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SYNTHESIS AND CHARACTERIZATION OF SOME NEW SUBSTITUTED FLAGYLE DERIVATIVES

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ABSTRACT

This work is including synthesis of several new shiff bases and β-lactame by reacting of metronidiazolewith ethylchloro acetate to give ester which has been converted to amine by treatment with hydrazine hydrate.Shiff bases have been synthesized by treatment of amine with different aldehyde,β lactam have been synthesized by treatment the last With chloracetylechlorid The synthesiscompound have been characterized by FT-IR, ^{1}H-NMR, and ^{13} C-NMR.

KEYWORDS: Metronidazole, Ethyl Chloro Acetate, shiffbase, β-lactam

INTRODUCTION

Metronidazole,2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol (1). Metronidazole is one of the nitroimidazole derivatives (2) .is an antimicrobial drug that is used to treat protzoal and anaerobic bacterial infections (3) . IntravaginalMetronidazole is effective in the treatment of bacterial vaginosis.Metronidazole, as benzoyl form, could be used as supportive suppressive and/or synergistic additive drug in treatment of africantrypanosomiasis(4) .Schiff base has been reported a new compound called imine, it has been obtained by condensation of aldehydes(aliphatic or aromatic) or ketons (aliphatic or aromatic) with primary amines(5) . Schiff bases are characterized by the –N=CH-(imine group) which is important in elucidation the mechanism of transformation in biological system. Due to great flexibility and different structural sides, a wide range ofSchiff's bases have been synthesized and their complexities have been studied.. β-Lactam is a four member cyclic amide which is consisting of three carbon atoms and one nitrogen atom (6) . The β-lactam ring is a part of the core structure of several antibiotic families, the principal ones being the penicillin, cephalosporin, carbapenems, and monobactamswhich are, therefore, also called β-Lactam antibiotics (7) .

- Chemicals& Instruments

- Chemicals and-Instruments

All chemicals used and were used without further purification-Melting points were determined on Sturat Scientific melting point SMPLU-K and were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Burker 500M Hzistrumentusing DMSO-d_6 as solvent and TMS as internal reference measurements were made at the Chemistry Department, Al-Albyt University, Jordan**.**

- ***Synthesis of Compounds :***
- ***Metronidazole -N-ethyl acetate [8]:***

A mixture of Metronidazole (17.11g,0.1mol) , ethylchloro acetate(12.2ml ,0.1mol) and triethyl amine(10 ml, 0.1mol) DMF as a solvent in (125ml) round bottom flask were heated for 6 hrs at (153^{0}C) .The resultant reaction

mixture was cooled at room temperature and the solid was filtered dried and recrystallized from ethanol.

Metronidazole -N-acetohydrazide [9]:

(12.85g,0.05mol) of compound [1] , was dissolved in absolute ethanol (25ml) and hydrazine hydrate (3ml, 0.05mol) was added The reaction mixture was refluxed for 9 hrs. The mixture was concentrated , cooled and the solid was filtered ,drided and recrystallized from ethanol . .

General Preparation of Schiff's Bases[10]:

A mixture of compound [2](0.262 g ,0.001mol)and different aldehydes (0.001mol) in (15 ml) absolute ethanol and (3)drops of glacial acetic acid were refluxed for (7hours). The mixture was cooled and collected by filtration and recrystallized from Methanol. The physical properties of compounds [3-15] .

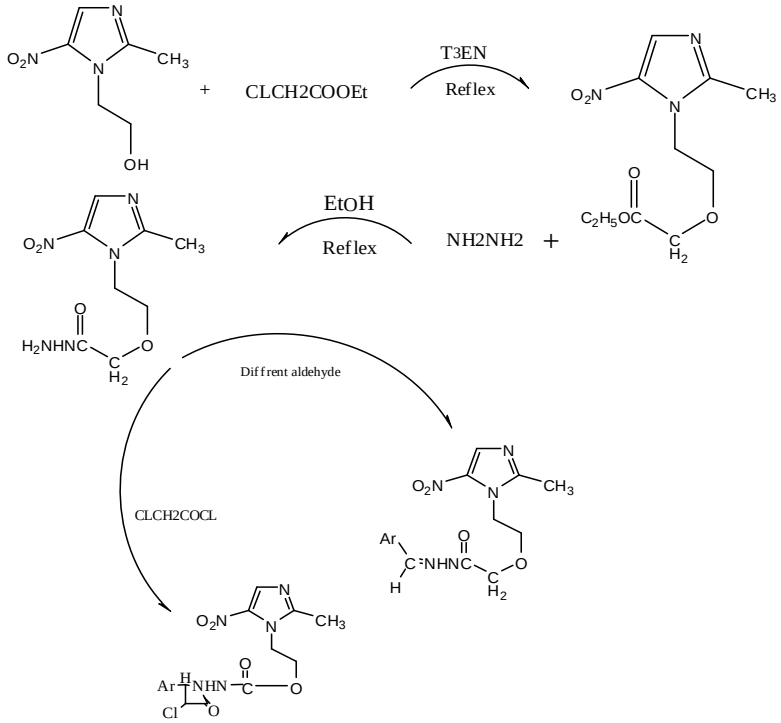
General preparation of β-Lactam [11]:

A mixture of (0.002mol) of Schiff base which prepared from aldehyde with (0.002mol) chloroacetyl chloride using DMF as a solvent with refluxed for (5) hr. Then (0.002) mole trimethylamine was added and refluxing for 1hr. The mixture was allowed to cool at room temperature. , And the crude mixture was filtered. And crushed of ice was added to filtrate to give precipitate which recrystallized from ethanol The physical properties of compounds [11-18].

RESULTS AND DISCUSSIONS

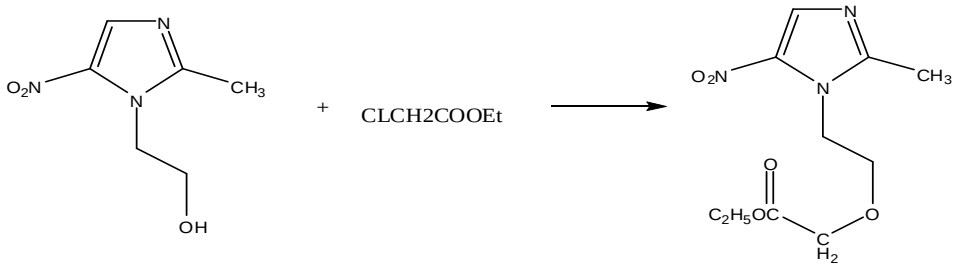
The synthesis sequences for preparation of series new Metronidazole derivatives are out lined in the following scheme (1).

Scheme - 1-

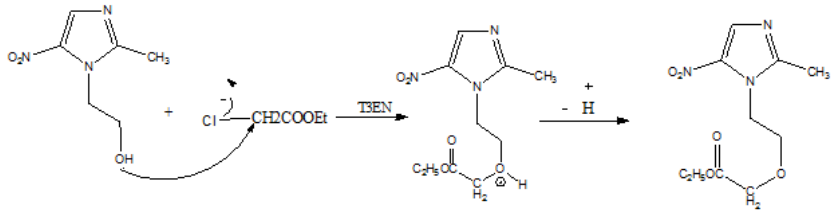


As starting material Metronidazole -N-ethyl acetate was prepared by reaction Metronidazole with ethyl chloro

acetate in the presence of triethylamine and DMF as a solvent , as shown in the following equation :

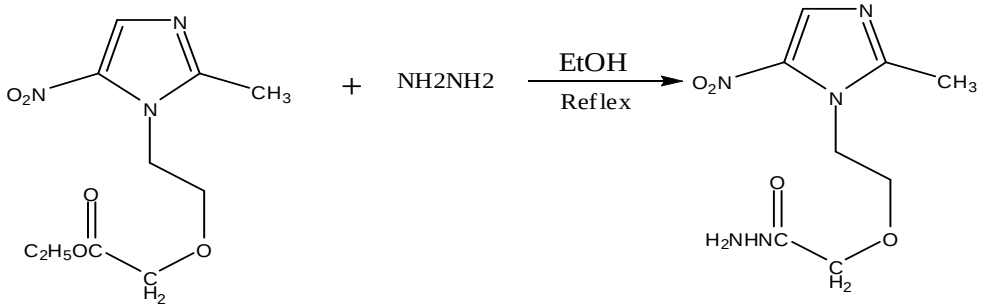


The mechanism for these reaction involves nucleophilic attack of oxo group in Metronidazole on reaction with carbon in Methelen in ethyl chloro acetate give the final product [1] , The suggested mechanism of the Esterafication is outlined in scheme (2).

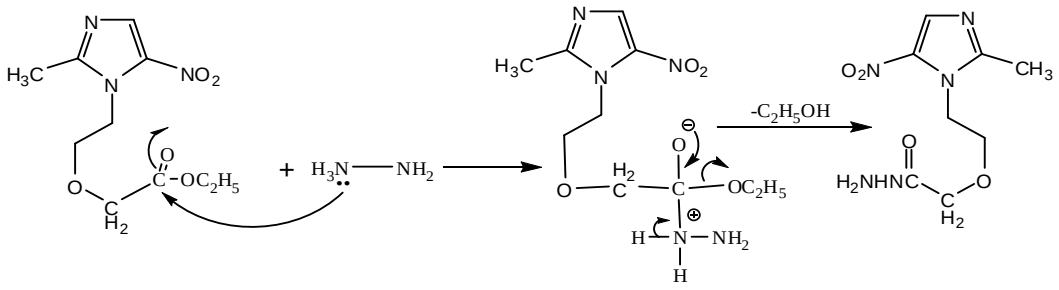


The physical properties of the compound (1) is listed in table(1-1).The structure of the synthesized compound has been characterized and confirmed by FT-IR spectrum alongside the (^{1}H-NMR and ^{13}C-NMR) . The physical properties of these compound [1] are listed in table (2-1). FT-IR spectrum of compound [1] shows the characteristic bands at [(1743) ,(1627) ,(2985) , (1539) (1222,1265)]cm^{-}caused by the ν(C=O) ester , ν(C=N), ν(C-H) aliphatic, υ (C-NO_2), and ν(C-O-C) stretching respectively. These bands and other are shown in table (1-2).

Hydrazide derivatives have been synthesized by the nucleophilic substitution from the compound (1) with hydrazine hydrate in absolute ethanol,to give the final product (2) as shown in the following equation.

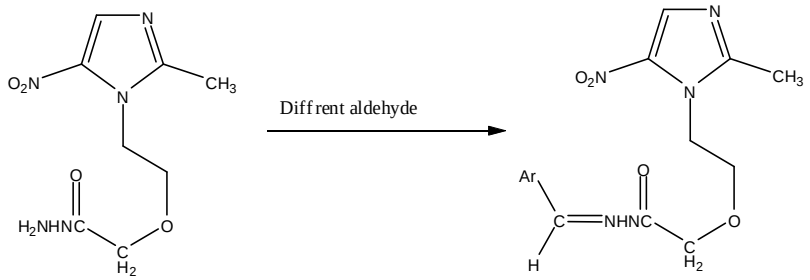


This reaction represents nucleophilic substitution reaction and The mechanism involved nucleophilic attack of amino group in hydrazine on carbonyl group in ester followed by elimination of ethanol molecule, as shown in the following Scheme:

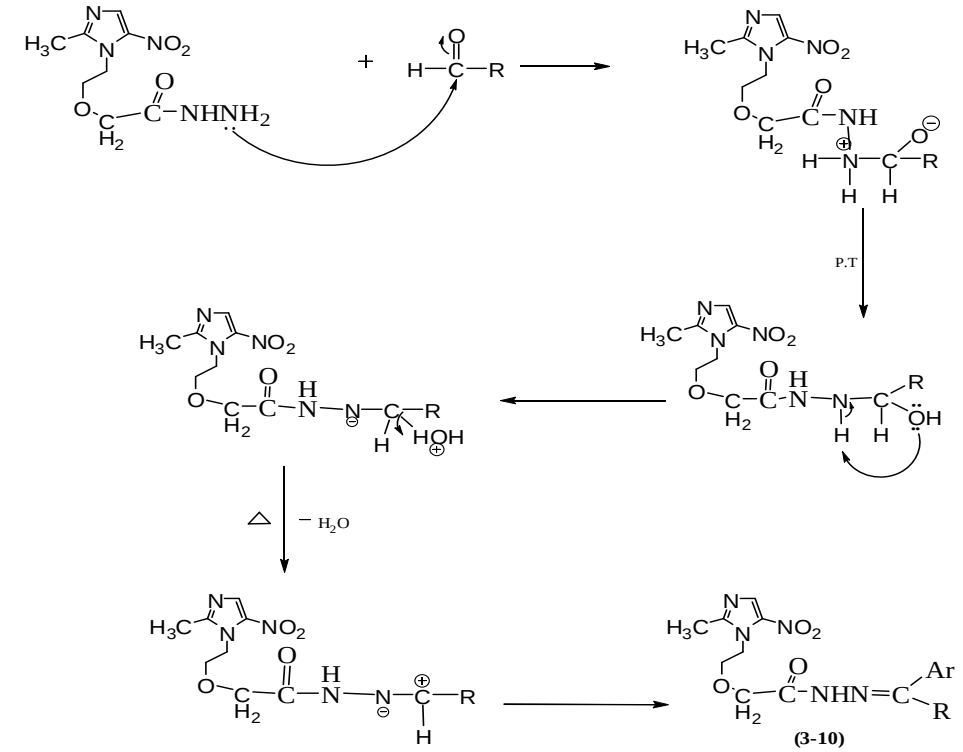


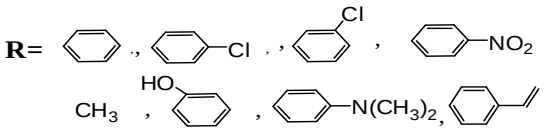
The physical properties of the compound (2) is listed in table (1-1).FT-IR spectrum of compound [2] shows the characteristic bands at at (NH_2) (3400) cm^{-1} , ν(C=N)(1627) and appearance of υ(NH) absorption bands at (3140,3248)cm^{-1} . These bands and other are shown in Table (1-2)

The title compounds[3-10] were synthesized from the reaction between compound [2] and many substituted aromatic aldehydes in absolute ethanol and glacial acetic acid resulted in the formation of Schiff's bases , as shown in equation (3):



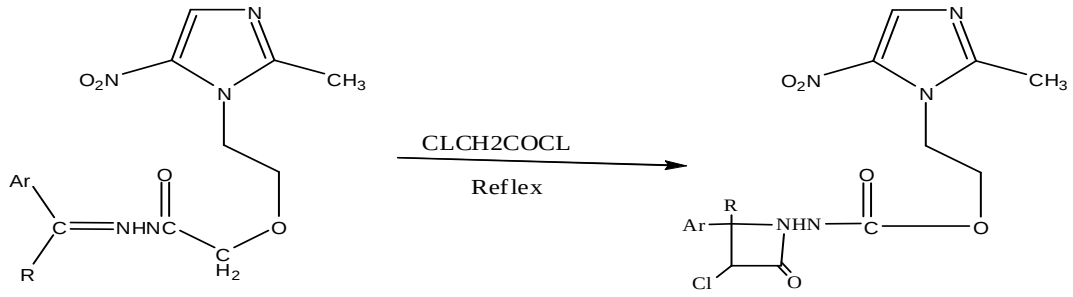
The mechanism representsnucleophilic attack of amine group of compound[2] on the carbon carbonyl group of aldehyde to form unstable compounds followed eliminate water molecule to give an amine compounds .The mechanism of the reaction can be outlined as the following scheme :



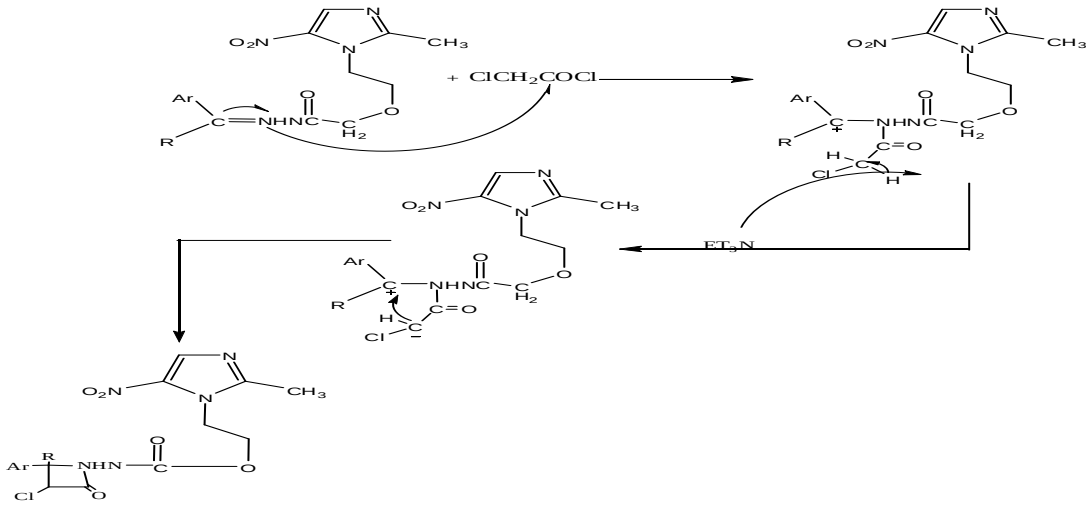


The structure of the synthesized compounds have been characterized and confirmed by FT-IR spectra beside the (^{1}H-NMR and ^{13}C-NMR) analysis .The physical properties of these Schiff bases (3-10) are listed in table (1-2) .The FT-IR spectra of compounds (3-10) show the characteristic bands at [(3001- 3110),(2885- 2997),(1616 – 1728),(1519- 1600),(3113 - 3464)] cm^{-1} due to ν(C-H) aromatic, ν(C-H) aliphatic, ν(C=O)amide, ν(C=C) aromatic and ν(N-H) respectively .These bands and other are shown in table (1-2).

A series of eight new β-Lactam compounds was synthesized by the reaction of Schiff's bases withchloro acetyl chloride followed by the addition of triethyl amine in the presence of DMF , as a solvent as shown in equation the following:

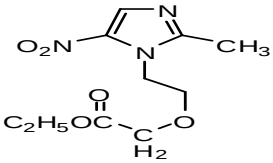
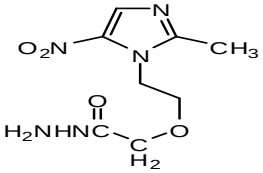
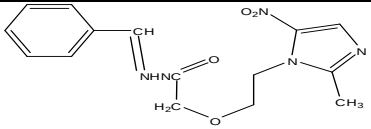


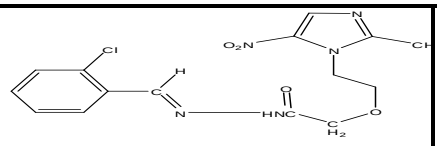
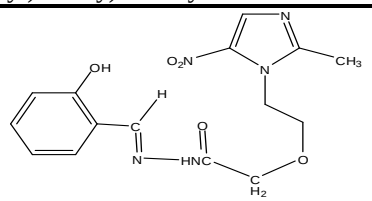
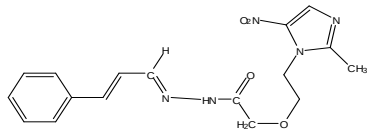
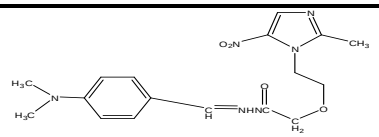
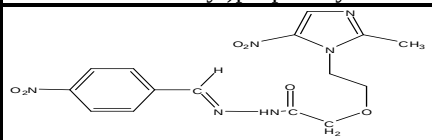
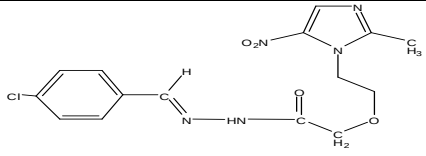
The suggested mechanism of these compounds,as shown in the following scheme :

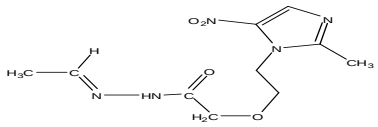
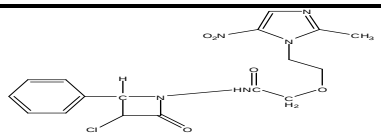
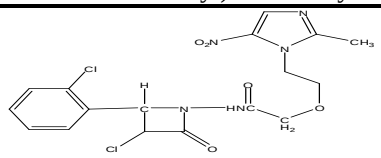
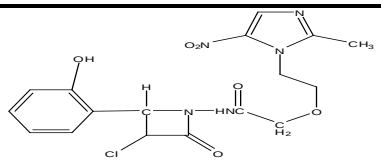
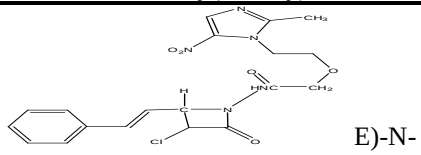
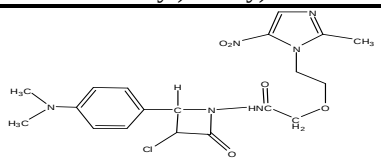
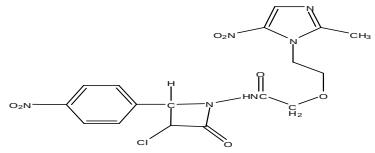


The structure of the synthesized compounds have been characterized and confirmed by FT-IR spectra. The physical properties of these compounds (11-18) are listed in table (1-1).The FT-IR spectra of compounds (11-18) show the characteristic bands at [(3002- 3101- 3113),(2908- 2997),(1600- 1797),(3110 - 3410)]cm^{-1} due to ν(C-H) aromatic, ν(C-H) aliphatic, ν(C=O)amide,ν(N-H) respectively. These bands and other are shown in table (1-2).

Table 1: The Physical Properties of Compounds (1-18)

NO OF COMP	**Structure product and Chemical formula**	**Yield %**	**Color**	**M. P. C**	RECERY SOLVENT
1	 ethyl 2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetate	**71**	**white**	**Oil**	ethanol
2	 2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetohydrazide	**76**	**brown**	**157-159**	ethanol
3	 N'-(4-formylbenzylidene)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetohydrazide	85	dark brown	Oil	ethanol

4	 (E)-N'-(2-chloro-4-(2-oxoethyl)benzylidene)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetohydrazide	73	Bile Brown	120-122	ethanol
5	 (E)-N'-(4-formyl-3-hydroxybenzylidene)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetohydrazide	71	Bile Wihte	125-127	ethanol
6	 (E)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)-N'-((E)-3phenylallylidene)ace- tohydrazide	82	Dark brown	118-120	ethanol
7	 E)-N'-(2-(dimethylamino)-4-formylbenzylidene)-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propanehydrazide	68	Redish Brown	260-262	ethanol
8	 (E)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)-N'-(4-nitrobenzylidene)acetohydrazide	61	yellow	249-251	ethanol
9	 (E)-N'-(4-chlorobenzylidene)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetohydrazide	71	Yellowish brown	208-210	ethanol

10	 E)-N'-ethylidene-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetohydrazide	80	Light yellow	252-254	ethanol
11	 chloro-1-(2-(2-(2-(2-methyl-5--3)-4 nitro-1H-imidazol-1-yl)ethoxy)acetyl)hydrazinyl)-4-oxoazetidin-2-yl)benzaldehyde	78	brown	More than 300	ethanol
12	 N-(3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetamide	66	Light brown	215-217	ethanol
13	 N-(3-chloro-2-(4-formyl-3-hydroxyphenyl)-4-oxoazetidin-1-yl)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetamide	67	Bile Yellow	296-298	ethanol
14	 E)-N-(3-chloro-2-oxo-4-styrylazetidin-1-yl)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetamide	77	Dark Brown	94-96	ethanol
15	 N-(3-chloro-2-(2-(dimethylamino)-4-formylphenyl)-4-oxoazetidin-1-yl)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetamide	65	Red	285-287	ethanol
16	 N-(3-chloro-2-(2-nitro-4-(2-	56	Brown	More than 300	ethanol

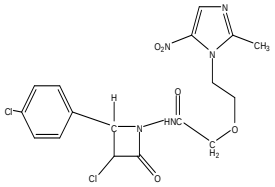
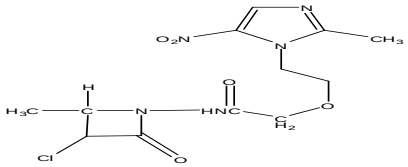
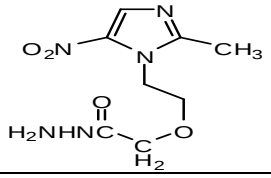
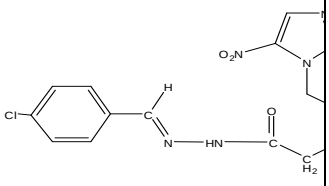
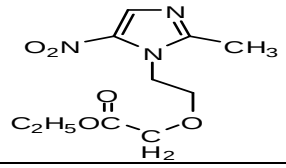
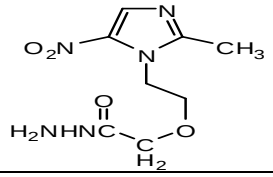
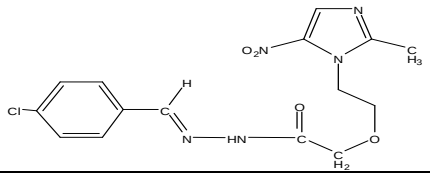
	oxoethyl)phenyl)-4-oxoazetidin-1-yl)-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propanamide				
17	 N-(3-chloro-2-(5-chloro-2-(2-oxoethyl)phenyl)-4-oxoazetidin-1-yl)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetamide	67	Bile Brown	224-226	ethanol
18	 N-(3-chloro-2-methyl-4-oxoazetidin-1-yl)-2-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy)acetamide	78	Yellow	More than 300	ethanol

Table (1-2): ^{1}H-NMR Spectral Data (δppm) of Compounds[2,9]

Com. NO	Compound Structure	^{1}H-NMR Spectral data ($^{\delta}$ ppm)
2		δ2.461(s,3H,CH$_3$), δ2.506 (s,2H , CH$_2$) , δ3.369(s, 2H, CH$_2$-C=Oester) ,δ5.88 (s, 2H ,NH2), δ6.779 (s, 1H ,NH), δ8.502 -7.636 (d, 1H, HAr)
9		δ0.98 (s,3H,CH$_3$) , δ2.21(s,2H,CH$_2$- C=O), δ2.99 (s,3H, NH-C=O- CH2) , δ4.535 (s, 2H ,NH2), δ5.031 (s, 1H ,NH), δ8.85 -7.78 (q , 1H, HAr)

Table(1-3): ^{13}C-NMR Spectral Data (δppm) of Compounds[1,2,9]

Com. NO	Compound Structure	^{13}C-NMR Spectral data ($^{\delta}$ ppm)
1		33.288(CH2-CH2);39.456 (CH_3); 69.108(NH-C=O- CH2); 129-135(C-CAr);164.65 (C=O)
2		34(CH_2-CH2);38(CH_3);); 48.215 (-C=O- CH2); 59.698(NH-C=O- CH2);132-111(C-CAr);159.781 (C=O)
9		36(CH_2-CH2);39(CH_3);); 49 (-C=O- CH2);60.307(NH-C=O-CH2);132-123(C-CAr);170 (C=O)

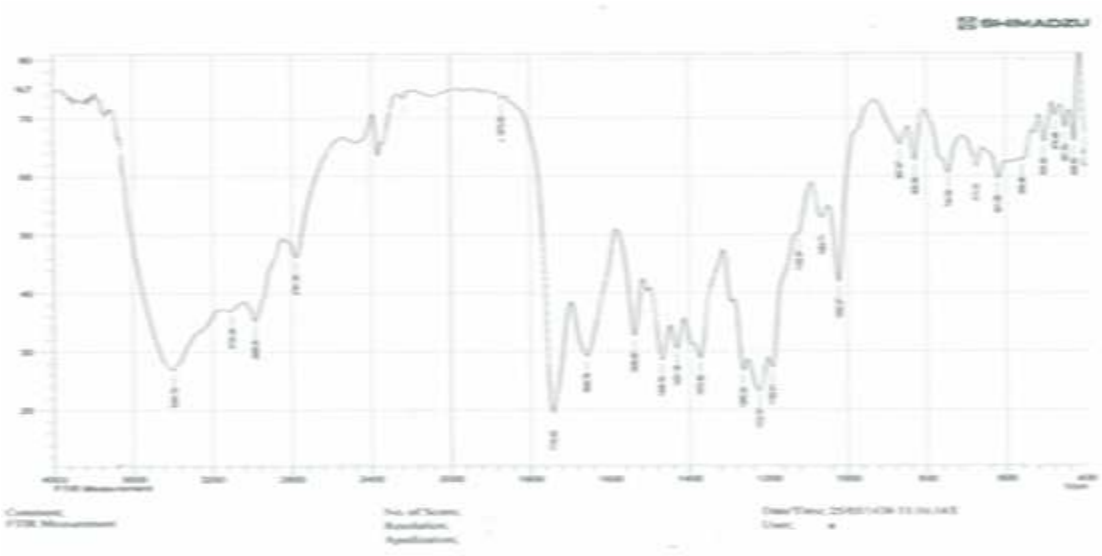


Figure 1-FT- IR Spectral Coumpund (1)

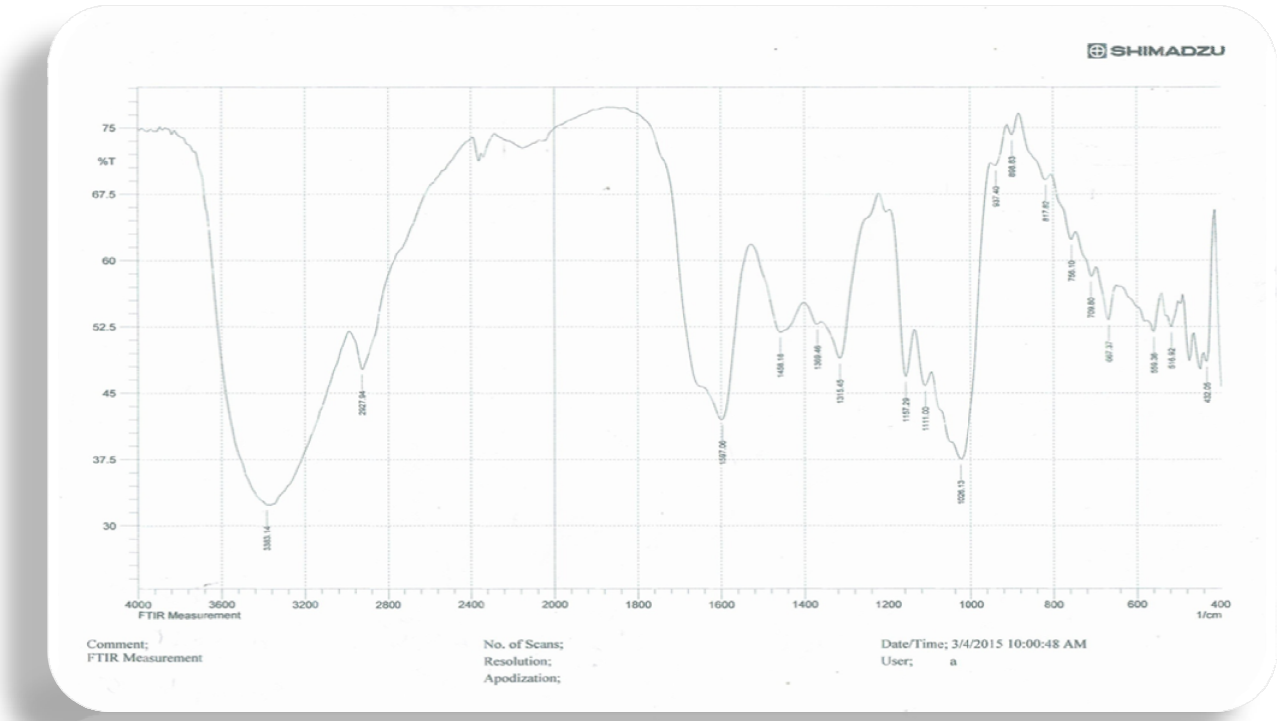


Figure 2-FT- IR Spectral Coumpund (2)

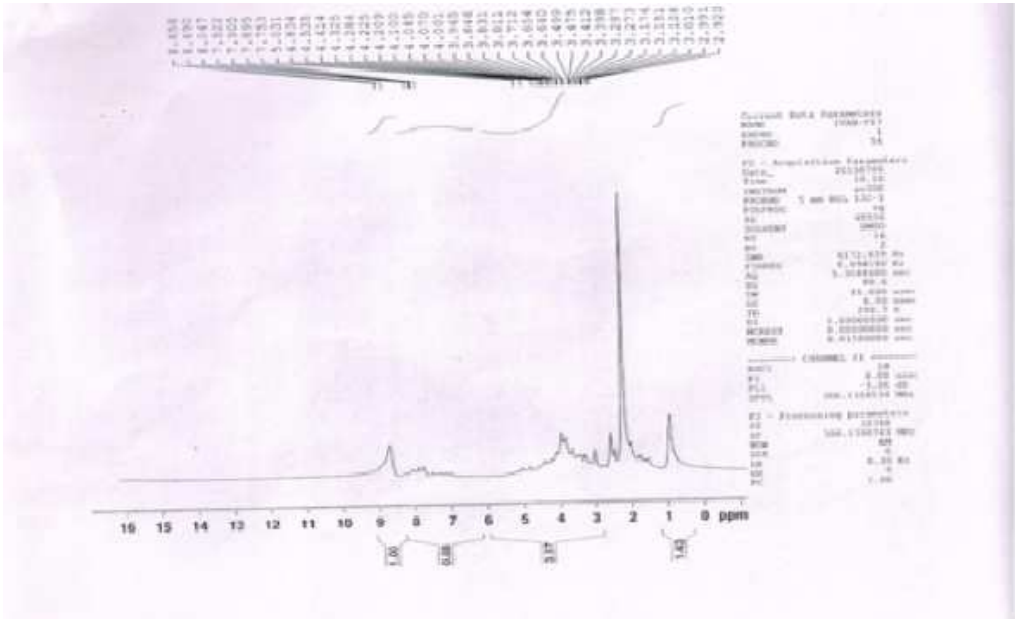


Figure 3-H- NMR Spectral Coumpund (2)

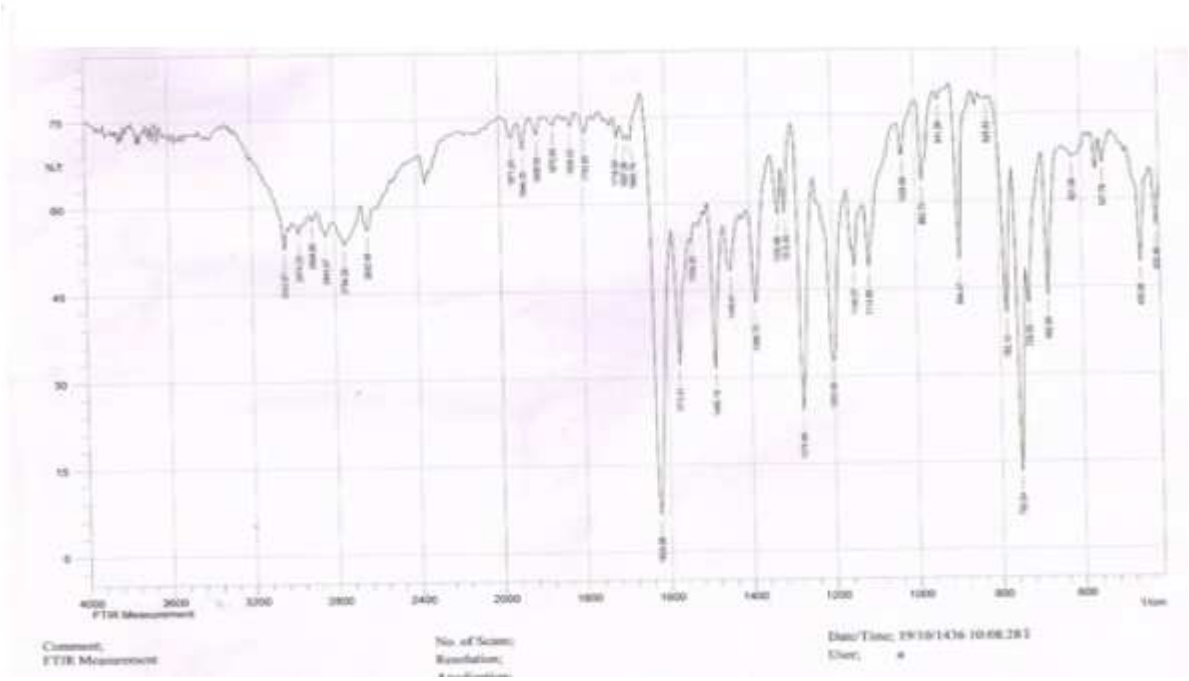


Figure 4-FT- IR Spectral Coumpund (7)

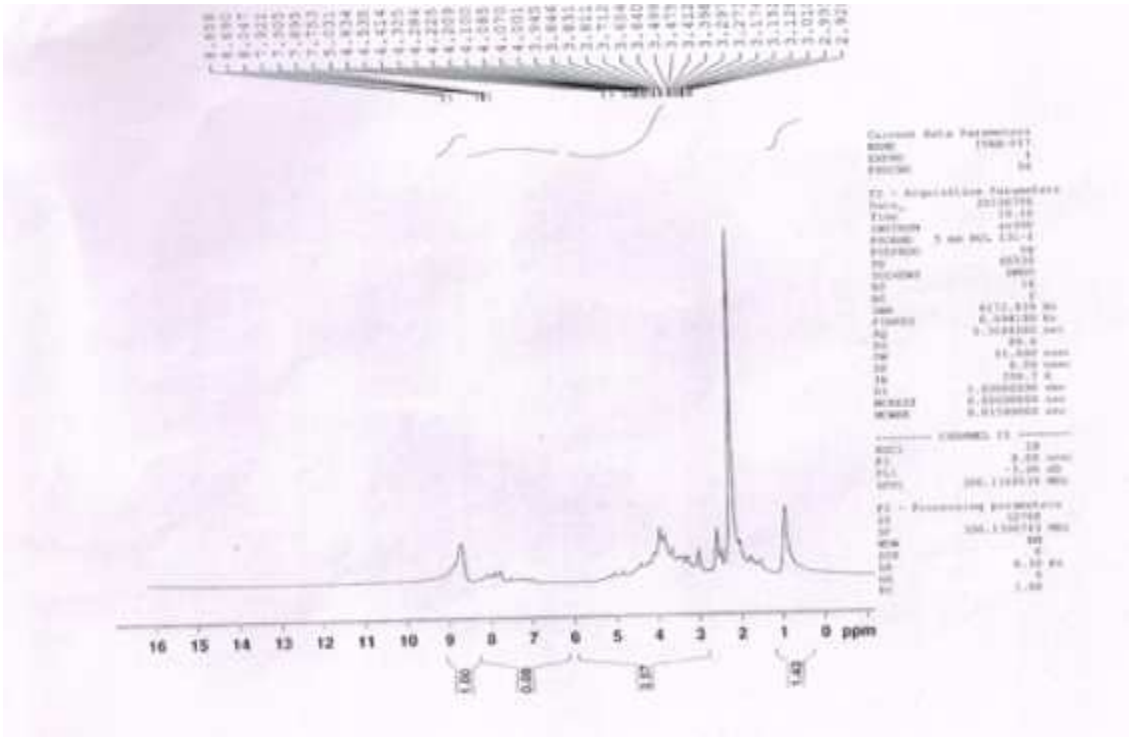


Figure 5-HNMR Spectral Coumpund (5)

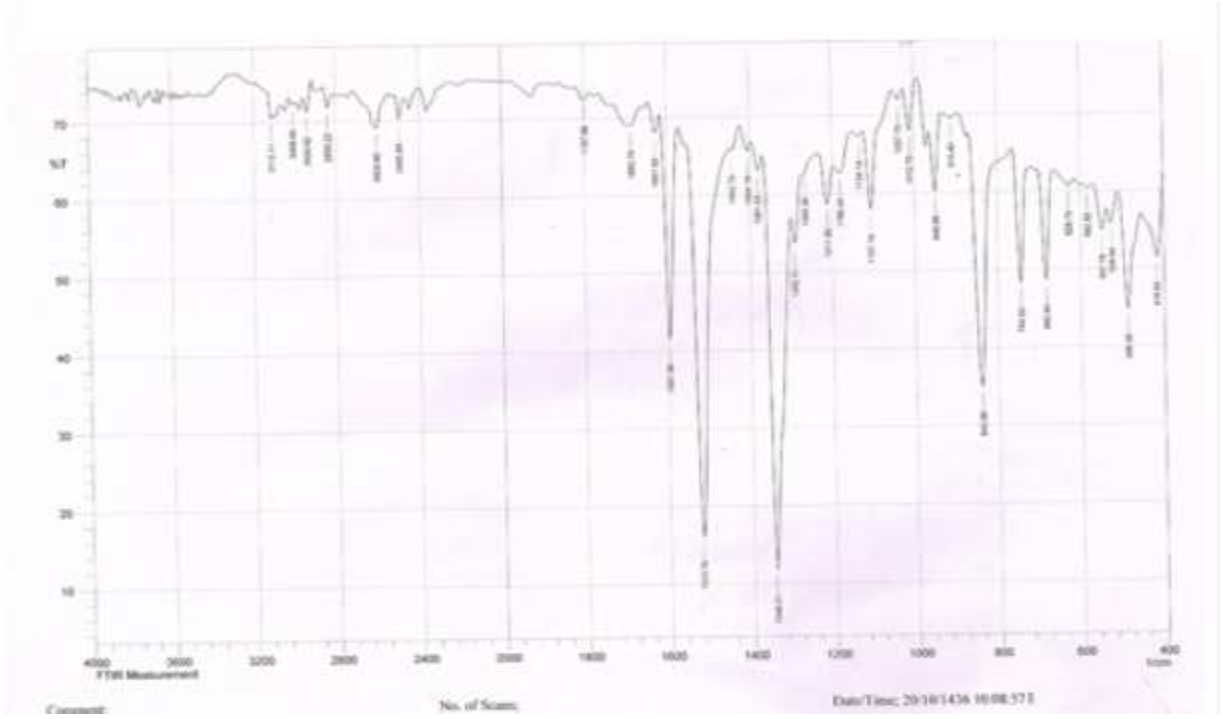


Figure -6- FT- IR Spectral Coumpund (11)

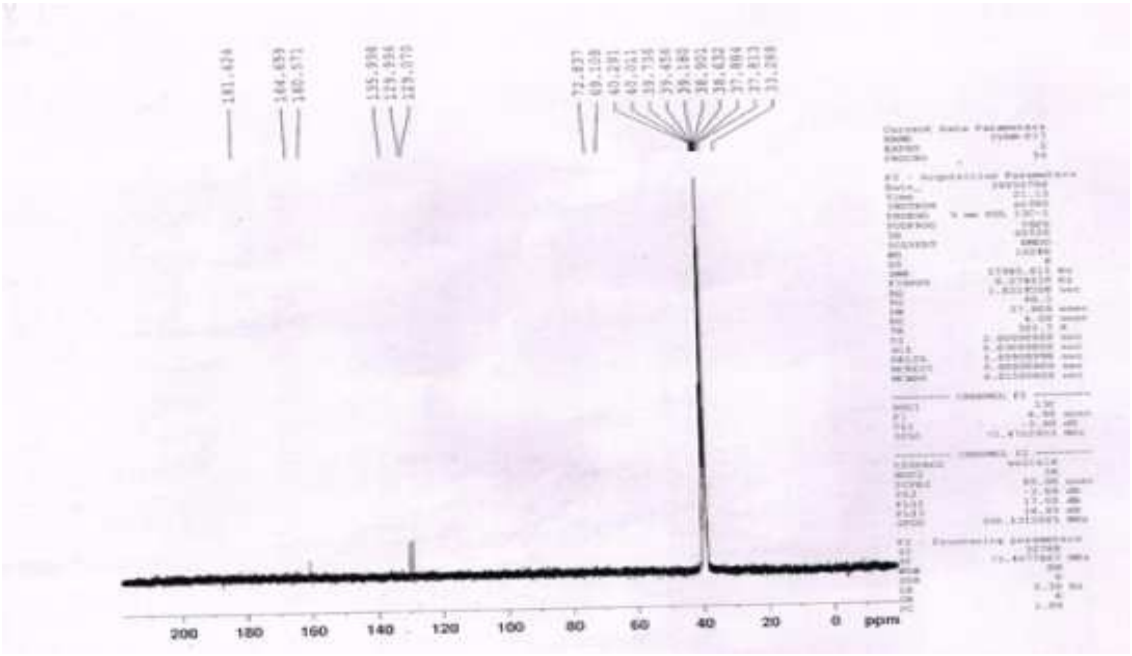


Figure 7-C- NMR Spectral Coumpund (1)

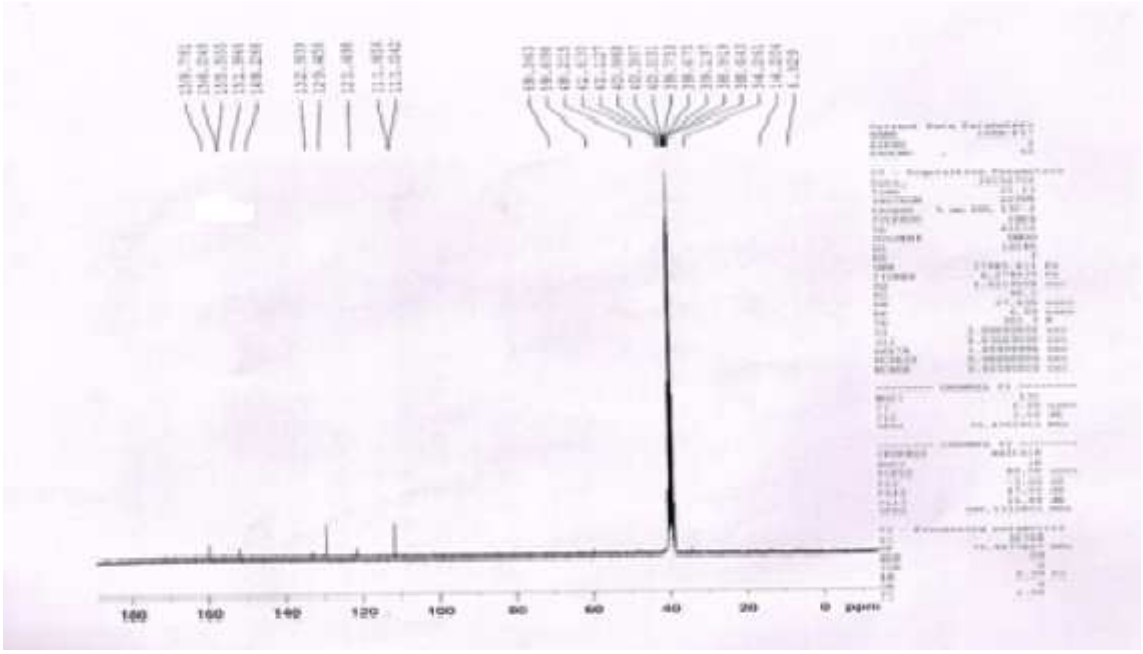


Figure- 8-C- NMR Spectral Coumpund (2)

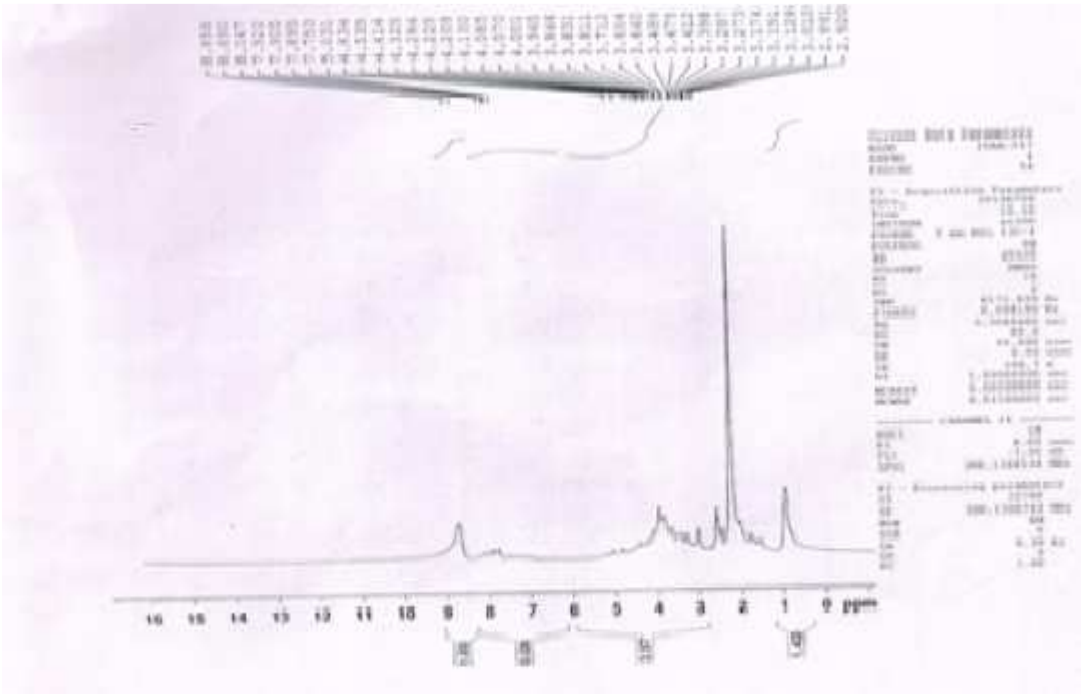


Figure -9-C- NMR Spectral Coumpund (5)

REFERENCES

1. Mohammed.A-Al-Mamun*1 Mohammed. R. Rahman2, Sujit B, Sukalyan .r. Kundu1 and Johir R/,2014,Formulation and Bioequivalence Evaluation of Extended Release Solid Drug Delivery System for Metronidazole Using Eudragit NM30D and Methocel Premium K4M as Retardant Material , American Journal of Advanced Drug Delivery[2014]039-051

2. Safila N, Fatima Q , 2014**,/*** Simple UV Spectrophotometric Assay of Metronidazole,*Open Access Library Journal*, **1**: e615. http://dx.doi.org/10.4236/oalib.1100615
3. JABER E, NEDA G, HAMED H, 2006, A RAPID AND SENSITIVE HPLC METHOD FOR THE ANALYSIS OF METRONIDAZOLE IN HUMAN PLASMA: APPLICATION TO SINGLE DOSE PHARMACOKINETIC AND BIOEQUIVALENCE STUDIES, Department of Pharmaceutics, Faculty of Pharmacy and pharmaceutical Sciences, Isfahan University of Medical Sciences, Iran, DARU Volume 14, No. 1.
4. Maadh Q. Abdul-Kadir*,1 , Nadhum E. AL-Ani * and Shakir M. Alwan, *2009* ,Synthesis of New Cyclic Amines-Linked Metronidazole Derivatives as Possible Prodrugs , *Iraqi J Pharm Sci, Vol.18(2) 2009 Cyclic amines derivatives of metronidazole**Department of Pharmaceutical Chemistry, College of Pharmacy ,University of Baghdad, Baghdad, Iraq
5. Raman,N. ; Esthar,S. ; and Thangaraja,C. (2004). "A new Mannich base and its transition metal (II) complexes – Synthesis, structural characterization and electrochemical study".J.Chem.Sci. 116(4): 209-213.
6. Ethiriaj, H.; Kimelahi, K. (2003).Biological activity of some monocyclic- and bicyclic beta-lactams with specified functional groups. Med chem. 305-513.
7. El. Gaby, M.; Abdel.Hamid, S.; Ghorab, M. (2002).Synthesis of Some Novel Thieno [2, 3-d] pyrimidines and their Antibacterial Activity .Med. chem. 10: 67-82.
8. 142-Al-Majidi ,S.M.H. and Al-Quaz,A.M.N.(2010)."Synthesis of some new N-Substituted -1,2,3,4-Tetrahydro carbazole derivatives and study their Biological Activity".Journal of Al-Nahrain University .13(1):26-35.
9. Mohan,S. Ananthan, S.and Murugan, K.R. (2010) ."Synthesis, Characterization and Biological activity of Some Novel Sulphur Bridged Pyrazoles.IJPSR.1(9):391-398.
10. Jalhan,S.Jindal.A.Gupta,A.Hemraj.(2012)."Synthesis ,Biological activities and chemistry of thiadiazole derivatives and Schiff bases".Asian J Pharm Clin Res. 5:199-208.
11. Nanyan .F, Thomas.T .Tidwell (2008) (Preparation of β-lactams by [2+2] cycloaddition of ketenes and imines) Tetrahedron,vol.64,155 us 46,10 November (2008),page. 10465-10496.