Synthesis of N-Substituted 3-Chloro-2-azetidinones for 2, 4-diamino-6-hydroxy pyrimidin

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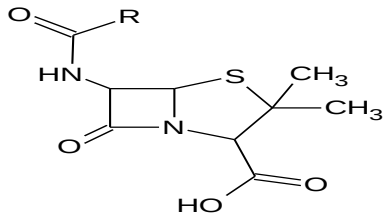
Abstract:

This search involved synthesis of several new N-Substituted -3-chloro-2-azetidinones which were known as a high medicinal effectiveness for 2, 4-Diamino-6-hydroxy pyrimidin in two steps. The first step included preparation Shiff bases (1-6) by condensation of 2, 4-Diamino-6-hydroxy pyrimidin with many substituted aldehydes(4-hydroxy benzaldehyde, 2-bromobenzaldehyde, 4-dimethyl amino benzaldehyde, 4-nitro benzaldehyde, salicylaldehyde, 4-chlorobenzaldehyde), then the second step included, preparation new six azetidinones compounds (7-12) by reaction of chloroacetylchloride with the prepared Schiff bases in the first step in the presence of triethylamine. The structures of synthesized compounds were- characterized by physical properties (FT-IR, UV and some of them by ^{1}H-NMR, ^{13}C-NMR spectroscopy) were recorded.

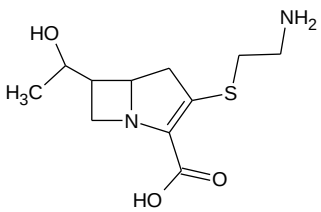
Keywords: 2,4-diamino-6-hydroxypyrimidine, Schiff bases, azetidinones, synthesis

Introduction

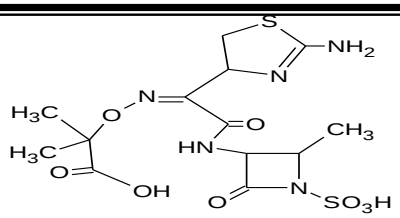
Azetidinones, commonly known as β-lactams ,were well-known heterocyclic compounds among the organic and medicinal chemists[1] are the derivatives of azetidines, four membered with carbonyl group at 2nd position [2,3] .They are still most prescribed antibiotics used in medicine, also considered as an important contribution of science to humanity[4]. The most widely used antibiotics such as the penicillins, cepholosporins, carumonam, azetreonam, thienamycine and the nocadincins all contain β-lactams ring [5].



Penicillin



Thienamycin



Azetreonam

The long term use of β-lactams antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms [6].A comparative study of current antibiotics with those from previous decodes shows an alarming increase in bacterial resistance to β-lactams antibiotics[7]. The development of several synthetic and semi-synthetic β-lactams antibiotics by the pharmaceutical industry is due to the growing resistance of bacteria towards the β-lactams antibiotics and the need for medicines with more specific antibacterial activity. An interesting group of β-lactams is the monocyclic β-lactams, which is molecules that does not contain another ring fused to the β-lactams one. [8]. A large number of 3-chloro monocyclic β-lactams possess powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant and ant tubercular activity [9]. Azetidinones which are producd by reaction Schiff bases with chloroacetylchloride, Schiff bases are characterized by the N=CH (imine) groups which are important compounds in medicinal and pharmaceutical field [10-12]. They show biological activities including antibacterial, antifungal [13], anticancer and herbicidal activities [14]. For their more Schiff bases have been widely used as protective group of amino group in organic synthesis [15] ·In this study, new compounds containing pyrimiden ring and azitidinone nucleus are synthesized from the reaction Schiff bases and chloroacetylchloride in presence triathylamine.

Material and Methods

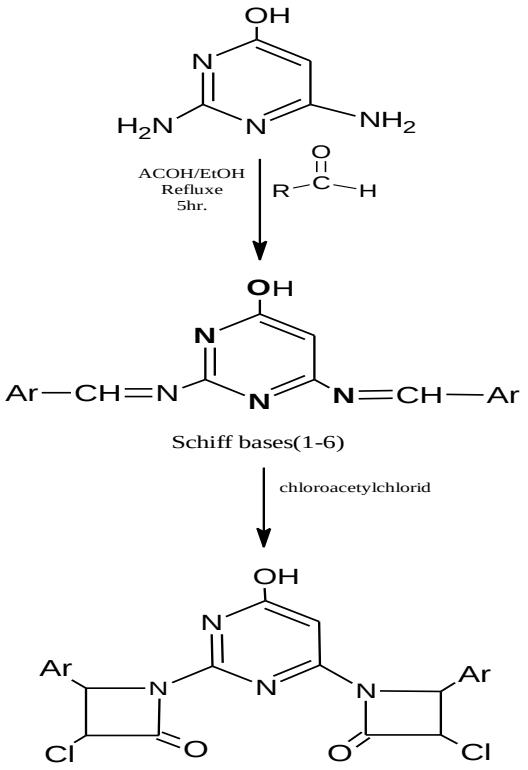
The chemicals used in this work were from BDH and Fluka used without further purification. Melting points were determined on Gallenkamp capillary melting point apparatus and were uncorrected. FT-IR spectra were recorded using KBr discs on SHIMADZU FT-IR 8400 Fourier Trans form Infrared spectrophotometer. U.V. spectra recorded using SHIMADZU UV-visible recording spectrophotometer U.V 160. ^{1}H-NMR and 13C-NMR spectra were recorded on Bruker specrospin Ultra shield 300 MHZ in strument using tetramethyl silane (TMS) as an internal standard and DMSO-d6 as a solvent in Al-Albate University in Jordan.

Preparation of Schiff base (1-6)

A series of Schiff bases (1-6) were prepared from the reaction of 2, 4-diamino-6-hydroxy pyrimidin (0.01mol) with different aldehyde (0.02mol) in 25 ml N,N' Dimethyl formamide (DMF) absolute and drops of glacial acetic acid. This mixture was refluxed for 5hrs. then poured into crushed ice. Separated solid was filtered and recrystallized from ethanol and water. Melting points, yield% data are listed in table (1).

Preparation of azetidinone from Schiff base (7-12) [9].

To a mixture of compounds (1-6) respectively (0.01 mol) in N,N' Dimethyl formamide (15ml) , triethylamine (0.025 mol), was added chloroacetylchloride (0.025 mol) drop-wise at 5-10 Cº. The reaction mixture was then stirred for 6 hrs. And left at room temperature for 24 hours then poured in to crushed ice. The solid separated was dried and recrystallized from ethanol and water. Melting points, yield% data are listed in Table (2)..



(7-12)

(Scheme 1)

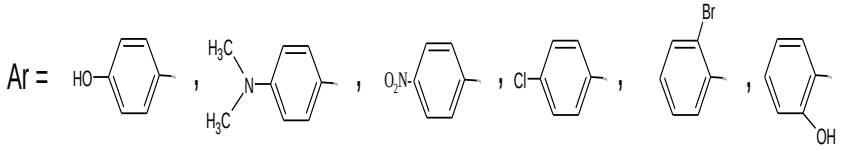
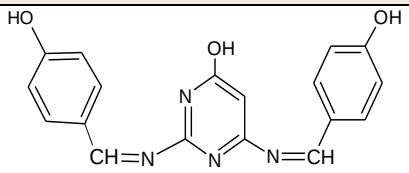
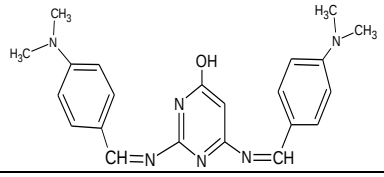
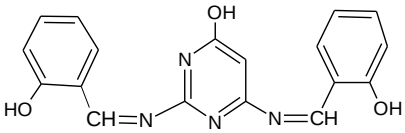
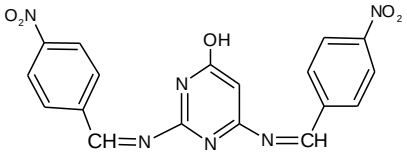
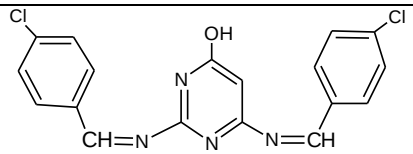
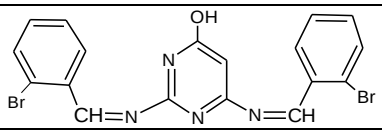
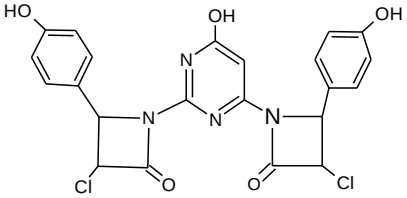
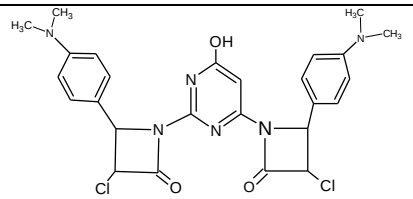


Table (1) physical properties of synthesized Schiff bases

Comp. No.	Compound structure	Melting Point C°	Color	Yield%	Molecular formula
1		140-142	Pink	70	$C_{18}H_{14}N_4O_3$
2		132-134	Orange	89	$C_{22}H_{24}N_6O$
3		> 300	Faint Yellow	85	$C_{18}H_{14}N_4O_3$
4		208-210	Dark Yellow	92	$C_{18}H_{12}N6O_5$
5		255-257	Yellow	81	$C_{18}H_{12}Cl_2\ N_4O$
6		118-120	Yellow	66	$C_{18}H_{12}\ Br_2N_4O$
7.		129-132	Yellow	61	$C_{22}H_{16}Cl_2N_4O_5$
8.		175-177	Pale brown	76	$C_{26}H_{26}Cl_2N_6O_3$

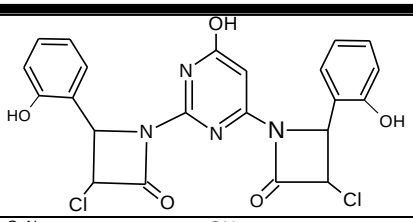
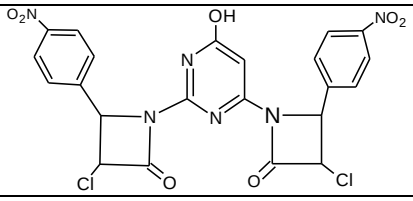
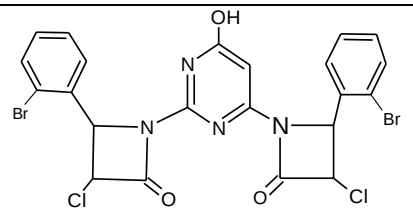
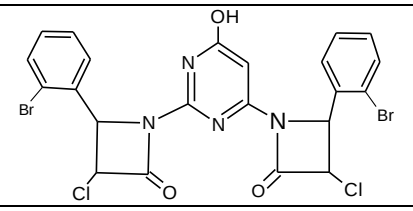
9.		138-140	Yellowish brown	70	$C_{22}H_{16}Cl_2N_4O_5$
10.		100-102	Chestnut	59	$C_{22}H_{14}Cl_2N_6O_7$
11.		123-125	Brown	68	$C_{22}H_{14}Cl_4N_4O_3$
12.		237-239	Deep brown	81	$C_{22}H_{14}Br_2Cl_2N_4O_3$

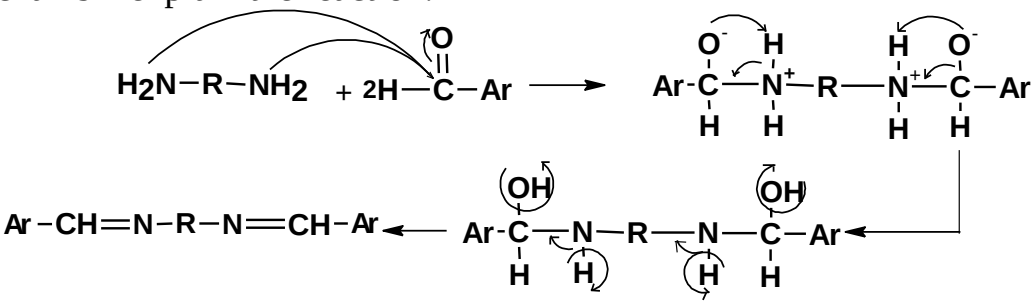
Table (3) FT-IR spectral data for some functional group for all product compounds

Comp. No	υ (C-H) aliphatic cm^{-1}	υ (C-H) aromatic cm^{-1}	υ (C=N) cm^{-1}	υ (C-OH) cm^{-1}	υ (C-N) cm^{-1}	υ (C=O) cm^{-1}	υ (C-Cl) cm^{-1}	Others cm^{-1}
1.	2900	3062-3167	1666	3325	1485	_	_	_
2.	2881-2947	3150	1627	3363	1477	_	_	_
3.	2924	3103	1695	3419	1490	_	_	_
4.	2852	3107	1707	3336	1448	_	_	υ(C-NO2) 1352 1521
5.	2868	3178	1674	3334	1489	_	879 1093	_
6.	2872	3142	1648	3358	1490	_	_	υ(C-Br) 549- 661
7.	2727-2831	3182	1651	3379	1458	1697	875 1161	_
8.	2738-2974	3030	1600	3410	1473	1647	848 1172	_

9.	2738-2939	3150	1651	3421	1473	1774	898 1126	–
10.	2738-2978	3085	1595	3352	1475	1700	850 1172	υ (C-NO2) 1365 -1580
11.	2738-2974	3194	1616	3371	1435	1654	806 1172	–
12.	2725-2929	3182	1661	3379	1415	1701	875 1159	υ(C-Br) 545- 609

Result and Discussion:

Schiff base synthesis in recent year due to their industrial and biological importance, therefore Schiff bases prepared from reaction varies aldehydes with 2, 4-Diamino-6-hydroxy pyrimidin show in scheme (1).The reaction proceeds the nucleophilic attach of the nucleophile nitrogen atom of the amine on the carbonyl group of aldehyde with the loss of water molecular to give a stable compound in good yield, the following mechanism explain the reaction:-

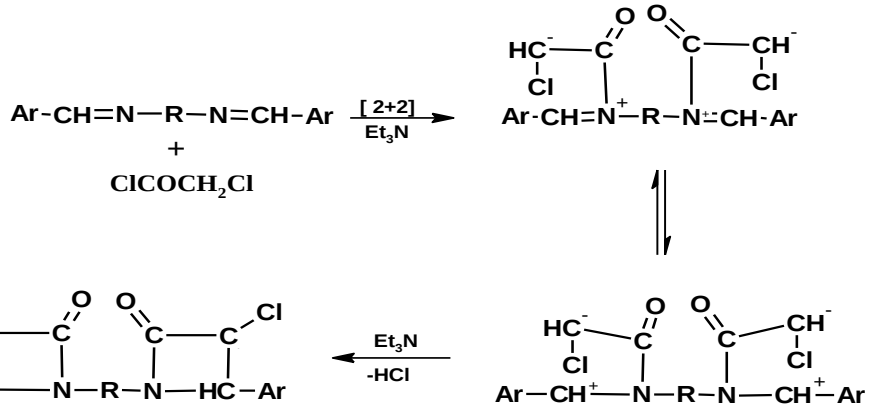


The formula structure of Schiff bases were identified using melting point that was explained in table(1), IR spectroscopy that was explained in table(3) as well as measure UV visible and ^{1}H-NMR, ^{13}C-NMR spectroscopy. In figure (5) the infrared absorption spectra indicated the formation of Schiff base(1) product by the absence of absorption band for NH_2 at (3200-3346)cm^{-1} and the appearance of assignable to the (C=N) imine group at (1666), showed also appearance of different beam for (C-H aromatic), (C-H aliphatic), (C-N), and(OH) at (3062-3167)cm-^{1} , (2900)cm^{-1}, (1485)cm^{-1} and (3325)cm^{-} respectively[16] . The U.V spectroscopy of compounds (4) and (6) were demonstrated absorption beam at (279 nm) and (279 nm) which to (π –π*) the absorption shown in fig. [1] and [3].

^{1}H-NMR spectrum data of compound (1) showed multiplied signals at (6.052-7.133) ppm due to aromatic proton , and signal at (8.19)ppm was attributed to proton in (N=CH) and signlet signal at (5.45)ppm due to (O-H) proton as shown in fig (9).In the^{13}C-NMR spectra of compounds (1)

showed signal at(114-131)ppm due to the aromatic carbons while the signal at (28.9-38.97) ppm for carbon of (C-H)group as shown in fig.(10).

Azetidinones derivatives (7-12) were prepared from reaction of corresponding Schiff bases (1-6) with chloroacetyl chloride (scheme 1) .The mechanism illustrated through (2-2) cycloaddition, proceeded smoothly in the presence of traiethylamin as catalyst. The suggested mechanism for the preparation compounds is shown below [17].



These compounds were identified by FT-IR, UV., 1H-NMR, and ^{13}C-NMR, spectroscopy. FT-IR spectrum of azetidinone derivatives showed the formation of monocyclic β-lactams product by the appearance of absorption for (C=O) group and disappearance of (C=N) of shiff bases. Compound (7) fig. (6) indicated the appearance a strong stretching band at (1697)cm^{-1} for(C=O) β-lactams ring is good evidence for the success of this step of reaction combined with absence of stretching band at(1666)cm^{-1} of (C=N), , as well as the appearance of different beam for (C-H aromatic), (C-H aliphatic), (C-N), (C-Cl) and (OH) at (3182)cm^{-1}, (2727-283)cm^{-1},(1458)cm^{-1}, (875 , 1161)cm-, and (3379)cm-^{1} respectively ,these band and other showed in table (3). The U.V spectroscopy of compounds (10) and (12) were demonstrated absorption beam at (278 nm) and (280 nm) which to ($\pi - \pi^*$) the absorption is shown in fig. [3] and [4].

^{1}H-NMR spectrum data of compound (7) showed multiplied signals at (6.543-7.879) ppm due to aromatic proton, and signal at (3.907-4.652) ppm attributed to (OH) proton as shown in fig (11).In the^{13}C-NMR spectra of the same compound showed signal at ((163.9) ppm for carbonyl group (C=O) β-lactams ring while the signal at (122-151) ppm for aromatic carbons. The signal at (69.298) ppm for carbon of (CH-Cl) as shown in fig. [12]

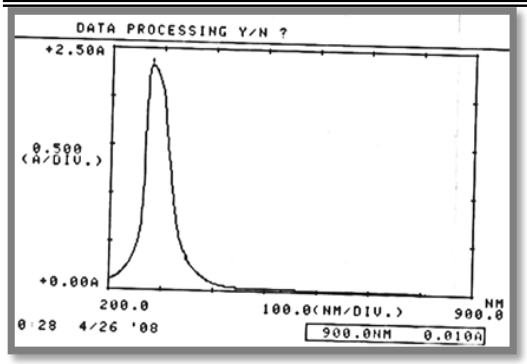


Fig (1): UV. Spectrum of compound (4)

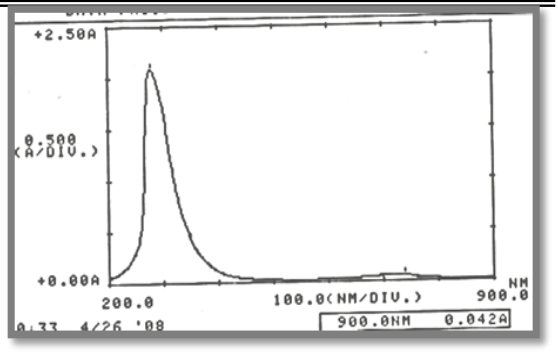


Fig (2): UV. Spectrum of compound (6)

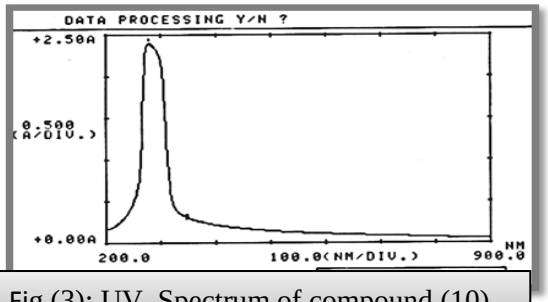


Fig (3): UV. Spectrum of compound (10)

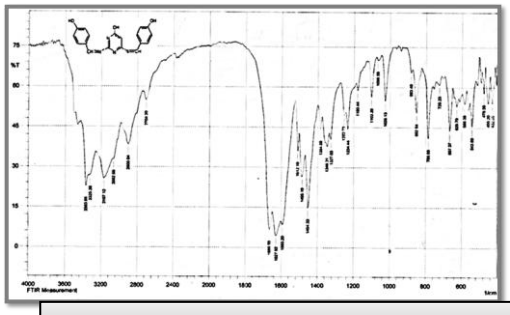


Fig (4): UV. Spectrum of compound (12)

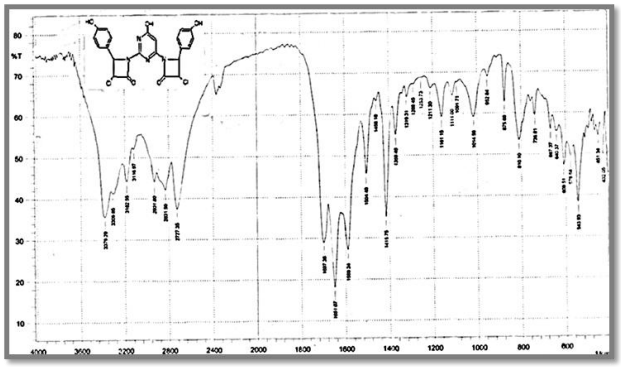


Fig (5) FT-IR spectrum for compound (1)

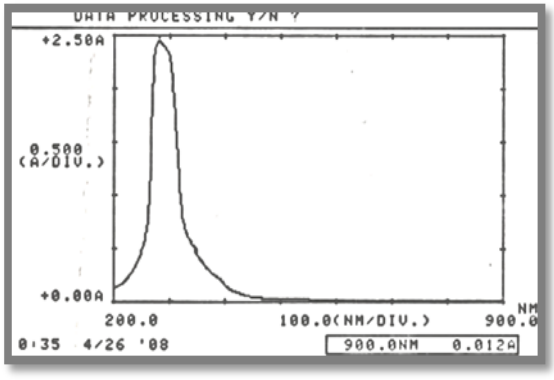


Fig (6) FT-IR spectrum for compound (7)

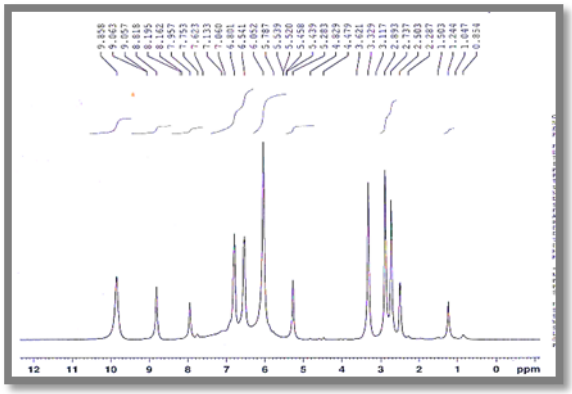


Fig (9)[1] H-NMR spectrum for compound (1)

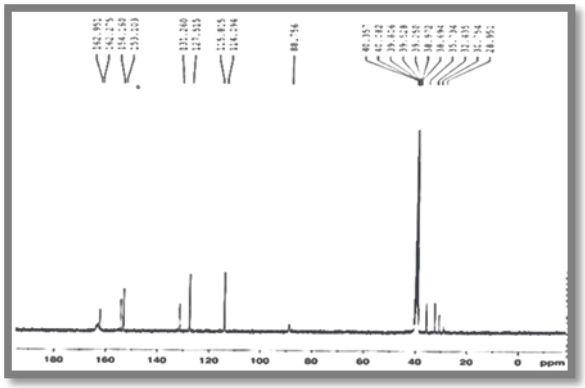


Fig (10)[13] C-NMR spectrum for compound (1)

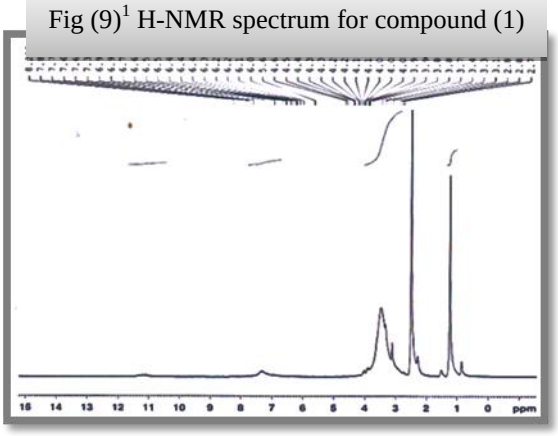


Fig (11)[1] H-NMR spectrum for compound (7)

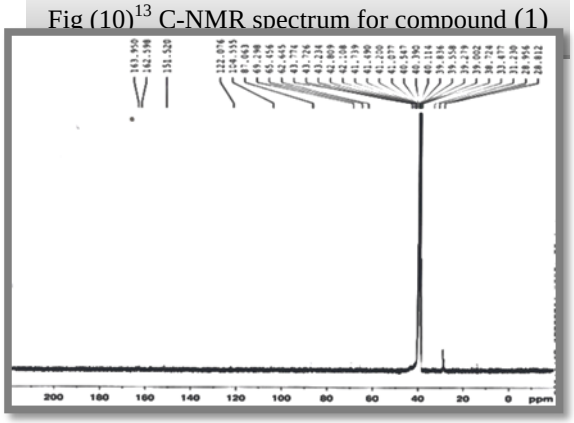


Fig (12)[13] C-NMR spectrum for compound (7)

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تحضير معوضات ٣-كلور-٢-ازتيداينون لمشتقات ٤،٢-داي امينو -٦-هيدروكسي بيرميدين

الخلاصة:

في هذه الدراسة تم تحضير مركبات جديدة تحتوي على معوضات 3-Chloro-2-azetidinonesوالتي تعرف على أنها كانت عالية الفعالية البيولوجية بأستخدام المركب الاساس 2, 4-Diamino-6-hydroxy pyrimidin بخطوتين . الخطوة الاولى تتضمن تحضير قواعد شف من خلال تكاثف 2, 4-Diamino-6-hydroxy pyrimidin مع الديهايدات متنوعة(٤-هيدروكسي بنزالديهيد, ٢-برومو بنزالديهيد, ٤-ثنائي مثيل امينو بنزالديهيد, ٤-نايترو بنزالديهيد, سلسلديهيد, ٤-كلورو بنزالديهيد) لنحصل على نواتج قواعد شف (١-٦) اما الخطوه الثانية تضمنت تحضير ستة مركبات تحتوي على azetidinones من خلال تفاعل كلورواسيتال كلوريد مع قواعد شف المحضرة سابقا بوجود ثلاثي اثل امين . لقد تم تشخيص هذه المركبات بواسطة مختلف التقنيات الفيزيائية متل:طيف الاشعة تحت الحمراء, وطيف الاشعة المرئية فوق البنفسجية وتحديد درجة الانصهار اضافة الى قياس طيف $H\text{-}^{13}C\text{-}NMR$, NMRلبعض المركبات.