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المجلة العراقية لبحوث السوق وحماية المستهلك

SYNTHESIS AND CHARACTERIZATION OF NEW β-LACTAM DERIVATVE FROM SULFADIAZINE DRUG BY MANY STEPS

***Radhiyah A. Aldujaili*[1], *Ezzat H. Zimam*[2]**
[1]Assistant Professor PhD., Department of Chemistry, Faculty of Educations for Girls, University of Kufa, Najaf, Iraq. radhiyah.aldujaili@uokufa.edu.iq
[2] Professor PhD., Department of Chemistry, Faculty of Sciences, University of Kufa, Najaf, Iraq. ezat_ahlam@yahoo.com

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ABSTRACT

This research involved synthesis of new β-Lactam derivative from Azo compound[4-amino-N-(pyrimidine-2-yl)-3-(pyrimidine-2-yldiazenyl) benzene sulfonamide] (S1) record previously by many steps. Starting conversion the free amino group in an azo comp. to chloro acetamide derivative(S2), then reacted it with urea to give the oxazole ring derivative (S3) that which containing free amino group. The condensation reaction between the amino group and P-bromobenzaldehyde to produce Shiff base (B14). Finally staudinger's cyclo addition reaction go run between the Shiff base derivative (B14) and chloro acetyl chloride in the presence of tri ethyl amine (Et_3N) as Base catalyst and dioxane as solvent at 5-10^oC to give β-Lactam derivative (L14). Most of these derivatives were confirmed by "FT-IR, 1HNMR and CNMR" spectra.

Keywords: Oxazole ring, Staudinger reaction, azetidinone, sulfadiazine.

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تحضير وتشخيص مشتق بيتا- لاكتام جديد من دواء السلفاديازين بعدة خطوات

رضية عبد الباقي الدجيلي[1]، عزت حسين زمام [2]
[1]استاذ مساعد دكتوره، قسم الكيمياء، كلية التربية للبنات، جامعة الكوفة، النجف، العراق. radhiyah.aldujaili@uokufa.edu.iq
[2]استاذ دكتوره، قسم الكيمياء، كلية العلوم، جامعة الكوفة، النجف، العراق. ezat_ahlam@yahoo.com

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الخلاصة

تضمن البحث تحضير مشتق البيتا-لاكتام الجديدة من مركب الازو المحضر سابقا [4-Amino-N-(Pyrimidine-2-yl)-3-(Pyrimidine-2- yldiazenyl) benzene sulfonamide]](S1) بخطوات عدة تضمنت تحويل مجموعة الامين الحرة في مركب الازو إلى مشتق الكلورو أسيت أمايد (S2)، ثم تفاعله مع اليوريا لتحضير مشتق حلقة الاوكسازول (S3) والذي يحتوي على مجموعة أمين حرة مرتبطة بحلقة الاوكسازول، ومن ثم تفاعل التكثيف بين مجموعة الامين هذه مع 4-برومو بنزلديهايد لتكوين قاعدة شف B14، ثم تفاعل ستادنكر المتضمن الاضافة الحلقية الذي تم إجراءه بين قاعدة شف B14 وكلورو اسيت أمايد في مذيب الدايوكسان وبوجود القاعدة تراي أثيل أمين كعامل مساعد وبدرجة حرارة 5-10م للحصول على مشتق البيتا-لاكتام الجديد، وتم التأكد من أغلب هذه المشتقات من خلال FT-IR و1HNMR وCNMR.

الكلمات المفتاحية : حلقة الاوكسازول، تفاعل ستادنكر، ازيتيدينون، سلفاديازين.

INTRODUCTION

Sulfadiazine is a sulfonamide antibiotic and it is recognized as one of the World Health Organization's list of essential medicines. It is the most important medications needed in a basic health system. Sulfadiazine removes bacteria that causes infections by stopping the production of folic acid into the bacterial cell, and is usually used to treat urinary tract infections (UTIs) and burns **(Radhiyah *et al.*, 2018; Who 2014)**. It has also been shown to be highly selective in the Yoshida sarcoma and new antitumor agents can be designed by combining sulfadiazine and antitumor agents in one compound **(Zhaohua *et al.*, 2001; Mostafa *et al.*, 2016)**. Sulfonamides and their derivatives which possess (-SO_2NH-) group as an important toxophoric function are among the most helpful antimicrobial factors due to their low cost, little poisoning and very large activity versus bacterial infections **(Valarmathy *et al.*, 2013; Raluca *et al.*, 2015)**. Azoles or oxazoles are doubly unsaturated five membered rings with an (O) and (N) separated by one carbon that which the parent compound for a large class of heterocyclic aromatic organic compounds. oxazole is a stable liquid at room temperature (b.p. 69ºC), and was first prepared in 1947 **(Cornforth *et al.*, 1947)**. It is also a weak base and aromatic ring with conjugate acid has a pK_a of 0.8 **(Zoltewicz *et al.*, 1978; Gilchrist 1985)**. Oxazole derivatives are among the most helpful heterocyclic compounds from both synthetic and medicinal chemistry sides where they showed various biological activities such as antibacterial, anti tuberculosis, antifungal, anti malarial and antiviral **(Peng Guo *et al.*, 2013; Wang *et al.*, 2015; Dabholkar *et al.*, 2010).**

β-lactam (also known 2-Azetidinone) are four-membered cyclic amide derived from 3-amino-propanoic acid **(Fred *et al.*, 1991; Deshmukh *et al.*, 2014)**. The parent heterocyclic ring of azetidinone is azetidine that is a four member heterocyclic ring system with (N) as hetero atom. 2-Azetidinone includes a carbonyl group on the second position which is one of the most common heterocyclic rings found in many antibiotics **(Rajasekaran *et al.*, 2010)**.

MATERIALES AND METHODES

All chemicals were of highest purity and supplied by Fluka and Merck-company. Measurements of the melting points were recorded by using electro thermal 9300, melting point engineering LTD, U.K. (T.L.C)Thin layer chromatography was performed on silica gel

and spots were visualized by Iodine vapors. FT-IR spectra, Fourier transform infrared shimadzu (8400) using potassium bromide (KBr pellets) and the values are expressed in cm^{-1}, 1H-NMR & 13C-NMR-spectra in (ppm) unit were operating in *DMSO -d6* as solvent using (Bruker-Ultra Shield 300 MHz Switzerland)- (Iran).

Synthesis of Azo Compounds (S1) [4-Amino-N-(Pyrimidine-2-yl)-3-(Pyrimidine-2-yldiazenyl) benzene sulfonamide] **(Radhiyah *et al.*, 2018)**.

This comp. Previously prepared according to what is mentioned in the literatureAromatic amine 2-amino pyrimidine (0.01 mol, 0.95 gm) was dissolved in 4mL of concentrated hydrochloric acid and 15 mL of distilled water. The mixture was cooled at (0-5ºC) in ice-water bath ,then a solution of sodium nitrite (0.01 mol, 0.69 gm) was dissolved in 10 mL of distilled water then it will be cooled at 0-5ºC. This solution was added a drop wise to the mixture with stirring at the same temperature. The diazonum salt solution was added portion wise to solution of (0.01 mol, 2.5 gm) sulfadiazine in 25mL aqueous solution of sodium hydroxide 5%. The basicity was neutralized by adding drops of HCl until the pH becomes 7 and temperature was maintained at 0-5ºC.The mixture was stirred for 30 min and was left over night. The product was precipitated and filtered, well washed with distilled water and re-crystallized from absolute ethanol .

Synthesis of N-ChloroAcetamide Derivative (S2) [2-chloro-N-(2-(pyrimidin-2-yldiazenyl)-4-(N-pyrimidin-2- ylsulfamoyl) phenyl) acetamide] **(Radhiyah *et al.*, 2018)**.

An equivalent moles (0.01 mol) of aromatic azo amine (S1) and tri ethyl amine in DMF, then 0.01 mol from chloro acetyl chloride was added drop-wise. The reaction mixture was stirred for 5 hr at room temp. The progress of the reaction was monitored by T.L.C. at the end of the reaction; the solvent was evaporated. The precipitate obtained was washed with distilled water, filtered and re-crystallized from absolute ethanol. The product has been confirmed to be formed by the sodium fusion processwhere the test was positive by forming a white precipitate when adding a solution of ($AgNO_3$).

Synthesis of 1,3-Oxazole Derivative (S3) [4-(2-amino-1,3-oxazole-4-ylamino)-N-(pyrimidin-2-yl)-3-(pyrimidin-2-yldiazenyl)benzenesulfonamide] **(Kamble *et al.*, 2012)**.

A solution contains equivalent moles (0.002 mol) from N-chloroacetamide derivative (S2) and urea was refluxed in ethanol 50 mL at 80ºC for 24 hr. The progress of the reaction was followed by T.L.C then the solvent was evaporated, the solid was collected and re-crystallized from abs. ethanol.

Synthesis of Schiff base derivative (B14) [4-(2-(4-bromobenzylideneamino) oxazol-4-ylamino)-N-(pyrimidin-2-yl)-3-(pyrimidin-2-yldiazenyl)benzenesulfonamide] **(Kamble *et al.*, 2012)**.

Equivalent moles (0.001 mol) from aromatic amine (S3) with P-Bromobenz aldehyde in 50 mL absolute ethanol and 3 drops of glacial acetic acid. This mixture was refluxed at 80ºC for 25 hr. The progress of the reaction was followed by TLC. After the completion the mixture was cooled down to room temperature then the solid was re-crystallized from absolute ethanol to form (B14).

Synthesis of 3-chloro-β- lactam derivative(L14) [4-(2-(2-(4-bromophenyl)-3-chloro-4-oxoazetidin-1-yl)oxazol-4-ylamino)-N-(pyrimidin-2-yl)-3-(pyrimidin-2-yldiazenyl) benzene sulfonamide] **(Radhiyah *et al.*, 2018)**.

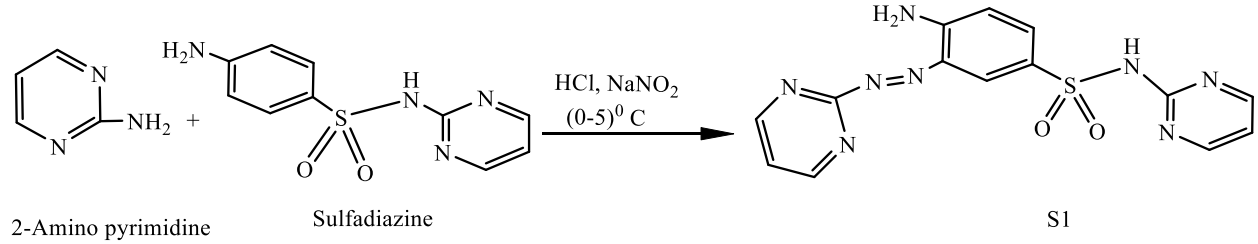
To a mixture of Schiff base (B14) (0.01 mol) in dioxane 30mL and Et_3N (3.49 mL, 0.025 mol), chloro acetyl chloride (1.99 mL, 0.025 mol) was added drop-wise at 5-10ºC. The reaction mixture was stirred for 48 hr at room temperature, then poured into crushed ice to dissolve the salt (Et_3N^+HCl) tri ethyl amine hydrochloride. The mixture was extracted by using

chloroform ($CHCl_3$), then the solvent was evaporated and the yield was re-crystallized from absolute ethanol. the reaction was monitored by (T.L.C).

RESULTS AND DICUSSION

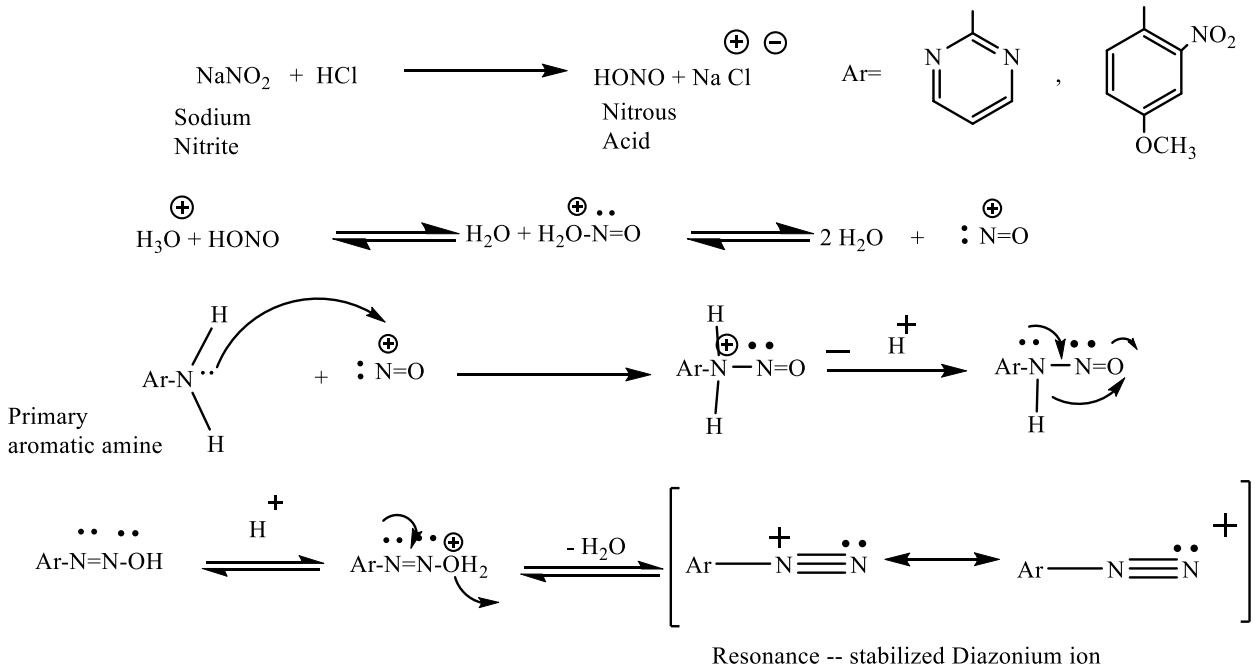
Identification of Azo compounds (S1) (Radhiyah *et al.*, 2018).

Sulfadiazine compound was the starting material for this study used as coupling compound to prepare Azo comp.(S1). 2-amino pyrimidine was converted to the corresponding "diazonium salt" by reaction with concentrated "HCl "and sodium nitrite $NaNO_2$ at 0-5ºC then directly introduced to Sulfadiazine to give azo -amine derivative (S1) (Equation 1).



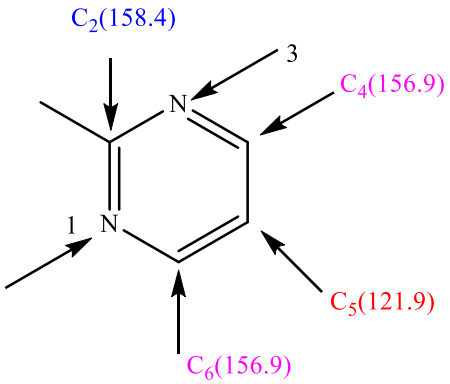
Equation (1): Preparation of Azo compound.

The mechanism of preparation An Azo comp. showed in (Scheme 1).



Scheme (1): Mechanism formation of Diazonium salt.

The azo compound was characterized by FT-IR through appearance of amine stretching band at 3427-3358 cm^{-1} and azo group (N=N) str. at 1440-1492 cm^{-1} (Figure 1). 1H-NMR spectrum (ppm)(DMSO-*d6*) (Figure 2) gives signals (s,2H,NH_2) at (6.015),(s,1H,NH) sulfonamide for the derivative(S1) at (11.294). 13C- NMR Spectrum (ppm)(DMSO-*d6*) (Figure, 3) for comp. (S1) showed the signals **(Diana *et al.*, 2007)** of (C) atoms for the pyrimidine ring in the Literature illustrated in the following structure.



Structure of pyrimidine ring

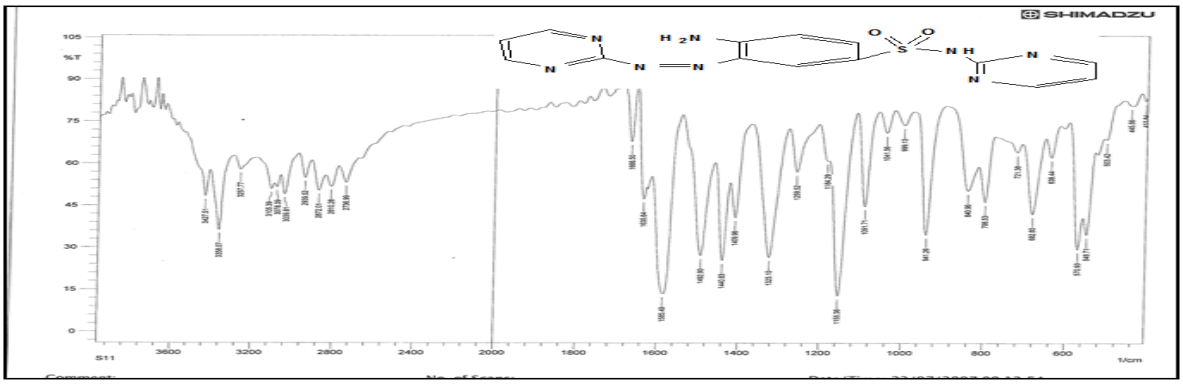


Figure (1): FT-IR spectrum of Azo comp. (S1).

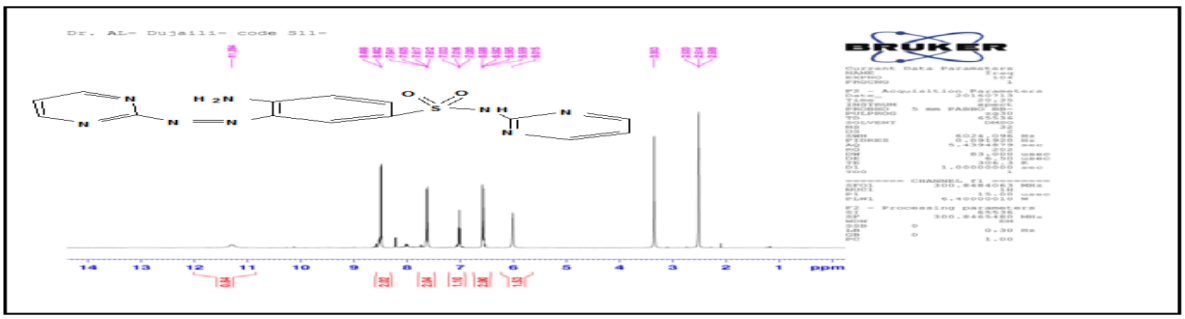


Figure (2): 1H-NMR spectrum of Azo comp. (S1).

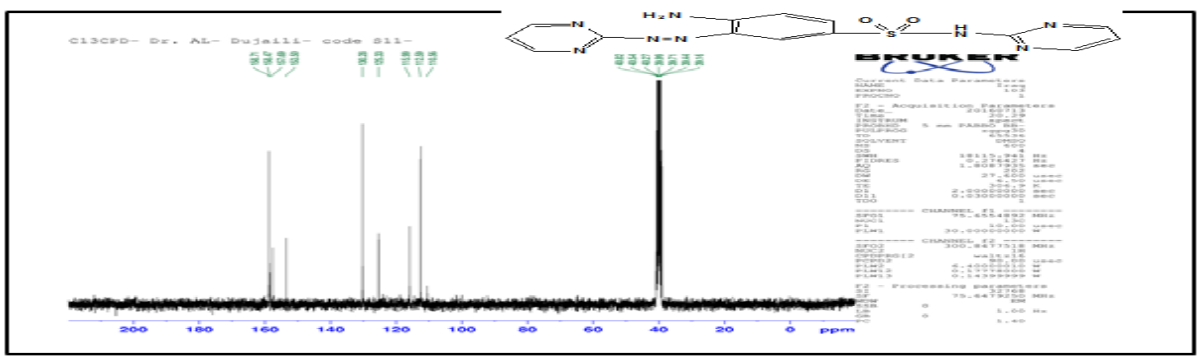
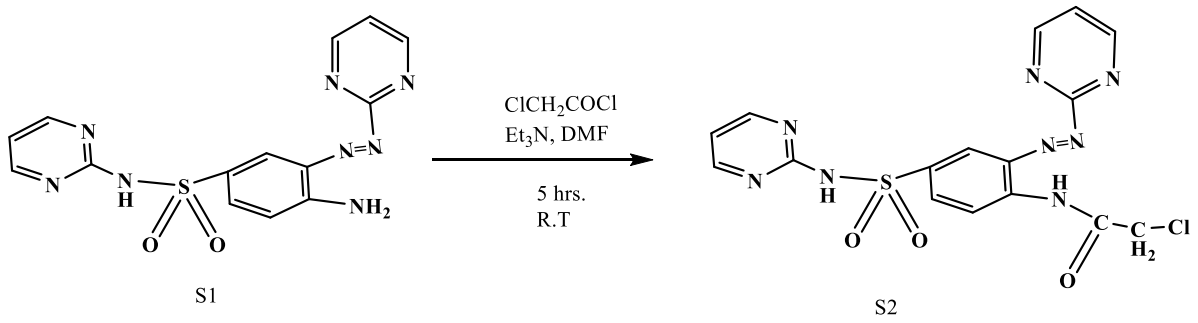
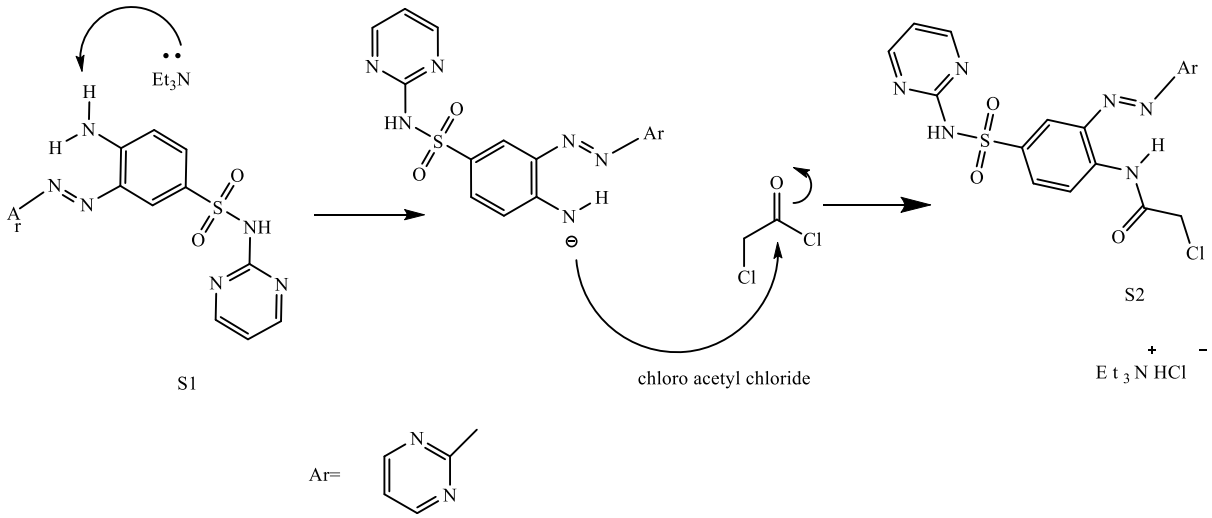


Figure (3): 13C-NMR spectrum of Azo comp. (S1).

Identification of N-ChloroAcetamide (S2): The derivative was prepared from azo amine compound (S1) with chloro acetyl chloride and Et_3N in DMF at 25ºC (Equation 2).



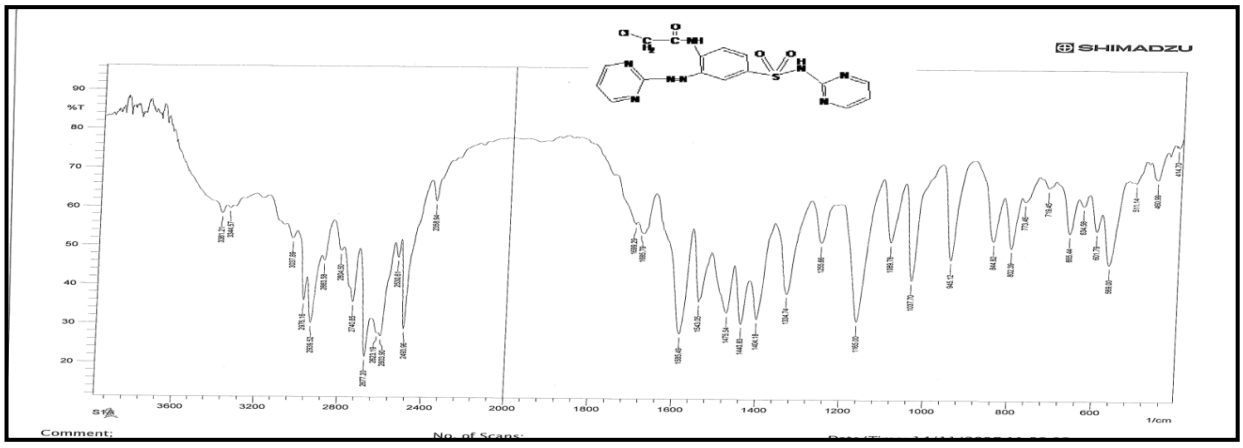
Equation (2): Preparation of chloro acetamide derivative the proposed mechanism for this reaction in the (Scheme 2).



Scheme (2): Mechanism formation of N-Chloroacetamide derivative (S2).

The newly derivative was identified by FT-IR, 1H-NMR and 13C-NMR spectra. in FT-IR spectrum (Figure 4) can confirmed by disappearance the vibration band for amine group in (S1) at 3427-3358 cm^{-1} and appearance distinguished band attributed to the carbonyl amide group (O= C- CH_2Cl) at 1699 cm^{-1} in (S2). The high value of absorption band for amide carbonyl is due to the link chloride atom which are characterized as strong electron-withdrawing group close to the carbonyl amide group as a result the increase of vibration frequency for this group. In the FT-IR spectrum also showed the stretching vibration of (NH) sulfon amide in high wave number than the vibration of (NH) amide which close to the carbonyl group at 3381 cm^{-1} at 3371 cm^{-1} in addition to the strong absorption band of (C-H) aliphatic at 2976-2939 cm^{-1}. 1H- NMR spectrum (ppm) (DMSO-*d6*) for (S2) (Figure 5) gives the signals at 4.380 attributed to (s,2H,CH_2-Cl) and the signals for (s,1H, NH sulfon and s,1H,NH amide) in the derivative at 11.256, 10.522, these signals are good evidence for formation the derivative.

^{13}C-NMR spectrum (ppm)(DMSO-*d6*) for (S2) (Figure 6) shows the signal of (C) carbonyl group in the derivative at 165.88 and the signal of (C)(CH_2Cl) at 45.



Figure(4): FT-IR spectrum of (S2).

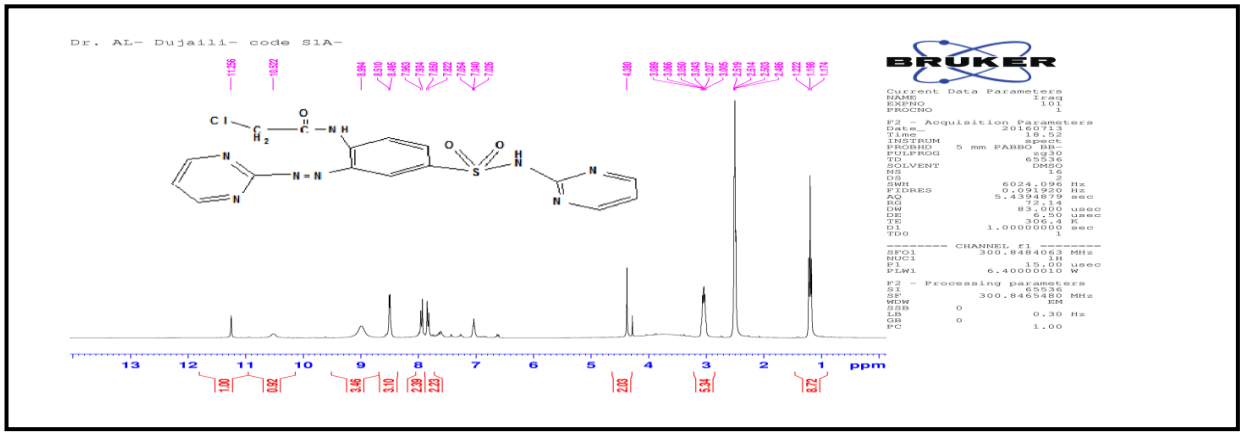


Figure (5): 1H-NMR spectrum (S2).

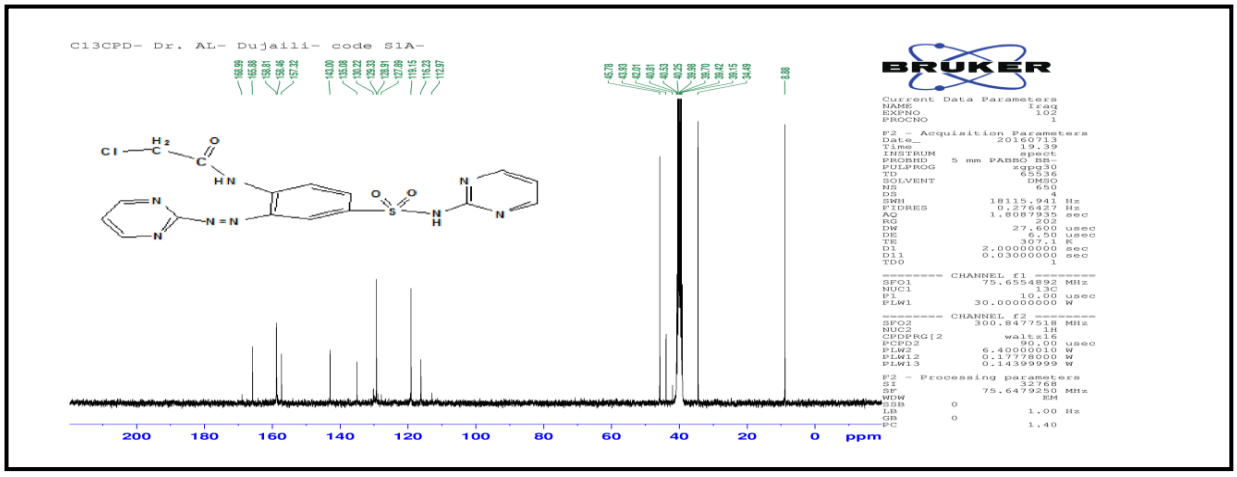
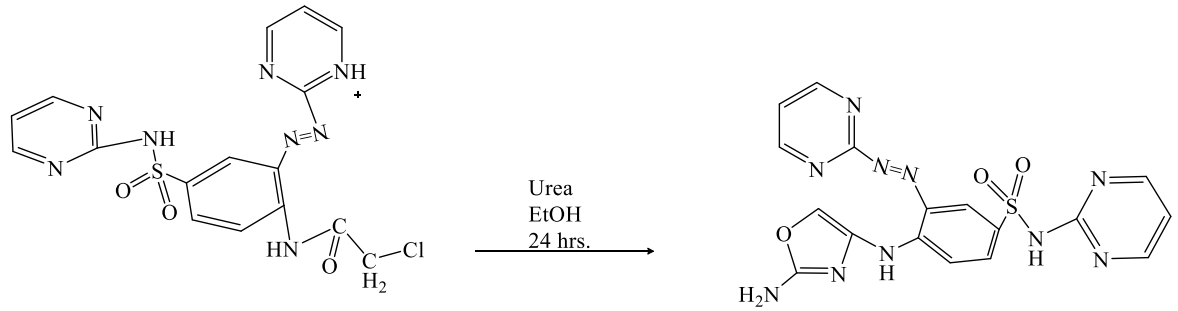


Figure (6): ^{13}C-NMR spectrum (S2).

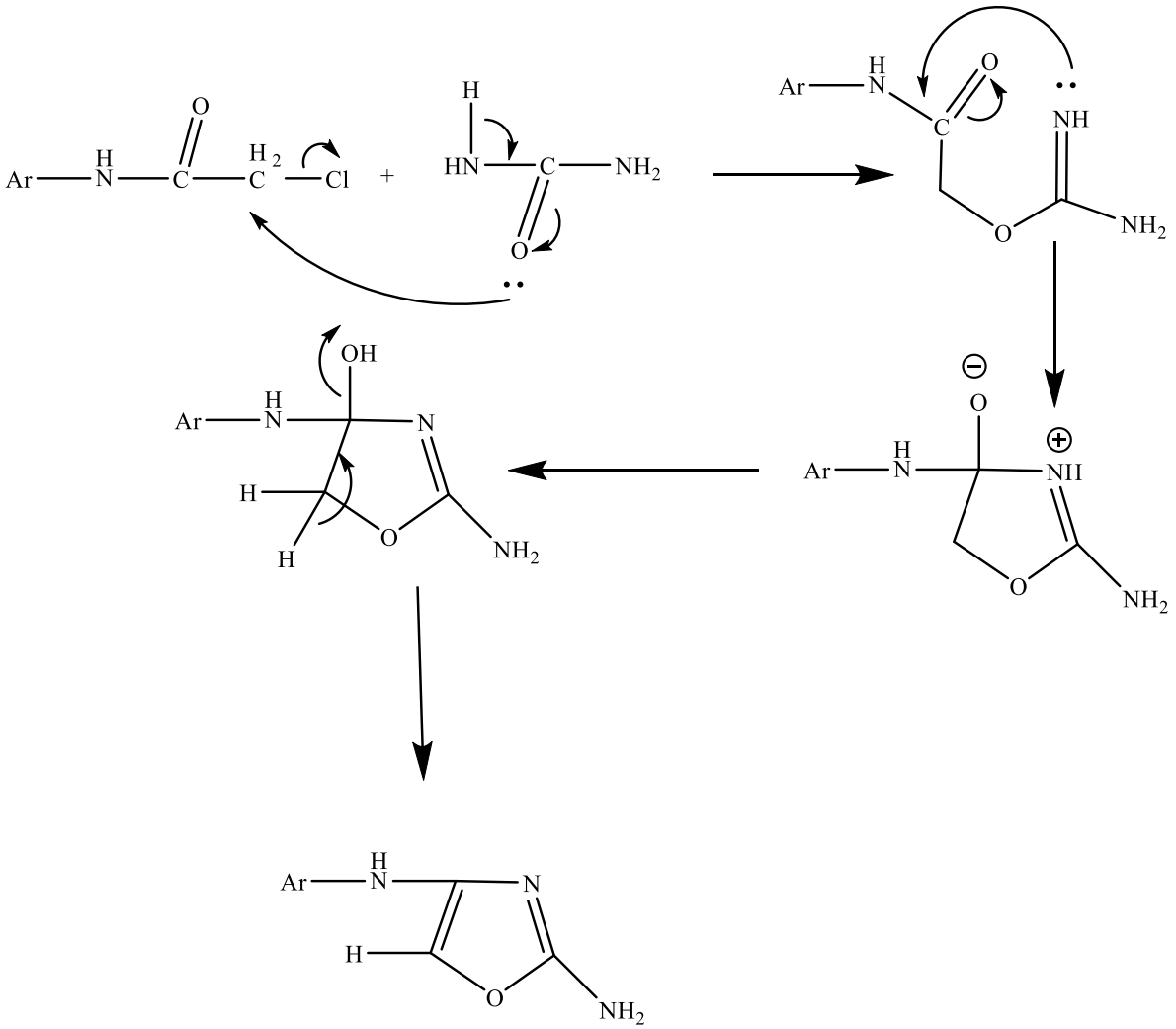
Identification of 1,3-Oxazole derivative (S3), the derivative was prepared from N-chloroacetamide derivative (S2) with Urea in absolute ethanol EtOH and the reflux at 80ºC (Equation 3).



S2 S3

Equation (3): Preparation of oxazole ring derivative.

The mechanism formation of oxazole ring **(Ammar 2009)** ring is explained in the (Scheme3).



Scheme (3): Mechanism formation of oxazole derivative (S3).

The derivative is identified by FT-IR spectrum (Figure 7) the thing is distinctive in this spectrum is disappearance the high value for vibration band of carbonyl amide group (O= C-CH_2Cl) in N-chloroacetamide derivative (S2)Which was observed at 1699 $cm^{-1}$and appearance the vibration bands for (C=N) pyrimidin and (C=N) oxazole respectively at (1668, 1625) cm^{-1}. The stretching band of aromatic amine group in (S3) appeared at 3442 cm^{-1} while the stretching band of (NH sulfonamide, NH-oxazole ring appeared at (3348, 3259) cm^{-1}.

1H-NMR spectrum (ppm)(DMSO-*d6*) (Figure 8) for the derivative (S3) gives the signal (s,2H,NH_2) at 6.84, the signals at (10.5, 11. 06) due to (s,1H , NH-oxazole ring) and (s,1H, N-H sulfonamide) respectively. other signals are (s,1H,=CH Oxazole) (7.61), (m ,Ar-H) (6.87 - 7.58) and (HC=N) pyrimidine (8.10-8. 13).

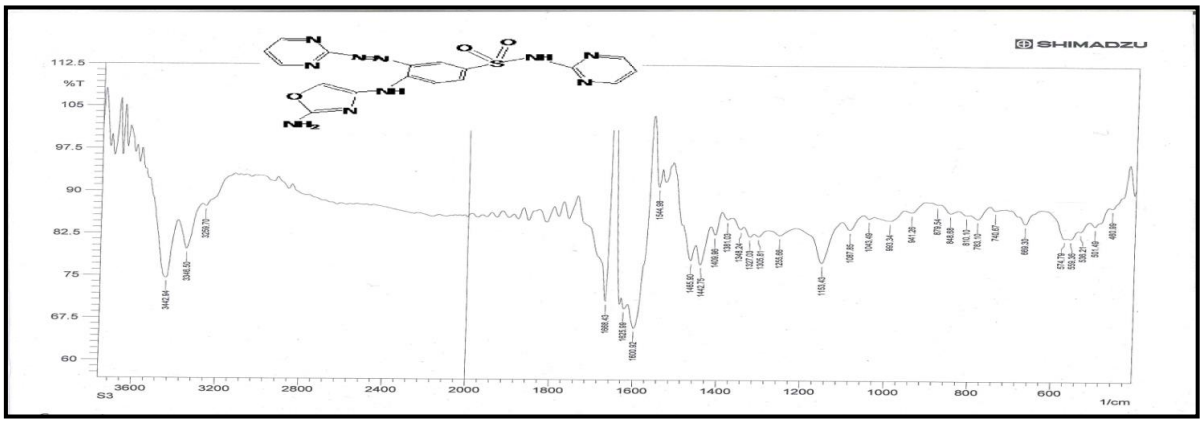


Figure (7): FT-IR spectrum (S3).

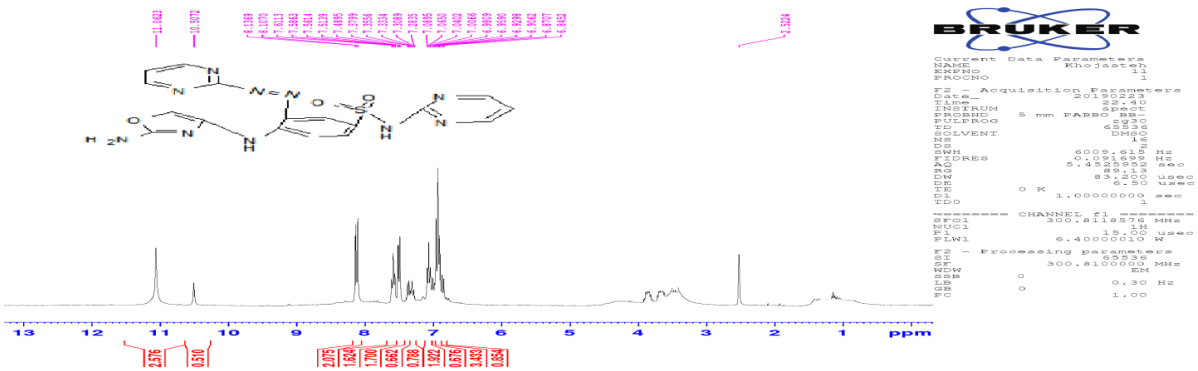
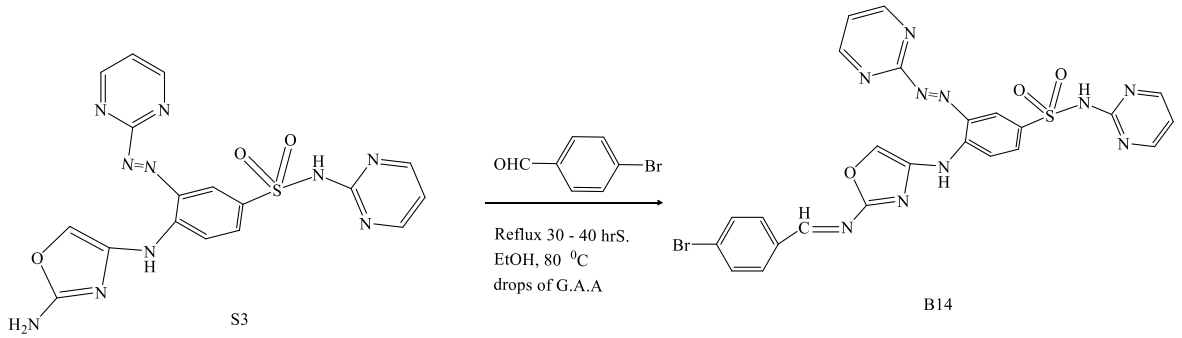


Figure (8): 1H-NMR spectrum (S3).

Identification of Schiff Base(B14), the derivative was synthesized from oxazole derivative (S3). oxazole derivative was reacted with p-Bromobenzaldehyde and drops of glacial acetic acid in absolute EtOH at 80ºC (Equation 4).



Equation (4): Preparation of Schiff base derivative.

Schiff base (B14) characterized by FT-IR spectrum (Figure 9) through disappearance the stretching vibration for the aromatic amine group and appearance the stretching vibration of imine group at 1641 cm^{-1}. The absorption bands back to (N-H) str. Sulfone and (N-H) str. associated with oxazole ring appeared at (3444, 3348) cm^{-1}. (C=N) oxazole ring observed at 1625 cm^{-1}, while the absorption band of (C=N) Pyrimidine ring at 1672 cm^{-1}.

Also characterized by 1H-NMR spectrum (ppm)(DMSO-*d6*) (Figure 10) gives (s,1H,HC=N) amine at 8.5, (s,1H,NH-oxazole) at 10.34, (s,1H, NH-sulfon amide) at 11. 83. Other signals are (s,1H, =C-H oxazole) 8.48, (m,Ar-H) (7.01-7. 92), solvent (DMSO-*d6*) at 2.5, The signal 3.37 ppm due to the solvent (DMSO-d6) and water dissolved in DMSO **(Mustafa *et al.*, 2012)**.

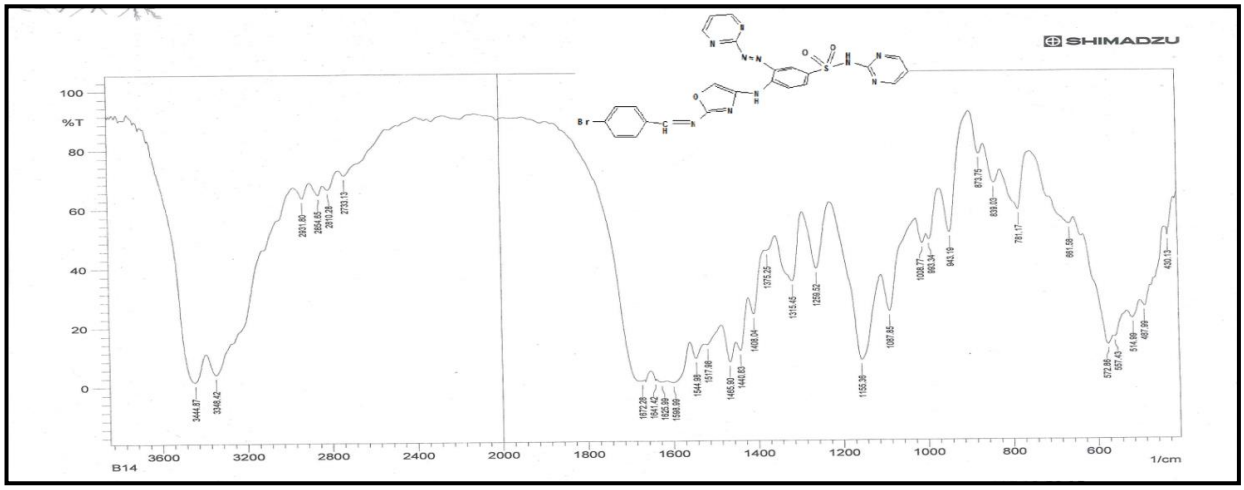


Figure (9): FT-IR spectrum (B14).

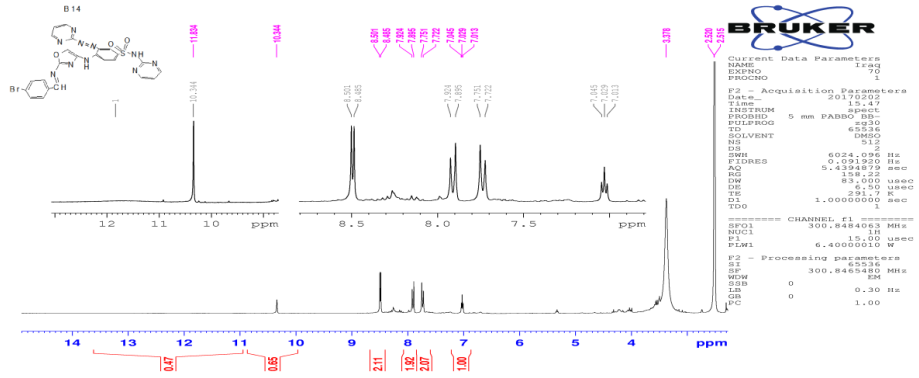
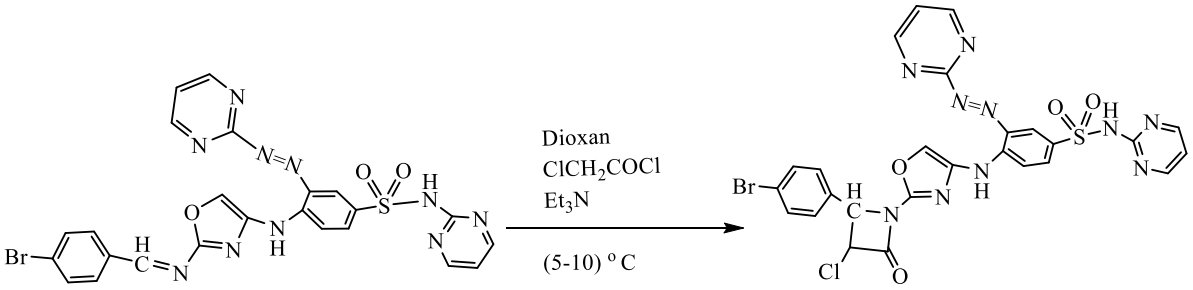


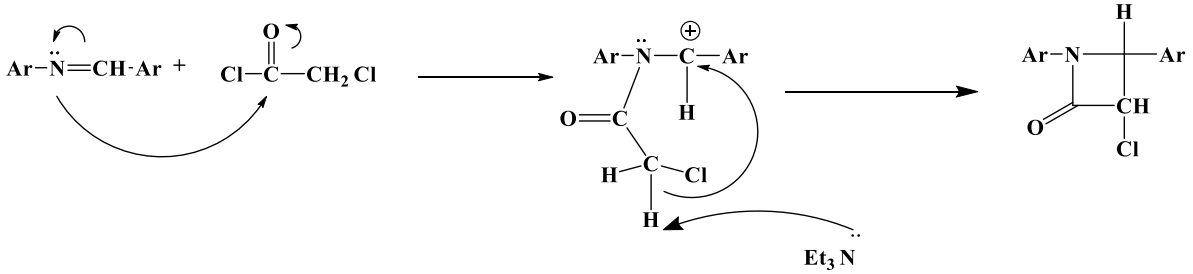
Figure (10): 1H-NMR spectrum (B14).

The β-Lactam derivative (L14) was prepared from Schiff Base (B14) by [2+2] cyclo addition with chloro acetyl chloride($ClCH_2COCl$)and Et_3N as base catalyst in 1,4-dioxane as solvent at 5-10 C with stirring to give (L14) derivative (Equation 5).



Equation (5): Preparation of β-Lactam derivative

The mechanism**(Hamza*et al*, 2014)(Entesar *et al*, 2015)** of [2+2] cyclo addition to prepare mono-β-lactam shown in the (Scheme4).



Scheme (4): Mechanism formation of mono-β-lactam ring.

The prepared derivative characterized by FT-IR spectrum (Figure 11) through disappearance the absorption band of imine group and appearance a clear band of carbonyl lactam ring at(1701) cm^{-1}. NH-oxazole and NH-Sulfonamide bands observed separated in (L14) at (3394 ,3246) cm^{-1}. (C-H)Aliphatic in Lactam ring were observedat (2972-2935) cm^{-1}.

1H-NMR spectrum (ppm) (DMSO-*d6*) (Figure 12) gives the signals (d,1H,CH-N-) at(5.429),(d,1H,-CH-Cl) at (5.501) for lactam ring, (s,1H,NH-oxazole ring) at (9.084) and (s,1H,NH-sulfon) at (11.129), (*m*,Ar-H) (7.003-7.817), (*m*, HC=N) pyrimidine (8.161-8.940) and (*s*,1H,oxazole ring) (7.944).

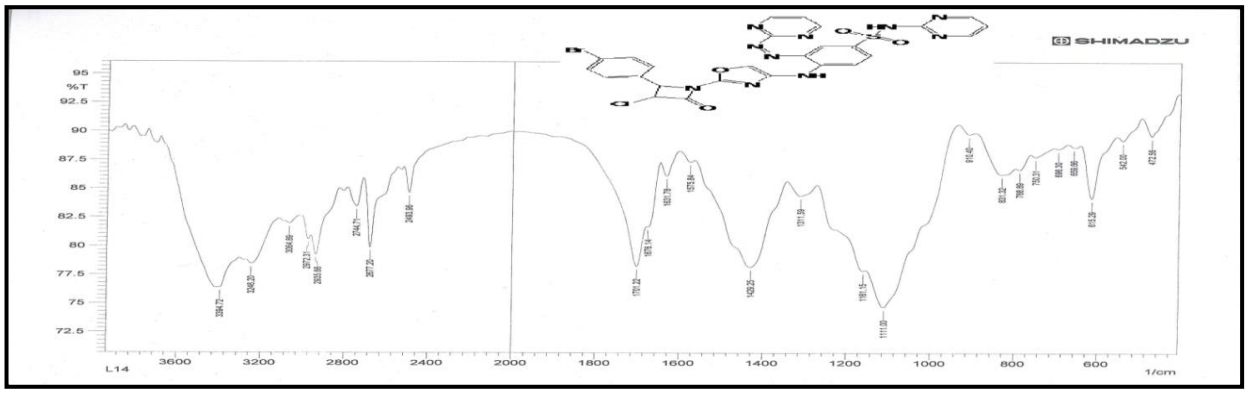


Figure (11): FT-IR spectrum (L14).

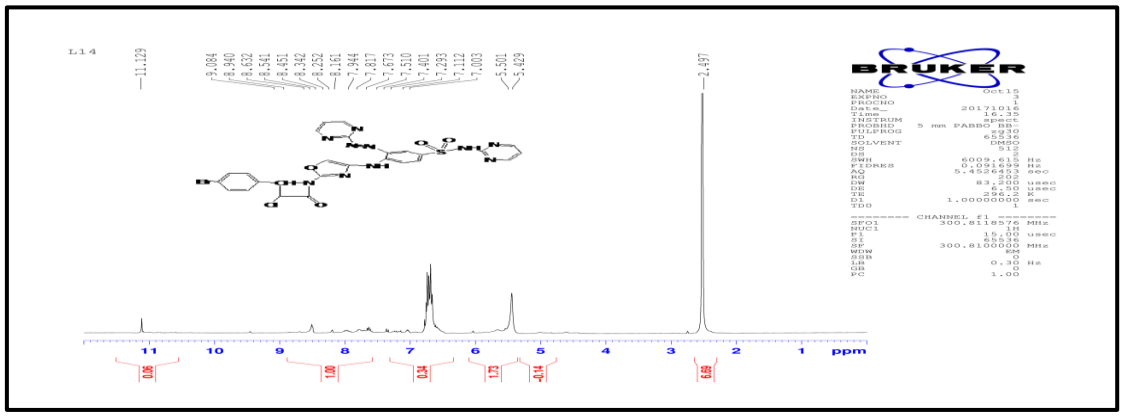


Figure (12): 1H-NMR spectrum (L14).

The physical properties For prepared derivatives are illustrated in (Table 1), the bands of FT-IR and signals of 1H-NMR ,13C-NMR For prepared derivatives are illustrated in (Table 2).

Table (1): some physical properties For prepared derivatives.

comp.	m.p. (ºC)	Yield (%)	M .Wt gm/ mol	Color	M.F	R f of T.L.C.
S1	248-249	89.5	356	Yellow	C14H12N8SO2	
S2	160-163	61	432.5	Dark orange	C16H13ClN8O3S	0.77 (Met: Tol) (1:4)
S3	120-123	54	438	Pale orange	C17H14N10O3S	0.72 (Met: Tol)(2:3)
B14	145-147	50	605	Dark golden rod	C24H17BrN10O3S	0.88 (Met: Tol)(2:3)
L14	Oily	44	681.5	Golden rod	C26H18BrClN10O4S	0.74 (Met: Tol)(2:3)

Table (2): FT-IR bands,1H&C-NMR signals for prepared derivatives.

Comp.	FT-IR bands(cm^{-1})	1H&C-NMR(ppm)
S1	(NH_2)str. (3427-3358),(N=N)(1440-1492) ,(C=C) str.Aromatic (1585), (N-H) str. Sulfone (3257),(C=N) str. Pyrimidine(1666-1635),(C-H) str. Aromatic(3039),SO2(1325).	($2H,NH_2$) (s,6.015)((Ar-H) (m,6.559-7.033), (HC=N) pyrimidine (m,7.612-8.498), (1H, N-H) Sulfone (11.294). (C)phenyl ring,110.56, 112.59 , 125.33, 130.28.(C) Pyrimidine rings, 115.99,153. 50 , 157.69 158.47, (C pyrimidine associated with NH sulfon amide)
S2	(N-H) str. sulfone amide (3381), (N-H) str. a mide (3344), (C-H) str. aromatic(3037), (C-H) str aliphatic (2976-2939), (C=O) amide str. (1699), (C=N) str. Pyrimidine (1685), (C=C) str. aromatic (1585-1543), (N=N)(1475-1440), SO2(1255), (C-Cl) 665.	($2H,CH_2$.Cl) (s 4.380) ,(Ar-H) (m,7.026 - 7.963), (HC=N) pyrimidine (m,8.495-8.994), (1H,N-H) a mide (s10. 522) , (1H,N-H) Sulfone (s 11. 256). (C) (CH_2Cl)45, (C)phenyl ring,112.97,119.15, 127.89,128.91,129.33, 130.22,135.08, (C)pyrimidine rings143.00,, 116.23,157.32, 158.46, 158.81, 168.99, (C)(C=O)165.88.
S3	(NH_2)str. (3442), (N-H) str. sulfone (3348), (N-H) str. near to oxazole ring (3259), (C=N)Pyrimidine(1668),(C=N) oxazole (1625),(C=C) aromatic(1600-1544),(N=N)(1465-1442),(SO_2) str.(1255),(C-O-C) oxazole ring(1087)	(s,2H,NH_2) (6.84), (10.5,11. 06) (s,1H , NH - Oxazole ring) and (s,1H , N-H sulfonamide), (s,1H,=CH Oxazole) (7.61),(m ,Ar-H) (6.87 - 7.58)and(HC=N) pyrimidine (8.10-8. 13).
B14	(N-H) str. sulfone (3444), (N-H) str. near to oxazole ring (3348),(C=N)Pyrimidine(1672), (C=N)imin (1641), (C=N) oxazole (1625),(C=C) aromatic(1598-1517),(N=N)(1465-1440),(SO_2) str.(1259), (C-O-C) oxazole ring(1087), (C-Br)(661) .	(s,1H,HC=N)imine (8.5), (s,1H,NH-oxazole)at (10.34),(s,1H, NH-sulfon amide) at (11. 83). (s,1H, =C-H oxazole) (8.48),(m,Ar-H) (7.01 - 7. 92)
L14	(N-H) str. sulfone (3394), (N-H) str. near to oxazole ring (3246),(C-H)aromatic (3064), (C-H) lactam ring(2972-2935),(C=O) lactam (1701), (C=N)pyrimidine(1676), (C=N) Oxazole (1631),(C=C) aromatic(1575),(N=N)(1429), (C-O-C) Oxazole ring(1111), (C-Br)(615) cm^{-1},(C-Cl)(910).	(d,1H,CH-N-) (5.429),(d,1H,-CH-Cl)at(5.501)for lactam ring, (s,1H,NH- oxazole ring)at(9.084) and(s,1H,NH-sulfon) at(11.129),(*m*, Ar-H) (7.003-7.817), (*m*, HC=N) pyrimidine (8.161-8.940)and (*s*,1H,oxazole ring) (7.944).

CONCLUSION

These derivatives of oxazole ring were found stable at room temperature. The β-lactam derivative possess strength oily. These derivatives confirmed from spectral data analysis FTIR, 1H-NMR and13C-NMR.

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