Open Access
Baghdad Science Journal **Vol. 13(2s(Supplement))2016**
The 2nd National Conference of Chemistry

DOI: http://dx.doi.org/10.21123/bsj.2016.13.2.2NCC.0307

Synthesis of New Some Imidazole Derivatives Containing β-Lactam Ring

Firyal Waly Askar* ***Rana Abid Ali*****
Thanaa Mahdi Al-Mouamin**

* Department of Chemistry, College of Science, University of Al-Mustansirya
** Department of Chemistry, College of Science, University of Baghdad

Email: Thanaa_ma2007@yahoo.com

Received 14/9/2015
Accepted 20/12/2015

Abstract

In this work 5-methylene-yl - (2-methy –oxazole-4-one) (1H) imidazole (1) were synthesized from the reaction of L-Histidine with acetic anhydride and which converted to the of 5-methylene-yl-(2-methyl 3-amino imidazole-4-one)-1H-imidazole (2) by reaction with hydrazine hydrate. Schiff bases (3-6) were synthesized from the reaction of compound (2) with different aromatic aldehyde. Reaction of compounds (3-6) with chloroacetyl chloride gives azetidinone one derivatives (7-10). These compounds were characterized by FT-IR and some of them with ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Key words: L-Histidine, Schiff base, Imidzole.

Introduction:

Imidazole is an organic aromatic compound with formula $C_3H_4N_2$. Many drugs contain an imidazole ring such as antifungal drugs and nitroimidazole [1]. Nitrogen bridge head-fused heterocyclics which contain an imidazole ring are common structural motifs in pharmacologically important molecules, with activities spanning a diverse range of target [2]. The imidazole nucleus appears in a number of naturally occurring product like the amino acid histidine and purines which comprise many of the most important bases in nucleic acid [3]. The most important four-member system is undoubtedly the azetidin-2-one, also called β- lactam. β- lactam contaning compounds have a wide spectrum antibiotic which found in natural and synthetic compounds, such as penicillin, cephalosporin, carbaphenems, and monobactams [4,5]. The chemistry of carbon – nitrogen double bond plays a vital role in the progresses of chemistry science [6]. Schiff bases can be synthesized by several methods but the most common method is the original reaction of an aromatic amines and carbonyl compounds by nucleophilic reaction with dehydration to generate imine [7,8]. They have been used as

analgestic, plan grouth regulator [9, 10], antitumor, and other biological activities [11, 12]. In this work, we reported synthesis of some new imidazole derivatives containing β-lactam ring starting from amino acid histidine.

Materials and Methods

Melting point was determined in open capillary tubes on Gallenkamp melting point apparatus and wasun corrected. FT-IR spectra were recorded on SHIMADZU FT-IR -8400 Fourier Transform Infrared spectrophotometer as KBR disk. ^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker 300MHz, instrument using TMS as internal reference and DMSO-d_6 as a solvent in Jordon.

Synthesis of 5-methylene-yl - (2-methy –oxazole-4-one) (1H) imidazole (1) [3]

A mixture of amino acid (L-Histidine) (1g, 0.0064 mole) and (2 ml, 0.0021 mole) acetic anhydride was refluxed for 3 hrs. Excess of acetic anhydride was neutralized with sodium bicarbonate then with water and dried over $CaCO_3$ then evaporated. An oily Brown color was obtained. (Yield 61%).

Synthesis of 5-methylene-yl-(2-methyl 3-aminoimidazole-4-one)-1H-imidazole (2) [3]

To a solution of compound [1] (2g, 0.01 mole) in absolute ethanol (15 ml), hydrazine (15 ml. 99%) was added .The mixture was refluxed for 7 hrs. The solvent was removed and slurry product was collected from methanol. (Yield 69%).

Table (1) lists physical properties and FT-IR spectral data of compounds (1) and (2).

Synthesis of Schiff bases (3-6) [13]

A mixture of hydrazine derivatives (0.01 mole) and substituted aldehyde (0.01 mole) was dissolved in 15 ml absolute ethanol and few drops of glacial acetic acid were added. The mixture was refluxed for 3 hrs. The separated solid was filtered, and then recrystallized from suitable solvent ethanol: water (7:3).

Table (2) lists physical properties and FT-IR spectral data of Schiff bases (3-6).

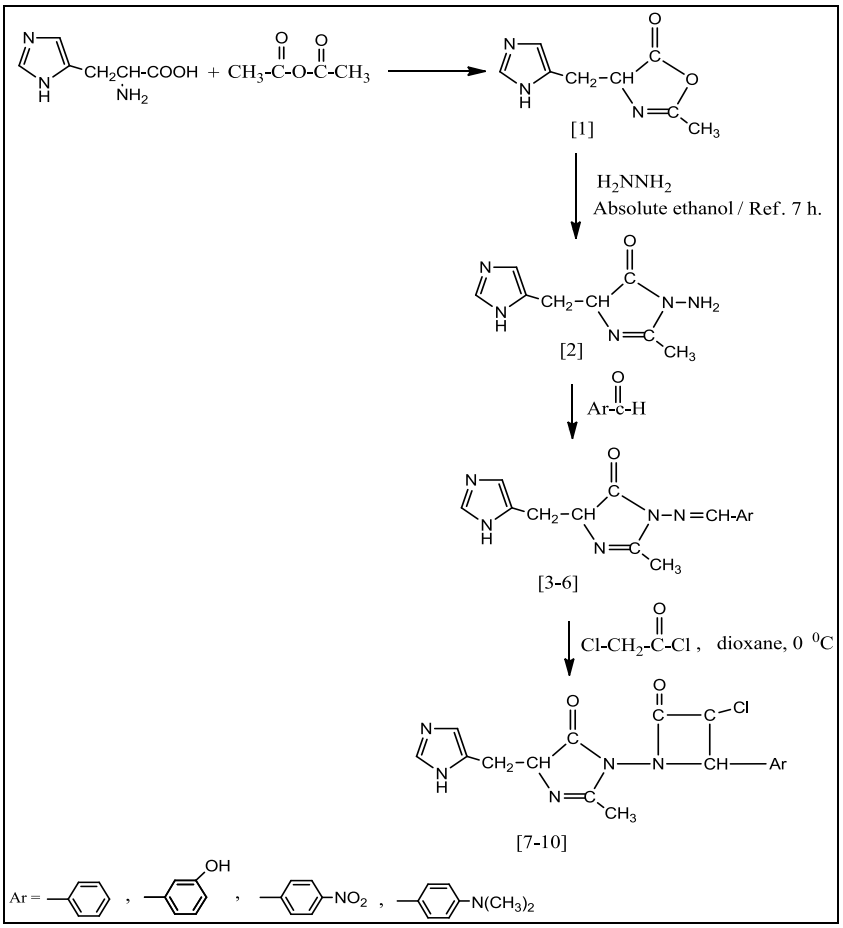
Synthesis of azetidinone(7-10) [3]

A mixture of Schiff bases (0.00055 mole) and tri ethylamines (0.0011 mole) were dissolved in 1, 4-dioxane (10 ml) cooled and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.0022 mole) was added drop wise for period 15 min at zero temperature. The reaction mixture was stirred for addition 3-6 hrs. And left at room temperature for 48 hrs.

Table (3) lists physical properties and FT-IR spectral data of compounds (7-10).

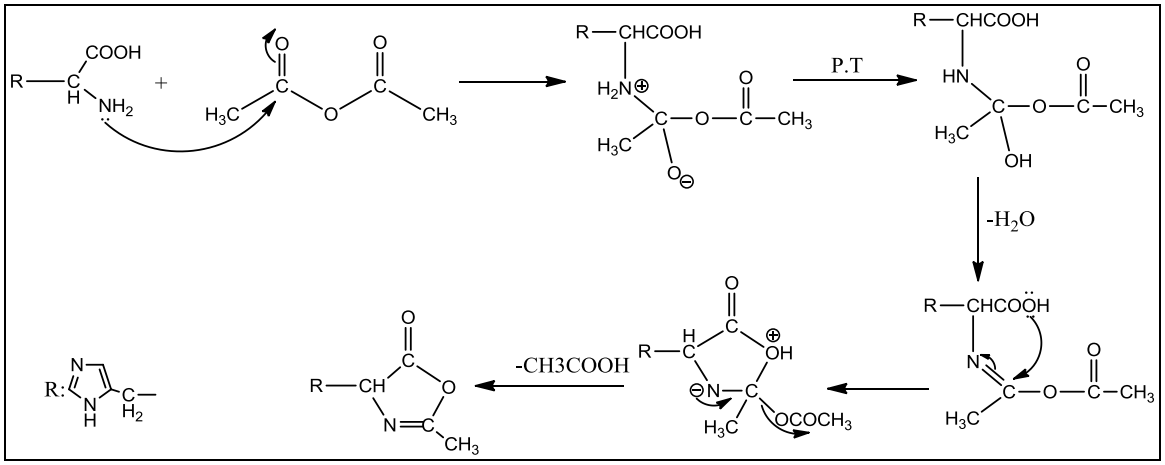
Results and Discussion

To obtain our target, the β-lactam cycle containing two imidazole ring, the amino acid L-histidine was chosen as starting material. The multistep synthetic route to these compounds are given in scheme (1).



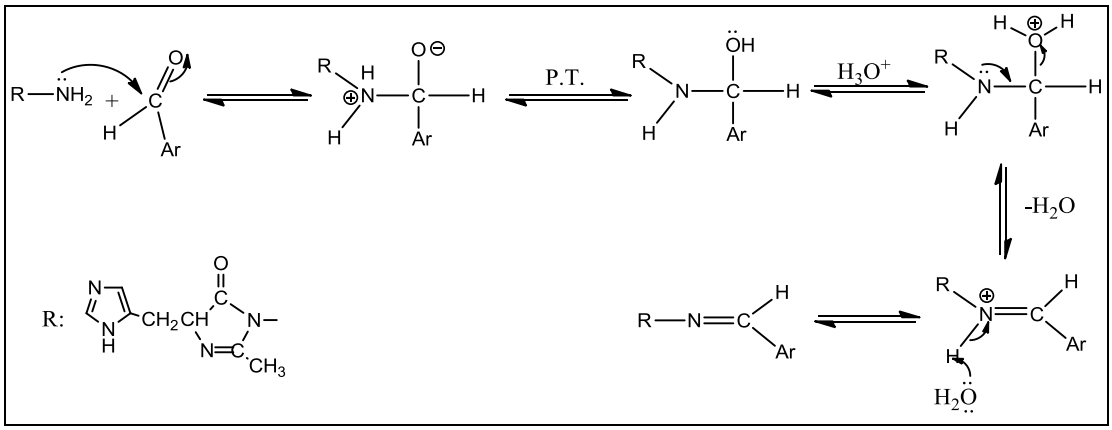
Scheme (1): Synthetic route for synthesis imidazole derivatives

The first step includes synthesis of compound (1) from the cyclization reaction between L-histidine and acetic anhydride. The mechanism of this reaction was started with nucleophilic attack of amino group on carbonyl carbon according the following mechanism, as shown in scheme (2):



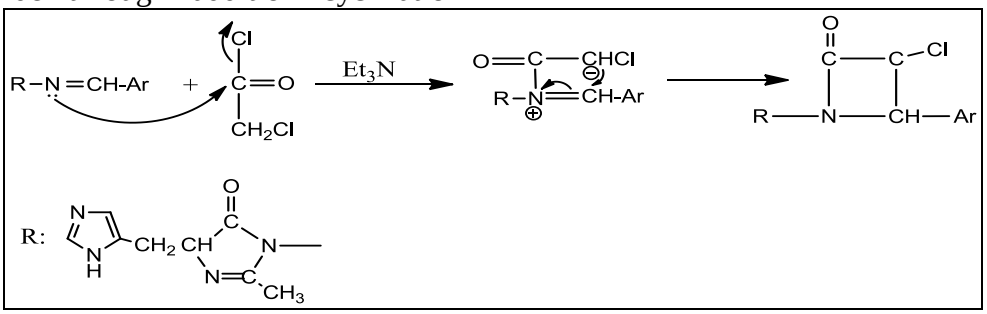
Scheme (2): Mechanism for synthesis of compound (1)

The second step includes synthesis of compound (2) the nucleophilic attack of hydrazine hydrate with compound (1), then compound (2) was introduced in reaction with substituted aromatic aldehyde in the third step to form Schiff's bases (3-6). The mechanism of Schiff base was started by nucleophilic attack on carbonyl by the lone-pair electron of amine gives a dipolar tetrahedral intermediate. Then a proton transferred from nitrogen to oxygen yielding a carbinolamine, which after protonation and dehydration gives an iminium ion. Losing hydride ion from nitrogen leading to form an imine as shown in scheme (3):



Scheme (3): Mechanism for synthesis Schiff base

The fourth step includes synthesis of compounds (7-10) from the reaction of compounds (3-6) with chloroacetyl chloride through addition cyclization reaction, yielding β-lactam ring according to the short mechanism in scheme (4).



Scheme (4): Mechanism for β- lactam formation

The percentage yield of the prepared Schiff's bases were in the range of {21-54} percent it was noticeable presence of electron with drawing substituent in aromatic ring caused increasing of yield percent of the prepared compounds. The percentage yield of the prepared compounds (7-10) was in the range of {23-96} percent.

These compounds were identified by FT-IR and some of them with ^{1}H-NMRand^{13}C-NMR spectroscopy.

FT-IR spectra of compound (1) and (2) shows clear absorption bands at (3441-3400)cm^{-1}, (1720-1690) cm^{-1}, (1647-1620) $cm^{-1}$and (1373-1385) cm^{-1} due to υ(N-H),υ , υ (C=O) , υ (C=C) aromatic and υ (C-N) respectively. While FT-IR spectra of Schiff's bases (3-6) shows clear absorption bands at (1633-1728) cm^{-1}, (1342-1344) cm^{-1} and (1568-1614) cm^{-1} due to υ (C=O), υ(C-N) and υ (C=N) respectively.

Figure (2) shows FT-IR spectrum of compound (5).

Compounds (4) Figure (1) and (6) shows in addition to the above absorptions a stretching band at (1317 - 1402) cm^{-1} and at (3126) cm^{-1} due to υ (NO_2) andυ (OH) respectively.

FT-IR spectra of compounds (7-10) showed clear absorption bands at (3427-3481) cm^{-1}, (1636-1647) cm^{-1},(1336-1398) cm^{-1}, (1608-1581) $cm^{-1}$and (628-817) cm^{-1} due to υ(N-H), υ(C=O), υ(C=N), υ(C-N) and υ(C-Cl) respectively[14,15]. Table (3) shows physical properties and FT-IR spectral data of compounds (3-6).

^{1}H-NMR spectraof compound(3) showed singlet signals at (1.2) ppm and (6.5) ppm due to (–$^{3}CH_3$) and (-^{4}CH-) group respectively , triplet signals at (3-3.5) ppm due to (-^{2}CH-) , doublet signals at (2-2.2) ppm due to (-$^{1}CH_2$-) , multiplet signals at (7-8.81) ppm due to aromatic protons , singlet signal at (4) ppm due to OH and singlet signal at (11.2) ppm due to aromatic amine(tautomerism) .

^{1}H-NMR spectra of compound (8) showed singlet signals at (0.9) and (1) ppm due to –($^{3}CH_3$) and (-^{5}CH-) group respectively , triplet signals at (2.7-2.8) ppm due to (-^{2}CH-) , doublet signals at (3.2) ppm due to (-$^{1}CH_2$-) , singlet signal at 4ppm due to (^{4}CH-Cl) and multiplet signals at (7-8.5) ppm due to aromatic protons and NH group.

^{1}H-NMR spectra of compound (9) showed singlet signals at (1.1) , (1.2) and (1.3) ppm due to (–$^{3}CH_3$) , (-^{6,7} CH_3) and (-^{5}CH-) group respectively, triplet signals at (2-3) ppm due to (-^{2}CH-) , doublet signals at (3-3.2) ppm due to (-$^{1}CH_2$-) , singlet signal at (4)ppm due to ^{4}CH-Cl and multiplet signals at (7-8.6) ppm due to aromatic protons and NH group. Finally, ^{1}H-NMR spectra of compound (10) Figure (3) shows singlet signals at 0.9 and 1.6 ppm due to –$^{3}CH_3$ and -^{5}CH- group respectively , triplet signals at(2.2-3) ppm due to (-^{2}CH-) , doublet signals at (3.1-3.9) ppm due to(-$^{1}CH_2$-), singlet signal at (4)ppm due to (^{4}CH-Cl),multiplet signals at (6.5-8.5)ppm due to aromatic protons and NH group and singlet signal at (10.1) ppm due to aromatic (O-H)[14,15].Table (4) shows ^{1}H-NMR spectral data for some of the prepared compounds.

^{13}C-NMR spectra of compound (3) Figure (4)shows signal at (20.1) ppm due to (–$^{3}CH_3$), signal at (45.3) ppm due to (-^{2}CH-),signal at (26.4) ppm due to (-$^{1}CH_2$-),signal at (52) ppm due C=N oxazoline(116.2) ppm due to (^{4}CH-) , tosignals at (126-145) ppm due to aromatic carbons , signal at (161.3) ppm due to C=N imine and signal at (171.8) ppm due to C=O imide.

^{13}-CNMRspectra of compound (8) showed signal at(8) ppm due to (–$^{3}CH_3$), signal at (26) ppm due to (-^{2}CH-) , signal at (40) ppm due to C-Cl, signal at (45) ppm due to (-$^{1}CH_2$-), signals at (51) ppm due to (-^{5}CH-), signals at (120-140) ppm due to aromatic carbons and signals at (169) ppm due to C=O imide.

^{13}-CNMR spectra of compound (9) showed signal at(8) ppm due to (–$^{3}CH_3$),($^{6}CH_3$) and ($^{7}CH_3$), signal at (25) ppm due to ((-^{2}CH-), signal at (40) ppm due to C-Cl, signal at (51) ppm due to (-$^{1}CH_2$-), signals at (40.3) ppm due to (-^{5}CH-), signals at (128-134) ppm due to aromatic carbons and signals at (169) ppm due to C=O imide.

Finally, ^{13}-CNMR spectra of compound (10) showed signal at (8) ppm due to (–$^{3}CH_3$), signal at (38)ppm due to (-^{2}CH-), signal at (40) ppm due to C-Cl, signal at (45) ppm due to (-$^{1}CH_2$-), signals at (41) ppm due to (-^{5}CH-), signals at (117-131)ppm due to aromatic carbons and signals at (170) ppm due to C=O imide[14,15] .

Table (5) shows ^{13}C-NMR spectral data for some of the prepared compounds.

Table (1):Physical properties and FTIR spectral data of compounds (1) and (2)

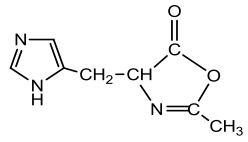
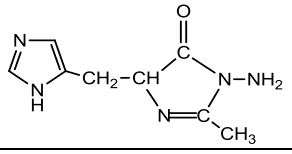
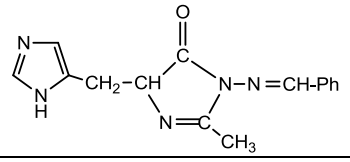
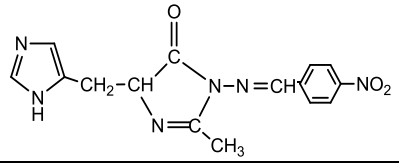
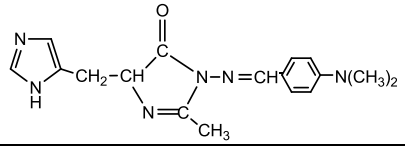
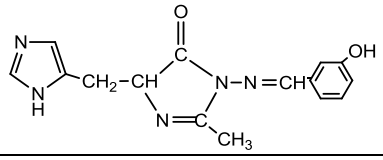
Compd. No.	Compd.structure	M.P ^{0}C	Yield %	color	Major FTIR absorption				
					C=O	N-H	C=C	N-H_2	C-N
1		syrup	61	Brown	1720	3441	1647	-----	1373
2		syrup	69	Off white	1690	3400	1620	3384 3363	1385

Table (2): Physical properties and FTIR spectral data of compounds (3-6)

Comp. No.	Compd.structure	M.P ^{0}C	Yield %	Color	Major FTIR absorption				
					C=O	C-N	C=N Aromatic	N-H	Other
3		198-200	21	White	1633	1342	1568	3433	-----
4		208-210	54	Yellow	1633	1344	1569	3481	C-NO_2 1317 1402
5		210-212	21	Deep Yellow	1728	1344	1614	3450	----
6		248-250	22	Gray	1631	1353	1539	3481	O-H 3126

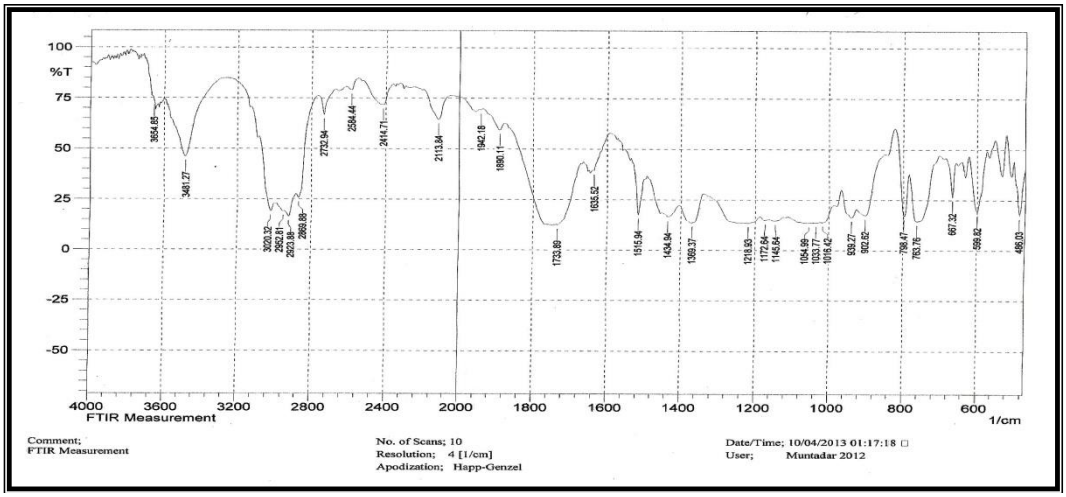


Fig. (1): FTIR spectrum of compound (4)

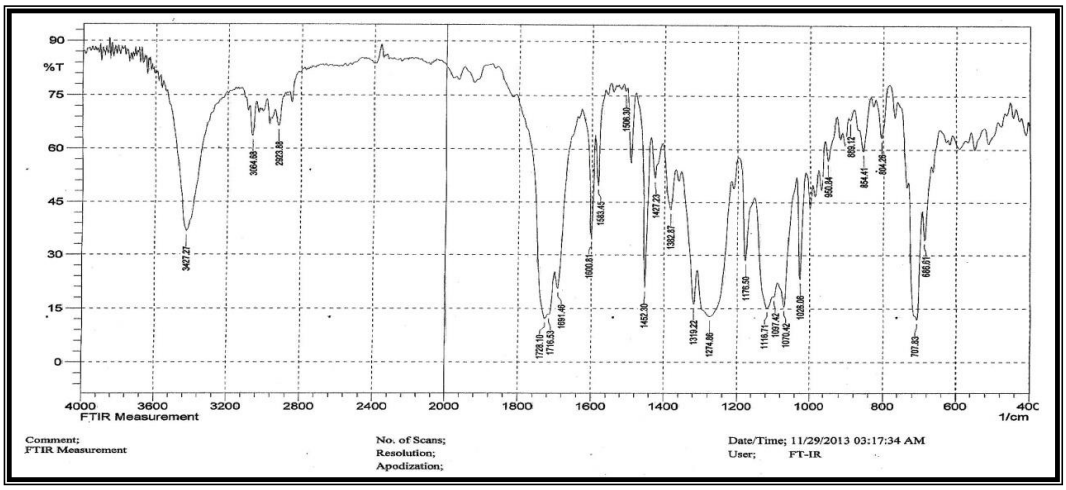


Fig. (2): FTIR spectrum of compound (5)

Table (3): Physical properties and FTIR spectral data of compounds (7-10)

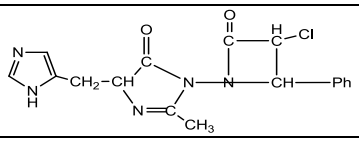
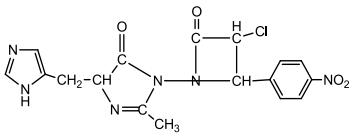
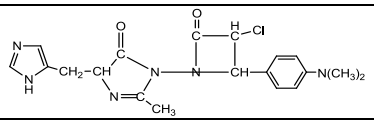
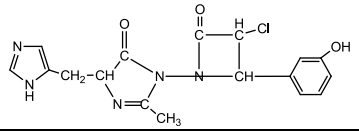
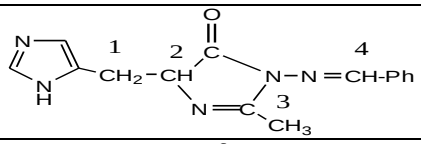
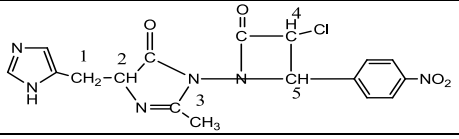
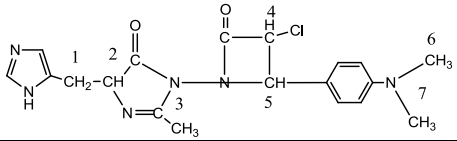
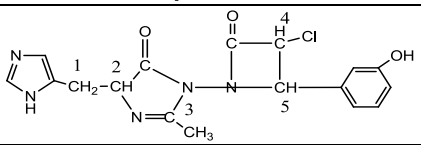
Comp. No.	Compd. structure	M.P ^{0}C	Yield %	color	Major FTIR absorption				
					C=O	C-N	C=N	N-H	C-Cl
7		168-170	40	White	1639	1336	1581	3427	696
8		180-182	23	Yellow	1636	1398	1608	3438	628
9		192-194	96	Red	1647	1371	1527	3429	817
10		160=162	60	White	1639	1336	1579	3481	696

Table (4): ^{1}HNMR spectral data of compounds (3 and 8-10)

Comp. No.	Compound structure	^{1}HNMR spectral data
3		δ= 1.2 ppm –^{3}CH$_3$, δ = 6.5ppm -^{4}CH- , δ= (3-3.15) ppm -^{2}CH- , δ= (2-2.2) ppm -^{1}CH$_2$- and δ= (7-8.81) ppm aromatic protons, 4ppm OH and 11.2 ppm aromatic amine.
8		δ = 0.9 1 ppm–^{3}CH$_3$, δ= 1 ppm -^{5}CH- , δ= (2.7-2.8) ppm -^{2}CH- , δ =(3.2) ppm -^{1}CH$_2$- , δ= 4ppm ^{4}CH-Cl and δ= (7-8.5) ppm aromatic protons and NH group.
9		δ= 1.1 , 1.2 and 1.3 ppm –^{3}CH$_3$, -^{6,7} CH$_3$ and -^{5}CH- , δ= (2-3) ppm -^{2}CH- , δ= (3-3.2) ppm -^{1}CH$_2$- , δ= 4ppm ^{4}CH-Cl and δ (7-8.6) ppm aromatic protons and NH group
10		δ = 0.9 and 1.6 ppm –^{3}CH$_3$ and -^{5}CH- group respectively , δ =(2.2-3) ppm -^{2}CH- , δ= (3.1-3.9) ppm -^{1}CH$_2$- , δ= 4ppm ^{4}CH-Cl , δ =(6.5-8.5) ppm aromatic protons and NH group and δ= 10.1 ppm aromatic OH

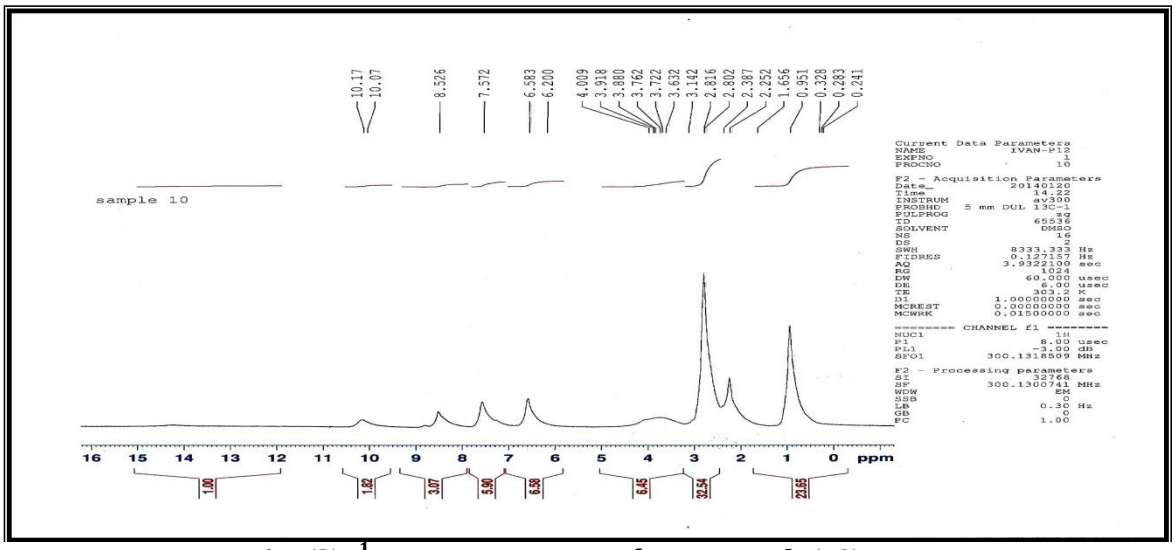
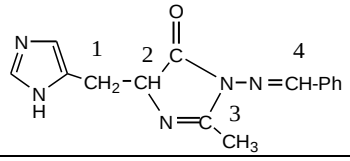
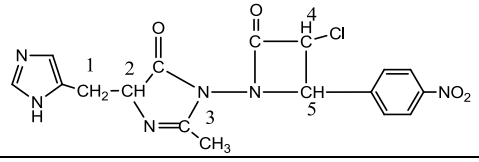
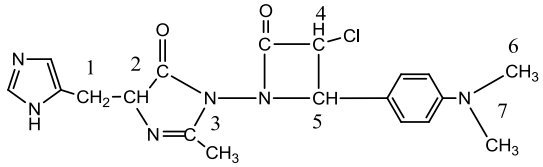
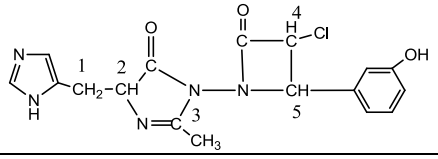


Fig. (3): ^{1}HNMR spectrum of compound (10)

Table (5): ^{13}C-NMR spectral data of compounds (3 and 8-10)

Comp. No.	Compound structure	^{13}C-NMR spectral data
3		δ= 20.1 ppm $-^{3}CH_3$, δ= 45.3 ppm $-^{2}CH-$, δ =26.4 ppm $-^{1}CH_2-$, 52 ppm C=N oxazoline, 116.2 ppm^{4} CH- δ= 126-145 ppm aromatic carbons, 161.3ppm C=N imine and δ =171.8 ppm C=O imide.
8		δ= 8 ppm $-^{3}CH_3$, δ= 26 ppm $-^{2}CH-$, δ= 40 ppm C-Cl, δ= 45 ppm $-^{1}CH_2-$, δ= 51 ppm $-^{5}CH-$, δ= 120-140 ppm aromatic carbons and δ= 169 ppm C=O imide
9		δ = 8 ppm $-^{3}CH_3$, $^{6}CH_3$ and $^{7}CH_3$, δ= 25 ppm $-^{2}CH-$, δ= 40 ppm C-Cl, 51 ppm due to $-^{1}CH_2-$, δ = 40.3 ppm $-^{5}CH-$, δ= 128-134 ppm aromatic carbons and δ= 169 ppm C=O imide
10		δ =8 ppm $-^{3}CH_3$, δ= 38 ppm d $-^{2}CH-$, δ= 40 ppm C-Cl, δ= 45 ppm $-^{1}CH_2-$, δ= 41 ppm $-^{5}CH-$, δ= 117-131 ppm aromatic carbons and δ= 170 ppm due to C=O imide.

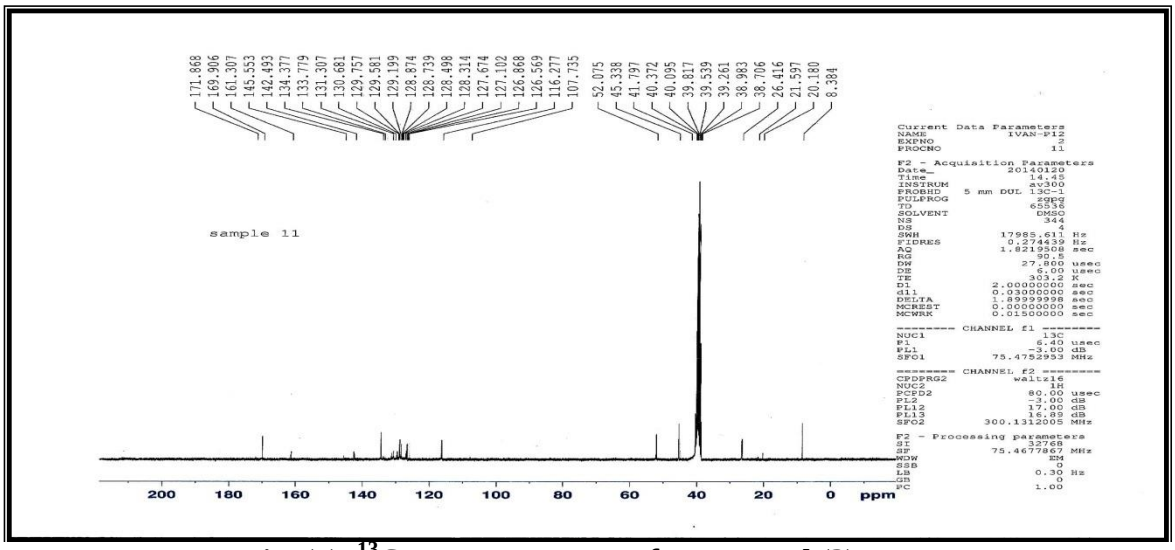


Fig. (4): ^{13}C-NMR spectrum of compound (3).

References

[1] Chawla, A.; Sharmand, A.K. 2012. A convenient approach for the synthesis of imidazole derivatives using microwaves, Der pharmachemica, 4(1):116-140.

[2] Desai, N. C.; Maheta, A. S. and Satodiya, H. M. 2014. Green synthesis of novel quinoline based on imdazole derivatives and evaluate of their antimicro-bialactivity,journalof saudichem.Soc.,18(6):963-971.

[3] Kadum, S. A. 2010. synthesis of new imidazole derivatives, journal of college of education, (1): 439-4.

[4] Dhooghe, M.; Van Barbandt, W.; Dekeukeleire, S.; Dejaegher, Y. and Dekimpe, N. 2008. Highly streoselective synthesis of beta-lactam utilizing alpha-chloroimines as new and powerful chiral inductors, Chem. Eur. J, 14(3):6336-6340.

[5] Georg, G. I. 1992. The organic chemistry of β- lactam, VCH: NewYork, NY.

[6] Yang, H.J; Sun, W. H ; Long, Z. and Ma, Z. 2002. The rapid synthesis of schiffs bases without solvent under microwave irradiation. Chin. Chem. ett., 13(1): 3-6.

[7] Wenling, Q., Long, S. Panunzio, M. and Biond, S. 2013.Schiffs bases:A short on an evergreen chemistry tool, Molecules, 18(1): 12264-12289.

[8] Vora, J. J; Vasava, S. B.; Parmar, C. P; Chauhan, S. K. and Sharma, S. S. 1990. Synthesis spectral and microbial studies of some Novel Schiffs bases derivatives of 4-methyl pyridine -2-amine, Journal of Chem., 6(4): 1205-1210.

[9] Hodnett, E. M. and Dunn, W. J. 1970. Structure-antitumor activity correlation of some schiffs bases, J. Med. Chem. 13(4): 768-770.

[10] Hu, G.; Wang, G.; Duan, N.; Wex, X.; Cao, T.; Xie, S. and Huang, W. 2012. Design synthesis and antitumor activities of fluroquinolone C-3 heterocycles (IV): S-triazoleShiff-Mannich bases derived from ofloxacin. Acta Pharm. Sinica B, 2(1): 312-317.

[11] Przybylski, P.; Huczynski, A.; Pyta, K. and Brzezinski, B., Barh, F. 2009. biological properties of Schiff base and azo derivatives of phenols, Curr. Org. Chem., 13(3): 124-148.

[12] Vukovic, N.; Sukdolak, S.; Solujic, S. and Niciforovic, N., 2010. substituted imino and amino derivatives of 4- hydroxyconumarins as Novel antioxidant, antibacterial and antifungal agents: synthesis and

in vitro assessments, Food Chem., 120(4):1011-1018.
[13] Ali, R. A., 2011. Synthesis of new Schiffs bases derived from 4-phthalimidylacetophenone, Journal of Al-Nahrain University 14(3): 1-8.
[14] Silverstein, R. M. and Basslar, G. C., 1981, Spectroscopic identification of organic compound, 4thedditionjhon and son, New Yourk.
[15] Williams, D. H. and Felming, 1986. Spectroscopic method in Organic chemistry, 1steddition New Yourk.

تحضير بعض مشتقات الاميدازول الجديدة التي تحتوي حلقةβ-لاكتام

فريال ولي عسكر* رنا عبد علي ثناء مهدي المؤمن****

*قسم الكيمياء ، كلية العلوم ، الجامعة المستنصرية
**قسم الكيمياء ، كلية العلوم ، جامعة بغداد

الخلاصة

في هذا البحث تم تحضير 5-مثيلينيل -2-(2-مثي اوكسازول -4-ون)-1-ايميدازول (1) من تفاعل ل-هستدين مع حامض الخليك اللامائي والذي تم تحويله الى 5- مثيلين- يل (2-مثيل -3- امينو اميدازول-4-ون)-1-ايميدازول (2) عن طريق التفاعل مع هيدرات الهيدرازين.تم تحضير قواعد شيف (3-6) من تفاعل المركب (2) معالديهايداتاروماتية مختلفة.تم الحصول على مركبات ازيتيدينون مختلفة (7-10) من تفاعل قواعد شيف المحضرة(3-6) مع كلوريد الكلورواسيتيل.شخصت المركبات المحضرة بواسطة FT-IR وبعضها بـ ^{1}H-NMR وبعضها بالمطياف ^{13}C-NMR .

الكلمات المفتاحية : لـ- هستدين ، قواعد شيف ، اميدازول