scheme 2

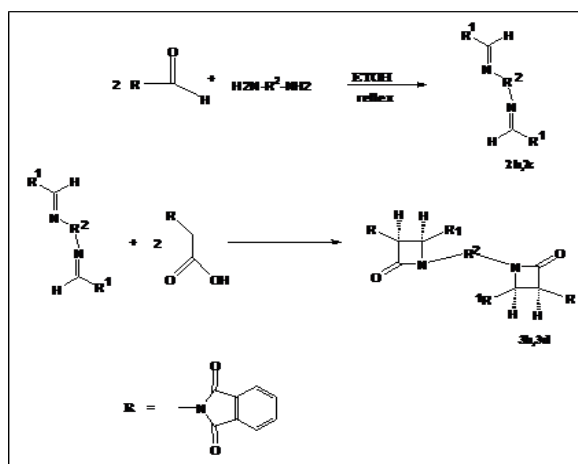
Table 1: The Schiff Bases 2(a-c)

Compd	Schiff Base	R ¹	R ²
1.	2a		
2.	2b		
3.	2c		

The target β -lactams **3 (a-d)** required for this study were prepared by treatment N-phthaloglycine/phenylthio acetic acid with appropriate schiff's bases **2(a-c)** using triethylamine as a base in methylene chloride at 0°C



Scheme 3



Scheme 4

Table 2: 3-Phthalimido/3-(Phenylthio) Azetidin-2-Ones 3 (a-d)

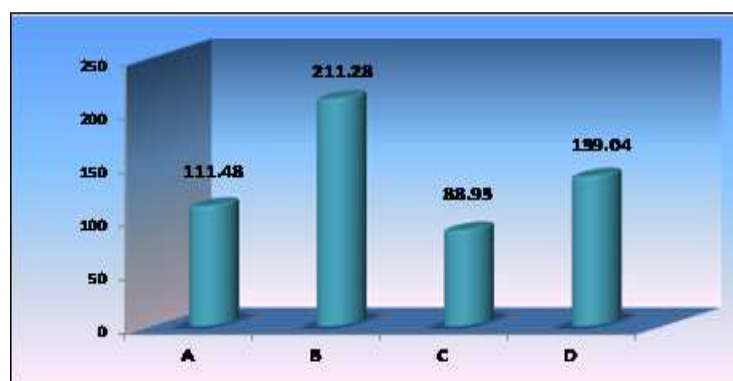
No	Symbol	R ¹	R ²
1	3a		
2	3b		
3	3c		
4	3d		

ANTIHYPERGLYCEMIC ACTIVITY

Serum glucose concentration was changed as shown in **table (3)** during experimental period, there was a significant increase ($P < 0.01$) in the serum concentration of glucose in group (2) as compared with other group. While groups (1, 4) don't appear significant differences between them, at these times there was not significant differences between group (3) and group (1).

Table 3

Groups	N	Mean \pm S.D
Group-1	6	111.48 ^{bc} \pm 27.95
Group-2	6	211.28 ^a \pm 18.74
Group-3	6	88.95 ^c \pm 14.26
Group-4	6	139.04 ^b \pm 35.29
L.S.D		41.65

**Scheme 5**

Alloxane a beta-cytotoxin induces chemical diabetes through damage of insulin secreting cells⁸. Test compound (3d) significantly lowered the serum glucose levels indicating their anti-hyperglycemic activity. In the diabetic rats, high glucose levels and depression in hepatic glycogen contents were observed which could be attributed to the less availability of active form of enzyme glycogen synthetase. Which in turn has been reported to be responsible for incorporation of glucose moieties in pre-existing glycogen chain^{9,10}. This activity of test compounds (3d) may be due to increased utilization of glucose as indicated by decreased serum glucose levels and an increase in the activity of glycogen synthetase enzyme as evidenced by rise in liver glycogen contents in test groups.

The structures of the azetidine-2-ones were established on the basis of spectral data, **IR**, **mass**, ¹H NMR, ¹³C NMR

The IR spectra of the imines **2 (a-c)**, as KBr disc showed absorption band at (1593-1620) cm^{-1} corresponding to the azomethine of imine compounds. The IR spectra of 3-(phthalamido) /3-phenylthio azetidines **3(a-d)** KBr disc and representative spectra are shown in Figure (1.1),(1.2)(1.3)and (1.4). The IR spectra of 3-(phthalamido)/3-phenylthioazetidines **3(a-d)** are characterized by the five bands corresponding to the stretching vibration of the aromatic C-H, aliphatic C-H, carbonyl group, alkene and substituted ring which occurs within the ranges 3005-3065, 2811-2942, 1711-1773, 1513-1644, and 816-993 cm^{-1} respectively.

The $^1\text{H-NMR}$ spectral data of the 3-phthalamido/3-phenylthio azetidines **3a,3b,3c and 3d** most of their spectra are shown in Figures (1-5),(1-6),(1-7) and (1-8).

The protons at C₃-H and C₄-H positions of the ring have been observed to. The $^1\text{H-NMR}$ of **3a** showed four distinct doublets C₃-H δ (4.31-4.33) and C₄-H δ (3.77-3.79) with $J = 5\text{Hz}$. The high value between C₃-H and C₄-H ($J = 5.0\text{Hz}$) is indicative of the *cis* configuration of **3a**. Also the $^1\text{H-NMR}$ spectra of **3a** showed at δ 3.46 ppm for anisole group (CH₃O-Ph) (*s*, 3H, OCH₃), δ (8.9) ppm for Hydroxy group (Ph-OH) (*s*,1H,OH). Also the $^1\text{H-NMR}$ spectrum of **3a** showed aromatic protons at δ 7.13-8.61 ppm.

The $^1\text{H-NMR}$ of **3b** showed four distinct doublets C₃-H δ (4.18-4.21) and C₄-H δ (4.12-4.15) with ($J=7.5\text{Hz}$). Because of C₃-H the $J_{\text{coupling}} = 7.5\text{Hz}$ and C₄-H in each pair and the amount of coupling constant ≥ 2.5 confirming these compound **3b**. The high value between C₃-H and C₄-H ($J = 7.5\text{Hz}$) is indicative of the *cis* configuration of **3b**. Also the $^1\text{H-NMR}$ spectrum of **3b** showed aromatic protons at δ 7.27-8.47 ppm.

The $^1\text{H-NMR}$ of **3c** showed four distinct doublets C₃-H δ (4.47-4.49)with $J= 5\text{Hz}$ and C₄-H δ (4.13-4.15) with ($J = 5\text{Hz}$). The high value between C₃-H and C₄-H ($J = 5\text{Hz}$) is indicative of the *cis* configuration of **3c**. Also the $^1\text{H-NMR}$ spectra of **3c** showed at δ 3.56 ppm for anisole group (CH₃O-Ph) (*s*, 3H, OCH₃), δ (10.15)ppm for Hydroxy group (Ph-OH) (*s*,1H,OH), δ (6.89-8.97) ppm for aromatic protons.

The $^1\text{H-NMR}$ of **3d** showed four distinct doublets C₃-H δ (5.39-5.40) with $J= 2.5\text{Hz}$ and C₄-H δ (5.19-5.20) with ($J = 2.5\text{Hz}$). The high value between C₃-H and C₄-H ($J = 2.5\text{Hz}$) is indicative of the *cis* configuration of **3d**. Also the $^1\text{H-NMR}$ spectra of **3d** showed at δ 3.16 ppm for methyl group (CH₃N-Ph) (*s*, 6H, N (CH₃)₂). \otimes (6. 63-8.02) ppm for aromatic protons.

The $^{13}\text{C-NMR}$ spectral data of the 3-phthalamido/3-phenylthio azetidines **3a, 3b, 3c and 3d**, most of their spectra are shown in Figures (1-9), (1-10), (1-11), and (1-12).

The resonance compound **3a** at δ 168.07 ppm assigned to the carbonyl carbon atom, whereas the singlet at δ (116-156) ppm were belonged to the aromatic carbons. where as the two singlet at δ 56.58 and 68.52 ppm were belonged to C-4 and C-3, respectively, where as the resonance at δ 34.55 ppm were assigned the methoxy carbon atom of anisol.

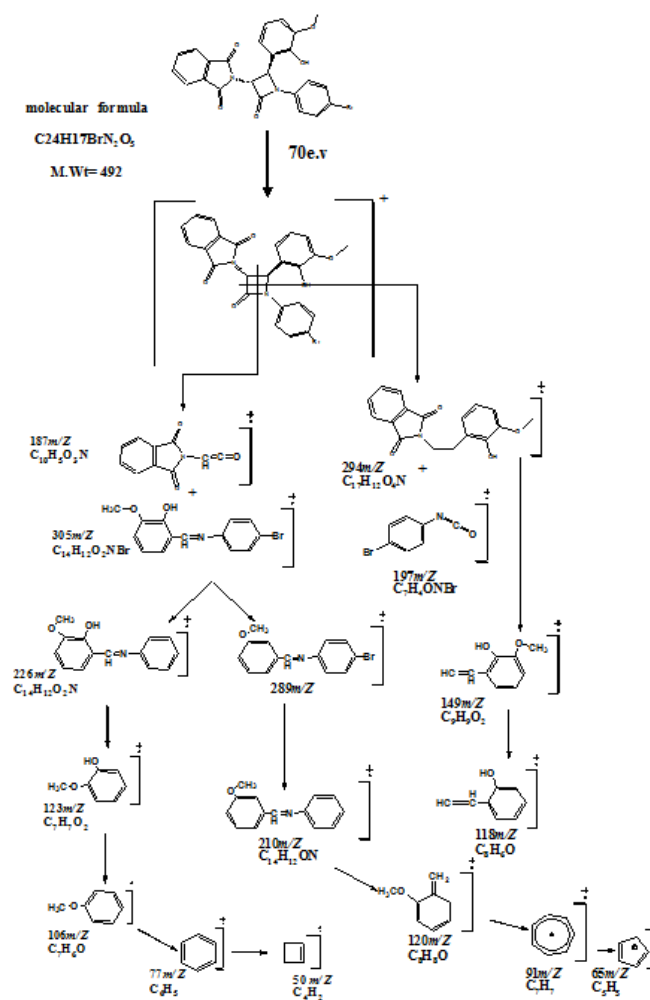
The $^{13}\text{C NMR}$ spectra of the **3b** showed two peaks where as the two singlet at δ 61.91 and 67.53 ppm were belonged to C-4 and C-3, respectively. Also the $^{13}\text{C NMR}$ spectra of **3b** showed singlet peak at δ 164.89 ppm for two carbonyl groups (equivalent carbon)

Finally the $^{13}\text{C NMR}$ spectrum of the **3b** showed carbonyl amide signal at 169.38 ppm as well as aromatic carbon at δ 120.08- 150.71, The $^{13}\text{C NMR}$ spectra of the **3c**, the tow singlet s at δ 167.9 and 164.5 ppm were assigned to the carbonyl carbon atoms (amide and phthalamide), respectively.

The resonances at δ 115.66 -124.29, ppm were attributed to the aromatic carbon atoms, where as the two singlet at δ 56.7 and 56.9 ppm were belonged to C-4 and C-3, respectively. The singlets at δ 56.2 ppm were assigned to methoxy.

The ^{13}C NMR spectra of the **3d**, the tow singlet s at δ 167.99 and 162.29 ppm were assigned to the carbonyl carbon atoms (amide and phthalimide), respectively. The resonances at δ 111.5-154.6, ppm were attributed to the aromatic carbon atoms, where as the two singlet at δ 61.9 and 62.6 ppm were belonged to C-4 and C-3, respectively. The singlets at δ 45.9ppm were assigned to carbon atoms.

The mass spectral data of the prepared derivatives are gathered in the Figures (1-13), (1-14), and (1-15), and the mass spectra of compound **3a**, **3b** and **3c** showed the molecular ion peak corresponding to the particular compound $[\text{M}^+]$, $m/z=456$, 660, 492,. The fragmentation of **3a**, **3b** and **3c** lead to ketene, isocyanates and imine. The fragmentation of **3(a-c)** leading to the ketene $m/z = 150$, 187, 187and the corresponding isocyanates $m/z = 197$, 160, 197, also the fragmentation of this compound **3a**, **3b** and **3c** showed the imine peaks $m/z = 305$, 284, 305,. The fragmentation mechanism of compounds **3c** is shown below^{11, 12}(Schemes 6).



Scheme 6

THE EXPERIMENTAL

All solvents were distilled / dried prior to use, when this seemed necessary by standard methods. All solvent extracts were dried over anhydrous sodium sulphate unless other wise specified. **FT-IR spectrophotometer** were recorded using shimadzu FT-IR affinity spectrophotometer in the Department of Chemistry, College of Science, Thi-Qar University,

Iraq, as KBr disks. Only principal absorption bands of interest are reported and expressed in cm^{-1} . ^1H NMR spectra were recorded, using gohari 810 (250 MHz) in the Department of chemistry, technology Shareef University, Tehran, Iran. The chemical shift values are expressed as δ (ppm), using TMS as reference and d_6DMSO as solvent, ^{13}C NMR spectra, using gohari 809 (70MHz). In the Department of Chemistry, technology Shareef University, Tehran, Iran. The chemical shift values are expressed as δ (ppm), using TMS as reference and d_6DMSO as solvent, **Mass spectra** were recorded at 70 eV using Agilent technologic mass selective detector 5973 wett work in the department of chemistry, Technology shareef University, Tahran, Iran.

General Procedure for the Preparation of Schiff's Bases 2(a-c).¹³

In general, the Schiff bases were prepared by heating the mixture of 0.01 mole amine with 0.01 mole aldehyde in 20 mL of ethanol in the presence of 2-5 drop glacial acetic acid was heated at 70-80 °C for 30 min. The progress of the reaction was followed by TLC, The solvent evaporated and recrystallized from a suitable solvent.

Preparation of Mono/Bis β -Lactams 3(a-d).^{14,15}

1-(4-Bromophenyl)-4-(2-Hydroxy-3-Methoxyphenyl)-3-(Phenylthio)azetidine-2-One (3a)

To a suspension of phenylthioacetic acid (0.5 gm, 0.003 mole), **2-((4-bromo phenyl imino) methyl)-6-methoxyphenol 2a** (0.9 g, 0.003 mole) and triethylamine (1.25ml, 0.9 g, 0.009 mole) in 40 mL of dry dichloromethane, was added dropwis, under nitrogen at 0°C, a solution of POCl_3 (0.4ml, 0.69 g, 0.0045 mole) in 20 mL of dry dichloromethane with stirring at 0°C. The reactants were stirred overnight at room temperature. There after, the contents were washed successively with 1N HCL (20 mL), water (2×20 mL), 5% NaHCO_3 (20 mL) and brine (20 mL). The organic layer was dried Na_2SO_4 The solvent was areported under vacuum to give a crude product which was purified on a silica gel column using 3:7 ethyl acetate/ hexane as eluent. Furnished pure β - lactam **3a**.

2, 2'-(1, 1'-(1, 4-Phenylene) Bis (2-Oxo-4-(Pyridine-2-yl) Azetidine-3, 1-Diyl)) Diisoindolin-1, 3-Dion (3b)

To a suspension of **2-(1,3-dioxoisindolin-2-yl)acetic acid** (1.23 g, 0.006 mole), N^1 , N^4 -bis (pyridine -2-ylmethylene) benzene-1, 4-diamine (**2b**) (0.858 g, 0.003 mole) and triethylamine (2.5ml, 1.8 g, 0.018 mole) in 40 mL of dry dichloromethane, was added dropwise, under nitrogen at 0°C, a solution of POCl_3 (0.8ml, 1.38 g, 0.009 mole) in 20 mL of dry methylene chloride with stirring. The reaction mixture was worked up as usual. The crude product was poured on a silica gel column using 3:7 ethyl acetate – hexane as eluent to give the pur β - lactam **3b**.

2-(1-(4-Bromophenyl)-2-(2-Hydroxy-3-Methoxyphenyl)-4-Oxoazetidin-3-yl) Isoindoline-1, 3-Dione (3c)

To a suspension of **2-(1, 3-dioxoisindolin-2-yl)acetic acid** (0.6 g, 0.003 mole), **2-((4-bromophenylimino) methyl)-6-methoxyphenol (2a)** (0.9 g, 0.003 mole) and triethylamine (1.26ml, 0.9 g, 0.009 mole) in 40 mL of dry dichloromethane was added dropwise, under nitrogen a solution of POCl_3 (0.4ml, 0.69g, 0.0045 mole) in 20 mL of dry methylene chloride with stirring. The reaction mixture was worked up as usual. The crude product was purified on a silica gel column using 3:7 ethyl acetate – hexane as eluent furnished the pure β -lactam **3c**.

2, 2'-(1, 1'-(1, 4-Phenylene) Bis (2-(4-(Dimethylamino) Phenyl)-4-Oxoazetidine-3, 1-Diyl)) Diisoindolin-1, 3-Dione (3d)

To a suspension of **2-(1, 3-dioxoisindolin-2-yl)acetic acid** (1.23 g, 0.006 mole), N^1 , N^4 -bis(4-(dimethylamino) benzylidene) benzene-1, 4-diamine (**2c**) (1.1 g, 0.003 mole) and triethylamine (2.5ml, 1.8 g, 0.018 mole) in 40 mL of dry

dichloromethane, was added dropwise, under nitrogen at 0°C, a solution of POCl₃ (0.8ml,1.38 g,0.009 mole) in 20 mL of dry methylene chloride with stirring. The reaction mixture was worked up as usual. The crude product was poured on column of silica gel using 3:7 ethyl acetate - hexane as eluent furnished the pure -β- lactam **3d**.

Evaluation of Antihyperglycemic Activity

Animals and Induction of Diabetes Mellitus

We used rats (*Rattus norvegicus*) of male weighing 120 - 180 g were used for the study of the effects of (**3d**) on the blood glucose levels of the animals. They were kept in standard cages at 25°C and 12 h light/dark condition in the animal house of the Department of Biology, college of science, university of The-Qar. They were fed on commercial rats' feeds and were given water *ad libitum*. The animals were fasted from feeds for 12 h before the commencement of each experiment, but were allowed water *ad libitum*. The rats assigned to the diabetic groups were injected with a freshly prepared alloxan monohydrate dissolved in sterile normal saline at a dose of 150 mg/kg body weight intraperitoneally. Since alloxan is capable of producing fatal hypoglycemia as a result of massive pancreatic release of insulin, the rats were treated with 20% glucose solution intraperitoneally after 6 h The rats were kept for the next 24 h on 5% glucose solution bottles in their cages to prevent hypoglycemia. After a period of two weeks the rats with a blood glucose levels greater than 150 mg/dl were considered diabetic and used for this research work¹⁶.

EXPERIMENTAL DESIGN

Animals were divided into different groups,

Group (1) received (dms) only.

Group (2) injected of alloxan monohydrate.

Group (3) received test compound (**3d**) (5mg/kg,)

Group (4) injected alloxan and test compound (3c) (5mg/kg).

The rats were treated for two weeks.

Determination of Serum Glucose Level

Used Colorimetric to Determination of Serum Glucose Level by spectro photometer mixed and let it about 10 minute at 37°, estimated absorption of sample and standard, wavelength 505 nanometer.

Procedure

Table 4

Solution	Blank	Standard	Sample
Standard	-	10 µL	-
Sample	-	-	10 µL
Working reagent	1 ml	1 ml	1 ml

CALCULATION

$$[\text{glucose}] = \frac{\text{absorption of sample}}{\text{absorption of standard}} \times \text{conc. of standard}(n)$$

$$n = 5.56 \text{ mmol/L (100mg/dl)}.$$

STATISTICAL ANALYSIS

Blood glucose levels were expressed in mg/dl as mean \pm SD and determination of LSD. The data were statistically analyzed using ANOVA. Values of $p < 0.01$ or less were taken as significant.

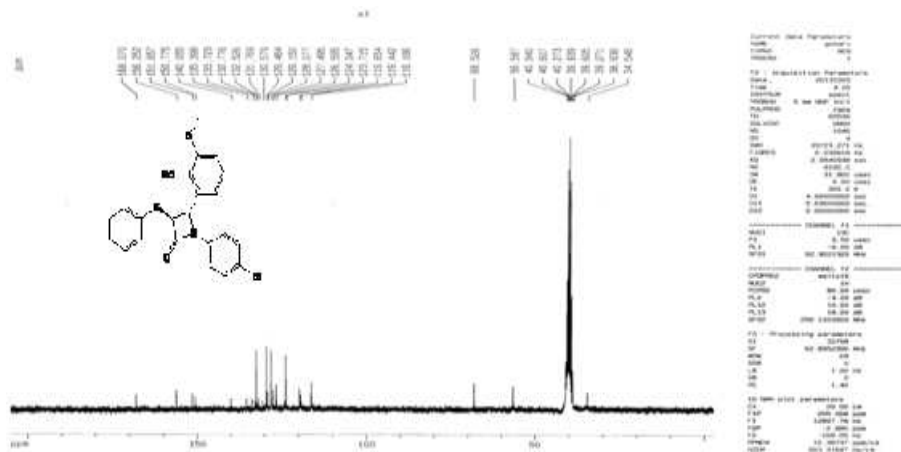


Figure (1-1): ¹³C NMR Spectra of 1-(4-Bromophenyl)-4-(2-Hydroxy-3-Methoxyphenyl)-3-(Phenylthio) Azetidine-2-One (3a)

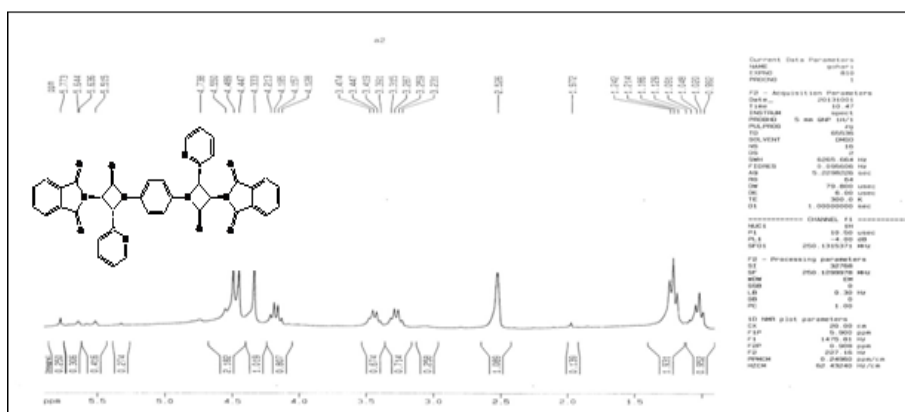


Figure (1-2): ¹H NMR Spectra 2, 2'-(1, 1'-(1, 4-Phenylene) Bis (2-Oxo-4-(Pyridine-2-yl) Azetidine-3, 1-Diyl)) Diisoindolin-1, 3-Dione (3b)

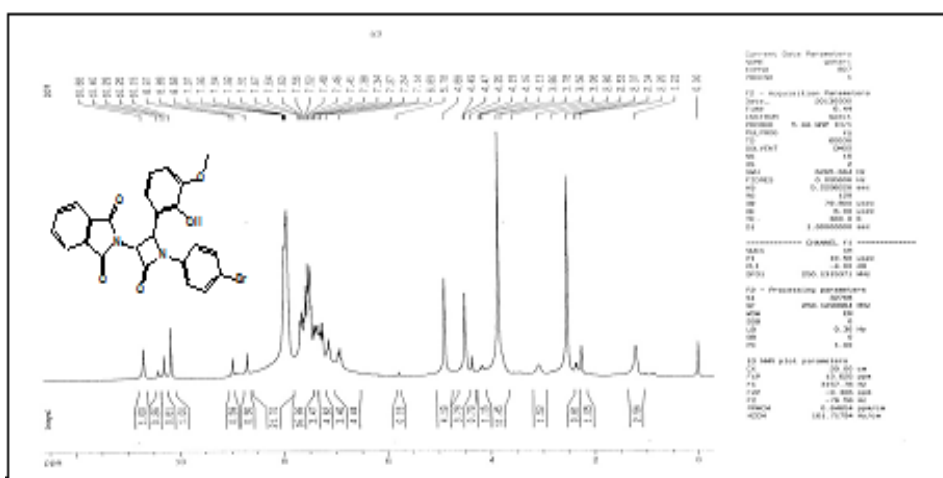


Figure (1-3): ¹H NMR Spectra of 2-(1-(4-Bromophenyl)-2-(2-Hydroxy-3-Methoxyphenyl)-4-Oxoazetidin-3-yl) Isoindoline-1, 3-Dione (3c)

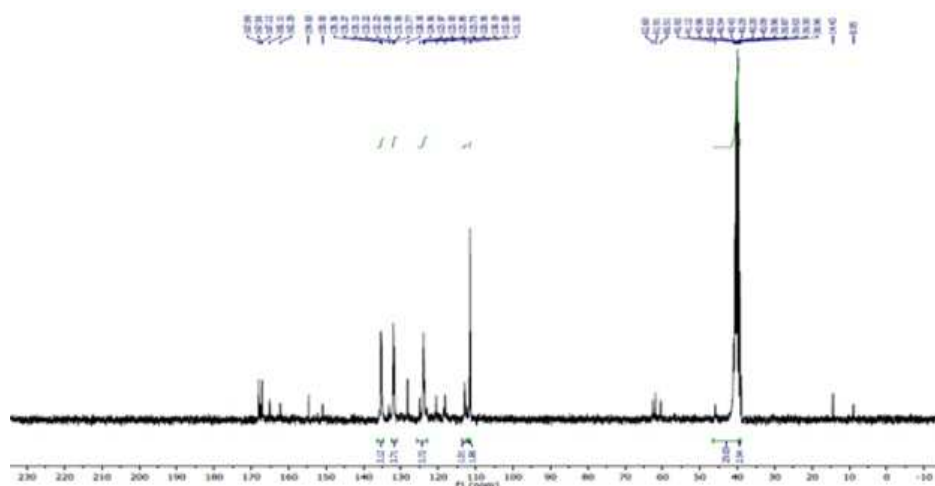


Figure (1-4): ^{13}C NMR Spectra 2, 2'-(1, 1'-(1, 4-Phenylene) Bis (2-(4-(Dimethylamino) Phenyl)-4-Oxazetidine-3, 1-Diyl)) Diisoindolin-1, 3-Dione (3d)

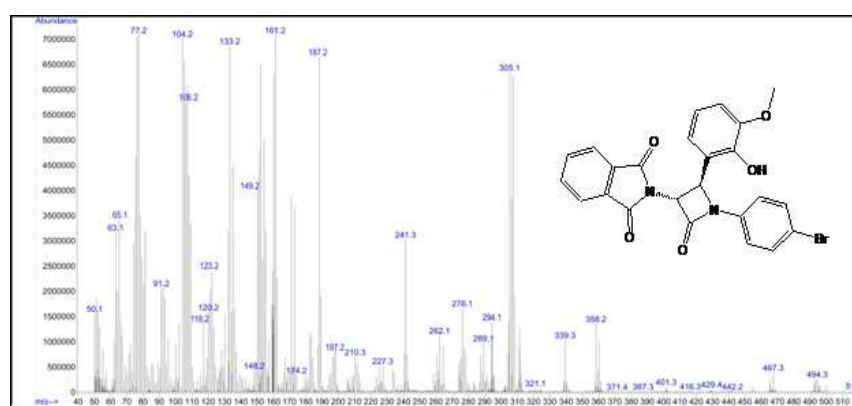


Figure (1-5): Mass Spectrum 2-(1-(4-Bromophenyl)-2-(2-Hydroxy-3-Methoxyphenyl)-4-Oxazetidin-3-yl) Isoindoline-1, 3-Dione (3c)

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APPENDICES

ودراسة فعاليتها الخافضة للسكر في الدم [2+2] تخليق وتشخيص بعض مركبات البيتا لاکتام الاحادية والثانية باستخدام تفاعلات الاضافة الحلقية

باد شلاكة فضالة, محمود شاكر مكطوف التميمي , محمد عجة عودة

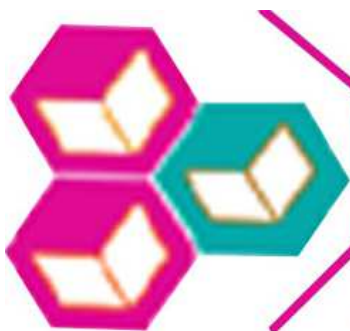
قسم الكيمياء , كلية العلوم جامعة ذي قار , العراق, الناصرية

الملخص

- فيثالايل N تم تحضيرها من تفاعل حامضي **3(a-d)** -3-فتاليميدو ازيبيدين-2- ون /تضمنت الدراسة تخليق و تشخيص بعض مركبات-3- فنيل ثايو كلايسين وحامض فنيل ثايو حامض الخليك مع بعض قواعد شيف , بوجود ثلاثي اثيل أمين وثلاثي كلورا يد اوكسي الفسفور في ثنائي كلورو ميثان الجاف عند 3-فتاليميدو ازيبيدين -2- و-/. فنيل ثايو 3 درجة 0°C حيث ينتج الكيتين والذي يتفاعل مع قواعد شيف ليعطي المركب الناتج

شخصت المركبات المحضرة بواسطة مطيافيات الأشعة فوق البنفسجية وتحت الحمراء وطيف الكتلة ومطيافية الرنين النووي المغناطيسي البروتوني حزمة امتصاص قويه في المنطقة المحصورة (1711 – 1773) سم⁻¹ تعود لمجموعة **3(a-d)** بينت اطيف الأشعة تحت الحمراء للمركبات. والكاربون 13 كاربونيل الامايد , تميز طيف الرنين النووي المغناطيسي للبروتون لمركبات ازيبيدين -2- ون بظهور اشارته أحادية عند (3.77-5.40) جزء بالمليون العائدة (169) جزء بالمليون تعود إلى حزمة أحادية عند **3(a-d)** 167 كما اظهر طيف الرنين النووي المغناطيسي الكاربون 13 للمركبات $H-C_4-H$, $H-C_3$ للبروتوني على التوالي. m/z , مطابقة للمركب عند M^+ 492,660,456 بينت قمة ذروة الايون الجزيئي **3(a-c)** الامايد . اما طيف الكتلة للمركبات (C=O)

تضمنت الدراسة ايضا الفعالية البايولوجية الخافضة للسكر في الدم , استخدمت الجرذان النرويجية (ذكور) تتراوح اوزانها من 120 الى 180 غم (وبينما حقنت المجموعة DMSO) على مستوى السكر في الدم. قسمت الحيوانات الى اربع مجاميع. جرعت المجموعة الاولى ب) (**3d**) لدراسة تأثير المركب (الثانية بالالوكسان لرفع مستوى السكر في الدم حيث يعمل الالوكسان على تعطيل خلايا بيتا في البنكرياس ويقلل افراز الانسولين. المجموعة الثالثة جرعت فقط (لمدة اسبوعين, بعد انتهاء مدة التجريب تم قياس مستوى السكر في الدم باستخدام **3d**), اما المجموعة الرابعة حقنت الالوكسان ثم جرعت بالمركب (**3d**) المركب (الطريقة الانزيمية.



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