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Synthesis & Characterization of Some 1, 3, 4-OxadiazoleDerivatives & new Cyclic Imides from Creatinine

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Abstract

A series of new 1,3,4- oxadiazole derivatives and cyclic Imides containing Creatinine heterocyclic molecule were prepared via following method:first step included Synthesis of amic acid from reaction between different cyclic anhydrides with Creatinine which subsequently dehydrated to the corresponding imide via treatment with acetic anhydride and anhydrous sodium acetate,.then,second step was tratedamic acid with Thionyl chloride producing acid chloride which on amination with hydrazine hydrate in thierd step and the last turn to 1,3,4-oxadiazole derivatives by condensation reaction with Phosphorous Oxychloride($POCl_3$) and different benzoic acids. Cyclization to 1, 3, 4-Oxadiazole derivatives. Antibacterial activity of some prepared new compounds against two types of bacteria were evaluated and result showed the new exhibit good moderate antibacterial activity.Prepared compounds were elucidated on the basis FT-IR,^{1}H-NMR and MASS spectro data which agreed with the proposed structures.

Keywords: Creatinine ,Amic Acid , cyclic Imide , 1,3,4-Oxadiazole

تحضيروتشخيصبعض مشتقات 1،3،4- اوكسادايازول وايمايداتحلقيةجديدةمن الكرياتينين

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قسم الكيمياء ، كليةالعلوم،جامعةبغداد ، بغداد ، العراق

الخلاصة:

تمفيهذاالبحثتحضير عددمنالايمايداتالحلقيةالجديدة وسلسلة من مشتقات 1،3،4- اوكسادايازول حاوية على حلقة الكرياتينين غير المتجانسة بإتباعطريقةتحضيرمتسلسلة،تضمنتالطريقة : الخطوة

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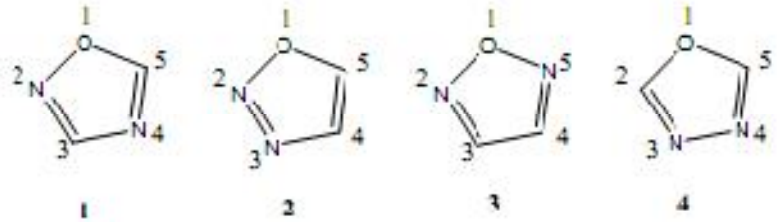
الاولتحضيرسلسلةمنحوامضالاميكالحاوية على حلقة
الكرياتينينوذلكمنخلالتفاعلانهيدريداتحلقيةمختلفةمعها،بعدهاتمسحبالماءمنحوامضالاميكالمحضرةباستخدامانهيدريدالخ
ليكوخلاتالصوديومماللامائيةكعاملساحبللماءللحصولعلىالايمياتالمقابلة .أماالخطوة الثانيةفقد تضمنتتفاعلحوامض
الاميك مع كلوريد الثايونيل للحصول على كلوريدات الحوامض المقابلة ،بعدها تمت معاملة الكلوريدات مع
الهيدرازين المائي في خطوة ثالثة واخيرا مشتقات من 4,3,1 - اوكسادايازولاتبطريقة الغلق الحلقي للتكاثف مع
$POCl_3$ وحوامض كربوكسيلية اروماتية مختلفة للحصولعلىالاوكسادايازولات
المطلوبة،تمتدراسةالفعاليةالمايكروبايولوجية لبعضالمركباتالمحضرةالجديدة ضدنوعين منالبكترياوقداظهرت
النتائجبانا غلبالمركبات اذاتفعاليةجيدةضدالمايكروباتقيدالدراسة.تم اثبات تراكيب المركبات المحضرة بواسطة اطياف
ال FTIR,^{1}-HNMR ,Mass

Introduction

Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom The replacementof two **(-CH=)** groups in furan by two pyridine type nitrogen **(-N=)** reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character ofconjugateddiene.There are four possible isomers of oxadiazole[1, 2, 3, 4]schem -1-. depending on the position of nitrogen atom in the ring and are numbered as shown[1-3]



Schem-1-possible isomers of oxadiazole

The electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant tonucleophilic attack. Halogen-substituted oxadiazole, however undergo nucleophilic substitution with replacement of halogen atom by nucleophiles [4,5]. Literature survey reveals that the 1,3,4 oxadiazole undergoes number of reactions such as Electrophilic substitution, Nucleophilic substitution, Thermal and Photochemical. This has been exploited in the preparation of 1,3,4oxadiazole therapeutic molecules for various applications [6,7].Inclusive of inductive effect &having efficient anticancer .antifungal. antimicrobial, insecticidal anti-allergic activity etc. 1,3,4-oxadiazole and its derivatives have been frequently employed in drug synthesis, various commercial and industrial applications. In fact, 1,3,4-oxadiazole ring carrying substitution in an appropriate position and substituent with a nucleophilic center are excellent precursors for further synthesis of heterocyclic compounds[8]. Resistance to number of antimicrobial agents among a variety of clinically significant bacteria is becoming increasingly important. There are various problems arising with the use of antimicrobials such as local tissue irritation, interference with wound healing process, hypersensitivity reactions, system toxicity, narrow antimicrobial spectrum, and emergency of resistance . So, the increasing clinical importance of drug resistant microbial pathogens has additional urgency in microbiological and antifungal research. A wide variety of heterocyclic systems have been explored for developing pharmaceutically important molecules. Among them the derivatives of oxadiazoles have been playing an important role in the medicinal chemistry. The 1,3,4-oxadiazolederivatives have been found to exhibit diverse biological

activities such as antimicrobial, anti HIV , ant tubercular antimalarial , anti-inflammatory , anticonvulsant , and antitumor The disubstituted-1,3,4-oxadiazole derivatives are known for various pharmacological activities such as antibacterial , antihypertensive ,anticonvulsant , and ant proliferative . The choice of 1,3,4-oxadiazole is due to its multi -applicability in the field of medicine [9,10].

Experimental

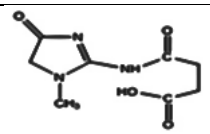
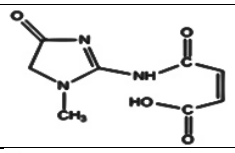
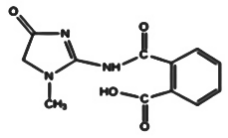
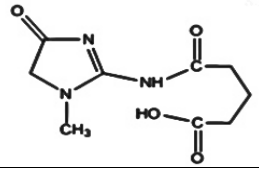
A- chemicals: All chemicals used in this work were from BDH, Merk, Fluka and were used without further purification. Compounds prepared were characterized by (FT- IR ,^{1}H-NMR & Mass spectral data). Melting points are uncorrected determined by using /SMP31 Thi-Qar University college of sciences

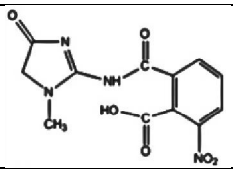
B-instruments: FTIR spectra were recorded using KBr discs on Shimadzu-8400 spectrophotometer, Al-Shatra technical institute, Southern Technical University.^{1}H-NMR spectra were recorded on near magnetic resonance Bruker DRX System , 500 MHz Using TMS as internal standard and DMSO as solvent , Sharif University of Technology, Tehran ,IranMass spectra by (Mass Selective Detector 5973 Network) 70 e/v, Sharif University of Technology, Tehran, Iran.

1-Synthesis of AmicAcid .[11-14]

In a 150 mL two- necked flask equipped with magnetic stirrer ,droop funnel and reflux condenser were placed (0.005mole 0.5 g) of different acid anhydrides (Maleic, Phthalic ,3-Nitro PhthalicSuccinic&Glutaric) and (25mL) of a suitable solvent such as dry acetone or THF . When all anhydride had been dissolved by stirring.a solution of (0.005 mole , 0.5 g) of Creatinine in (25 mL) of acetone was allowed to run through the dropping funnel dropwise for 30 min under cooling range (0-5 C^0). continued stirring under room temperature for 2 hrs.precipitatesettled out and filtered by suction filtration. Washed with solvent dried and recrystallized from ethanol .physical properties of prepared Amic acids are listed in table 1 .

Table1-Physical properties of prepared Amic acids

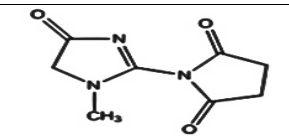
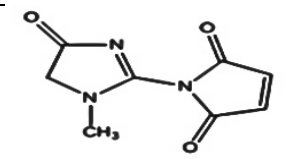
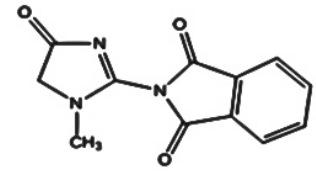
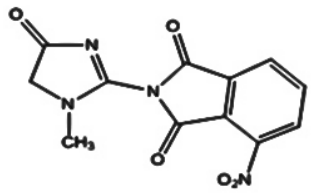
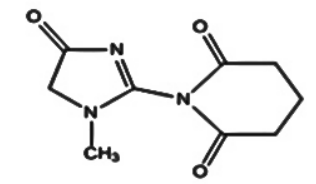
Comp. No	Structure	Molcul.Form.	Color	Yield %	m.p^{0}C
1		$C_8H_{11}N_3O_4$ M.W 213.19	White	75	131-133
2		$C_8H_9N_3O_4$ M.W 211.13	Pale brown	80	170-172
3		$C_{12}H_{11}N_3O_4$ M.W 261.24	Off white	68	69-71
4		$C_{12}H_{10}N_4O_6$ M.W 306.23	yellow	70	66-68

5		**$C_9H_{13}N_3O_4$ M.W 227.22**	**white**	**78**	**70-72**

2-Synthesis of imides .[15,16]

In 250 mL two- necked flask equipped with magnetic bar stirrer, drooping funnel and reflux condenser, were placed (0.3 g) of amic acid . A mixture of (5 mL) acetic anhydride and (5-10% weight of amic acid)anhydrous sodium acetate was allowed to run through the dropping funnel drop wise with stirring for half hr. the resulting mixture was refluxed over water path for 3 hr. the reaction mixture was cooled to room temperature and poured into a large amount of ice water . the product precipitated was collected by suction filtration and washed with ice water and recrystallization from ethanol. physical properties of the Imides are listed in table 2 .

Table 2- Physical Properties prepared Imides

Comp. No	Structure	Molcul.Form.	Color	Yield %	m.p^{0}C
6		**C8H9N3O3 M.W 195.18**	**white**	**68**	**100-102**
7		**C8H7N3O3 M.W 193.16**	**yellow**	**60**	**89-88**
8		**$C_{12}H_9N_3O_3$ M.W 243.22**	**white**	**70**	**117-119**
9		**C12H10N4O3 M.W 258.24**	**yellow**	**79**	**218-220**
10		**C9H11N3O3 M.W 209.20**	**Off white**	**85**	**133-135**

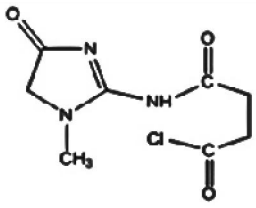
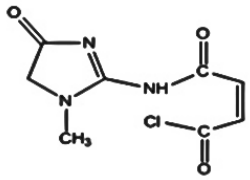
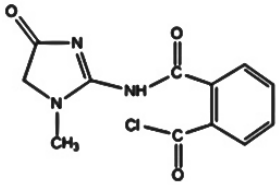
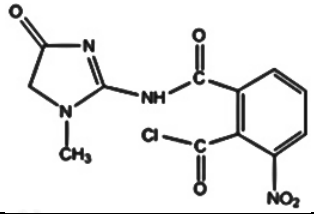
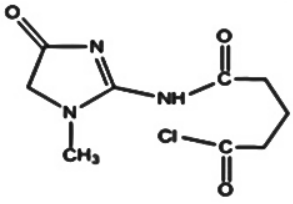
3-Synthesis of 1,3,4-Oxadiazole Derivatives

A series of steps as followed below to get the oxadiazolederivatives .

3.1-Synthesis of acid chlorides [17]

Amic acid from step **(1)** (0.01 mole) was converted to acid chloride by treating with(0.6 ml) thionyl chloride . the mixture was put in (10 ml) round – bottom flask . then add drops of DMF along with boiling chip . The refluxing continued for 30 min in fume hood. After the mixcher cool the reaction in an ice path until well chilled .The reaction completion was monitored by TLC.The product precipitated was collected by suction filtration and washed with ethanol.Physical properties are listed in table 3.

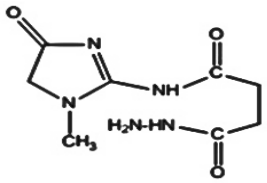
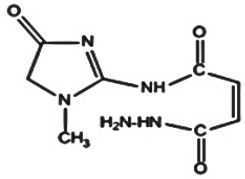
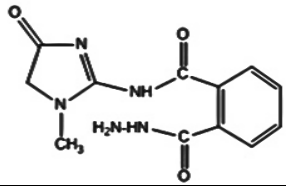
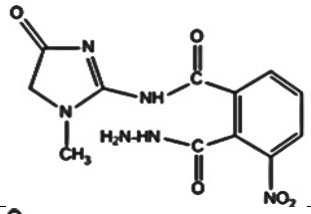
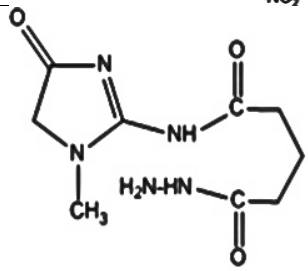
Table 3- Physical properties of prepared acid chlorides

Comp. No	Structure	Molcul.Form.	Color	Yield %	m.p^{0}C
11		C8H10ClN3O3 M.W 231.64	brown	65	97-99
12		C8H8ClN3O3 M.W 229.62	brown	67	110-112
13		C12H10ClN3O3 M.W 279.68	0ff white	57	278-280
14		C12H9ClN4O5 M.W 324.68	yellow	60	168-170
15		C9H12ClN3O3 M.W 245.66	white	68	187-188

3.2- Synthesis of acid hydrazide [18,19].

In(50) ml round bottom flask put acid chlorides from step**(3.1)** (0.01 mole) and ethanol (10 ml) at temperature(0-5C^{O}) hydrazine hydrate (0.01 mole) was added .Tthe reaction refluxed for 6 hrs. Reaction completion was monitored by TLC.Then filtered and washed with ethanol,the precipitate was dried to get product. physical properties are listed in table 4.

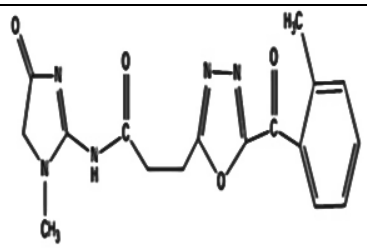
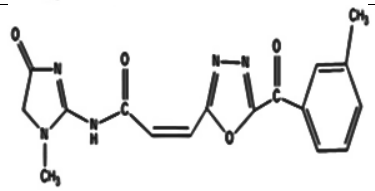
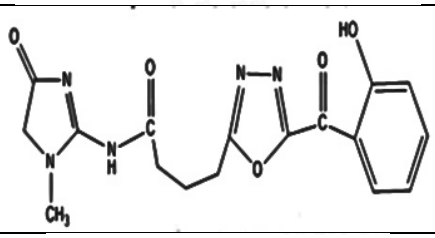
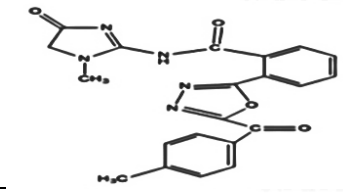
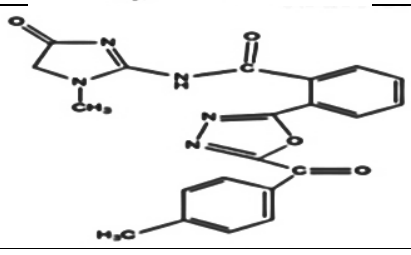
Table 4-Physical properties of prepared acidhydrazides

Comp. No	Structure	Molcul.Form.	Color	Yield %	m.p^{0}C
16		**C8H13N5O3 M.W 227.22**	**yellow**	**66**	**198-200**
17		**C8H11N5O3 M.W 225.21**	**Yellow**	**75**	**187-189**
18		**C12H13N5O3 M.W 275.27**	**Off white**	**80**	**210-212**
19		**C12H12N6O5 M.W 320.26**	**yellow**	**79**	**204-205**
20		**C9H15N5O3 M.W 241.25**	**Brown**	**77**	**170-172**

3.3- Synthesis of 1,3,4 –Oxadiazole Derivatives [20] .

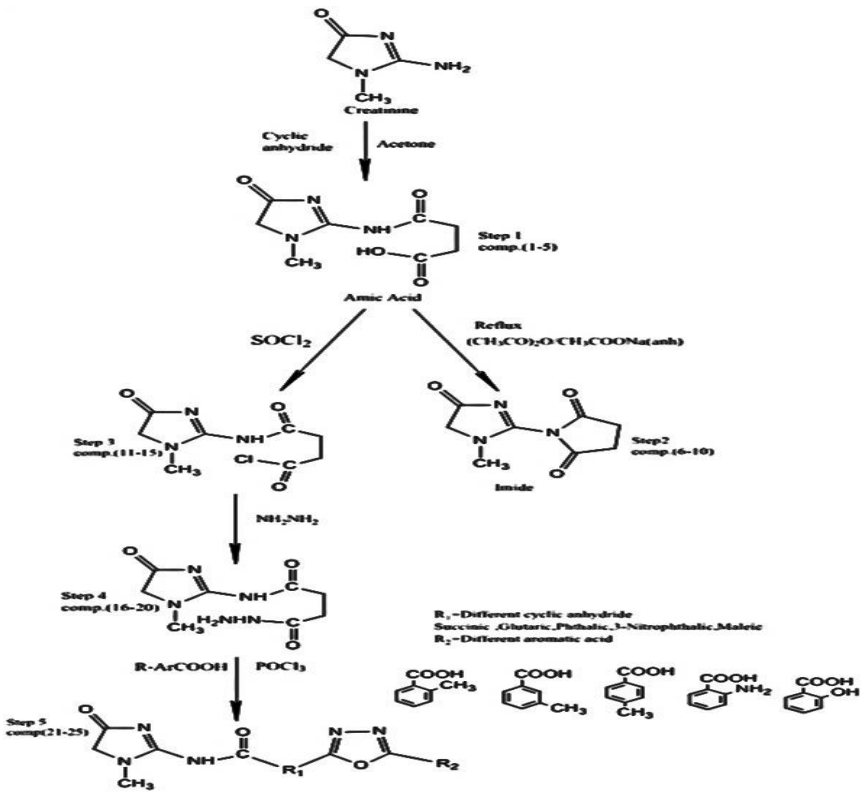
In (50) ml round bottom flask put an equimolar of acid hydrazide from step **(3.2)** (0.02 mole) with different aromatic carboxylic acids (0.001mole) were refluxed with phosphorous Oxychloride (5 volume with respect to the weight of five compound from (2.3 acid hydrazide). The was refluxed at 100 C^0 for 4 hrThe reaction completion was monitored by TLC. The reaction was cooled to room temperature and quenched with ice water and stirred for 1hr .the solid obtained was filtered and washed with water. And was dried to get product .physical properties are listed in table 5.

Table 5 - Physical properties of prepared 1,3,4-oxadiazole derivatives

Comp. No	Structure	Molcul.Form.	Color	Yield %	m.p^{0}C
21		**C17H17N5O4 M.W 355.35**	**White**	**88**	**204-206**
22		**C17H15N5O4 M.W 353.34**	**Off white**	**90**	**212-214**
23		**C17H17N5O5 M.W 371.35**	**White**	**83**	**235-234**
24		**C12H12N6O5 M.W 320.26**	**Yellow**	**79**	**204-205**
25		**C21H17N5O4 M.W 403.40**	**White**	**87**	**225-227**

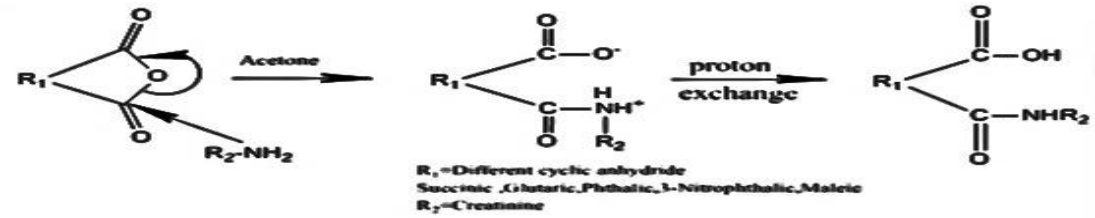
Result and dissection.

The novel 1,3,4-oxadiazole derivativewere synthesized according to Scheme -2-



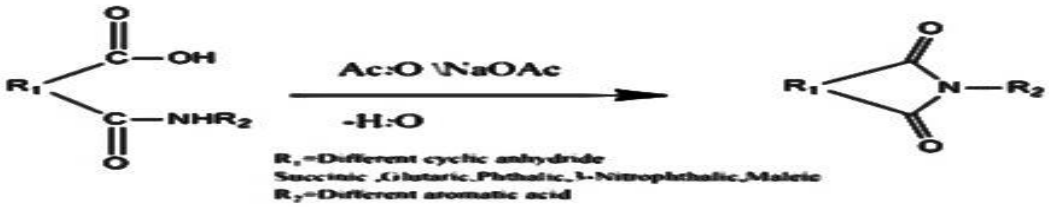
Scheme (2)-1,3,4-Oxadiazols synthesis steps

This research include five steps , the first step include preparation of amic acids, step **(1)** which synthesized by reaction of different cyclic anhydride with the (R-NH_2) of Creatinine in acetone as solvent. The mechanism involves nucleophilic addition reaction ,as following schem-3 :-



Scheme(3)-Mechanisim reaction to prepare amic acids

Then amic acid (1-5) converted to cyclic imide(6-10) by losing water molecule and we used for that (Acetic Anhydride & Anhydrous Sodium Acetate) as dehydrating agent, as following schem-4:-



Scheme (4)-prepare of cyclic imide

FT-IR spectra of Amic acid (1-5) figure-1, showed absorption band at (3483.44 cm^{-1} – 3375.43 cm^{-1}) due to υ(OH), 3271.27 cm^{-1} due to υ(N-H) band, and other absorption bands appeared at 2873.94 cm^{-1}, 1600.92 cm^{-1}, 1690.86 due to υ(C-H) aliphatic υ(C=O) ,υ(C=N).table 6.

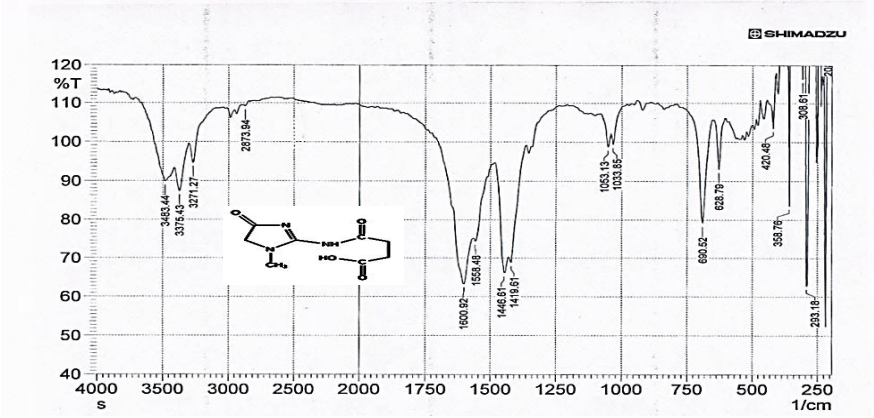


Figure 1- FTIR spectrum for comp.1

Table 6-FTIR spectral data of componds(1-5)

Comp No.	FT-IR spectral data cm^{-1} of comp.(1- 5)						
	υ(OH)	υ(N-H)	υ(C-H) Aliphatic	υ(C=O)	υ(C=N)	(C-N-C) Sy , Asy	(C-N-C) Structural
1	3483.44 cm^{-1}	3271.43 cm^{-1}	2873.94 cm^{-1}	1600.92 cm^{-1}	1558.48 cm^{-1}	1446.61 cm^{-1} 1419.61 cm^{-1}	1053.13 cm^{-1} 1033.85 cm^{-1}
2	3375.85 cm^{-1}	3272.68 cm^{-1}	2868.06 cm^{-1}	1610.87 cm^{-1}	1560.63 cm^{-1}	1442.78 cm^{-1} 1420.89 cm^{-1}	1060.15 cm^{-1} 1034.67 cm^{-1}
3	3377.14 cm^{-1}	3269.03 cm^{-1}	2877.79 cm^{-1}	1622.82 cm^{-1}	1554.77 cm^{-1}	1432.06 cm^{-1} 1415.25 cm^{-1}	1056.33 cm^{-1} 1050.98 cm^{-1}
4	3369.54 cm^{-1}	3270.66 cm^{-1}	2859.11 cm^{-1}	1645.00 cm^{-1}	1575.90 cm^{-1}	1429.00 cm^{-1} 1418.70 cm^{-1}	1044.90 cm^{-1} 1051.73 cm^{-1}
5	3374.89 cm^{-1}	3271.88 cm^{-1}	2866.09 cm^{-1}	1626.20 cm^{-1}	1571.01 cm^{-1}	1451.07 cm^{-1} 1412.80 cm^{-1}	1067.30 cm^{-1} 1056.81 cm^{-1}

FT-IR spectra of imides (6-10) figure-2, it's showed disappearance of (OH) carboxylic & (N-H) bands. With keeping other absorption band at 3047.53 cm^{-1} due to υ(C-H) aromatic. 2809.09cm^{-1} 1631.78 cm^{-1} 1612.49 cm^{-1}, 1330.88 cm^{-1} due to υ(C-H) aliphatic υ(C=O) ,υ(C=N), nitro group .table7.

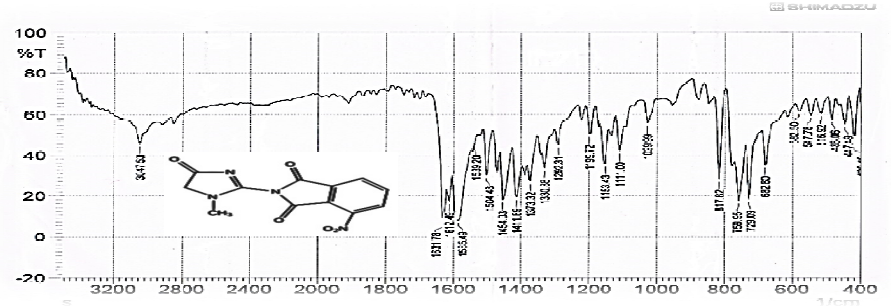


Figure 2-FTIR spectrum for (comp.9)

Table 7- FTIR spectral data of compounds (6-10)

CompNo	FT-IR spectral data cm^{-1} of compound (6-10)				
	υ(C-H) aromatic	υ(C-H) aliphatic	υ(C=O)	υ(C=N)	υ(C-N-C)
6	3047.53 cm^{-1}	2809.09cm^{-1}	1631.78 cm^{-1}	1612.49 cm^{-1}	1411.89cm^{-1}
7	3040.18 cm^{-1}	2823.22 cm^{-1}	1633.34 cm^{-1}	1620.01 cm^{-1}	1415.78 cm^{-1}
8	3020.33 cm^{-1}	2859.11 cm^{-1}	1640.02 cm^{-1}	1622.34 cm^{-1}	1420.05 cm^{-1}
9	3045.65 cm^{-1}	2870.54 cm^{-1}	1622.01 cm^{-1}	1610.26 cm^{-1}	1409.69 cm^{-1}
10	3022.11 cm^{-1}	2868.33 cm^{-1}	1635.12 cm^{-1}	1626.31 cm^{-1}	1412.55 cm^{-1}

The FT-IR spectra of(comp. 21-26)showed absorption band at(3224-3270)cm^{-1} due to υ(N-H)and 3097.98 cm^{-1} due to υ(C-H) aromatic , 2990.89 cm^{-1} due to υ(C-H) aliphatic, And other absorption band 1635.64 cm^{-1} , 1543.05 cm^{-1} due to υ(C=O) ,υ(C=N) The FT-IR spectra of(comp. 22) showed distinguish absorption at 1720 cm^{-1} 1627.92 cm^{-1} due to υ(C=O) imide , υ(C=N),as well as another band at 1612.49 cm^{-1}du to , υ(C=C) olefins bond Figure-3, .table8.

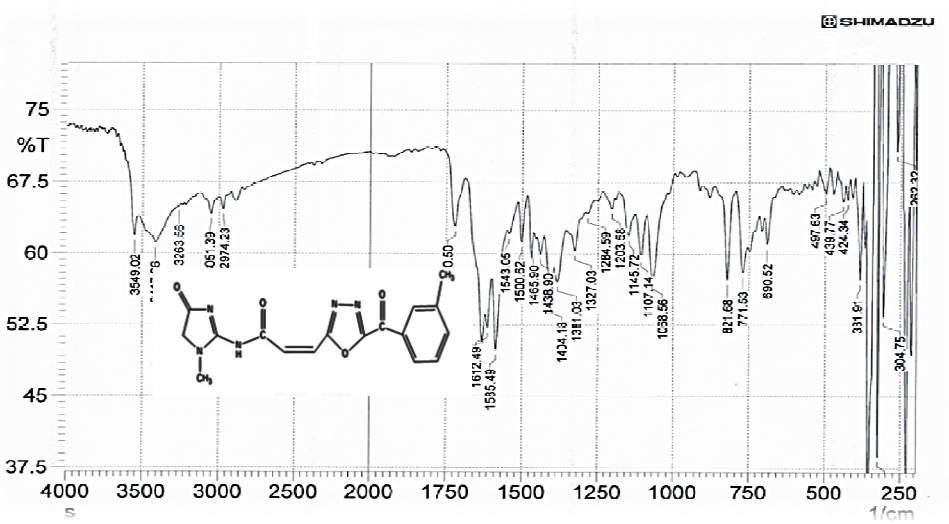
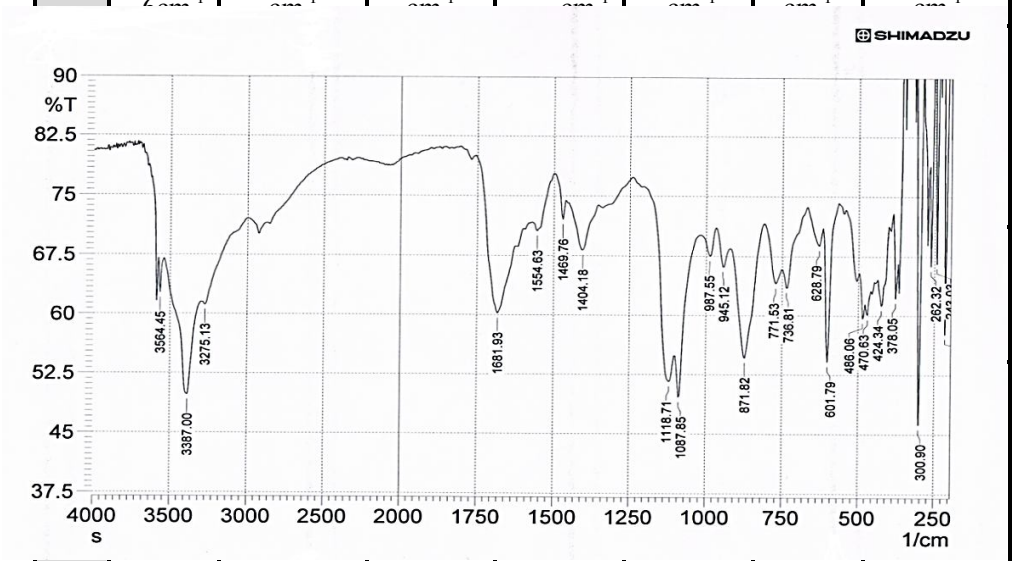


Figure 3-FTIR spectrum for (comp.22)

Table 8 -FTIR spectral data of compounds (21-25)

	υ(N-H)	υ(C-H) aromatic	υ(C-H) aliphatic	υ(C=O)	υ(C=N)	υ(C-N-C) Sym	υ(C-O-C) Asy	υ(C-O-C) υ(C-N-C) structural	
21	3224.9 cm^{-1}	3097.98 cm^{-1}	2990.89 cm^{-1}	1635.6 cm^{-1}	1543.05 cm^{-1}	1473.62 cm^{-1}	1415.75 cm^{-1}	1060.85cm^{-1}	
22	υ(N-H)	υ(C-H) aromatic	υ(C-H) aliphatic	υ(C=O)	υ(C=N)	υ(C-N-C) Sym	υ(C-O-C) Asy	υ(C-O-C) υ(C-N-C) structura	υ(C=C)

								l	
	3263.56cm^{-1}	3051.39 cm^{-1}	2974.23 cm^{-1}	1720 cm^{-1}	1627.92 cm^{-1}	1404.1 cm^{-1}	1381.03 cm^{-1}	1068.56 cm^{-1}	1612.09 cm^{-1}
								υ(C-O-C) Sym	υ(C-O-C) υ(C-N-C) structural
								1404.18 cm^{-1}	1118.71 cm^{-1}
								υ(C-O-C) Sym	υ(C-O-C) υ(C-N-C) structural
	3270.89 cm^{-1}	3051.39 cm^{-1}	2863.63 cm^{-1}	1724.36 cm^{-1}	1651.07 cm^{-1}	1612.09 cm^{-1}	1404.18 cm^{-1}	1327.03 cm^{-1}	1107.14 cm^{-1}
25	υ(NH_2) aromatic	υ(N-H) imide	υ(C-H) aliphatic	υ(C=O) carboxylic	(υ(C=O Imide	υ(C=N)	υ(C-N-C) Asy	υ(C-O-C) Sym	υ(C-O-C) υ(C-N-C) structural
	3414-4472 cm^{-1}	3265 cm^{-1}	2985.81 cm^{-1}	1700.09 cm^{-1}	1616.35 cm^{-1}	1593.20 cm^{-1}	1519.91 cm^{-1}	1404.18 cm^{-1}	1080.14 cm^{-1}

Another distinguish band was appear at FT-IR spectra of(comp. 23) at 3564 cm^{-1} due to phenolic υ(O-H), and 3275cm^{-1} due to υ(N-H), 3045.45 cm^{-1} , υ(C-H) aromatic, 2909.09 cm^{-} υ(C-H)aliphatic. And other absorption band 1681.93 cm^{-1} , 1554.63 cm^{-1} due to υ(C=O) , υ(C=N)Figure-4, table8.

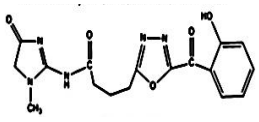


Figure 4-FTIR spectrum data of comp. 23

Where FT-IR spectra of (comp. 25)showed absorption 3414-3471 cm^{-1}due to υ(N-H_2)aromatic amine, 3236.55 cm^{-1} due to υ(N-H)imide , 3066.82 cm^{-1} due to υ(C-H) aromatic , 2985.81 cm^{-1} due toυ(C-H) aliphatic. And other absorption band 1700.09 cm^{-1} ,1616.35cm^{-1} due to υ(C=O) carboxylic ,υ(C=O) imide Figure-5 ,table 8.

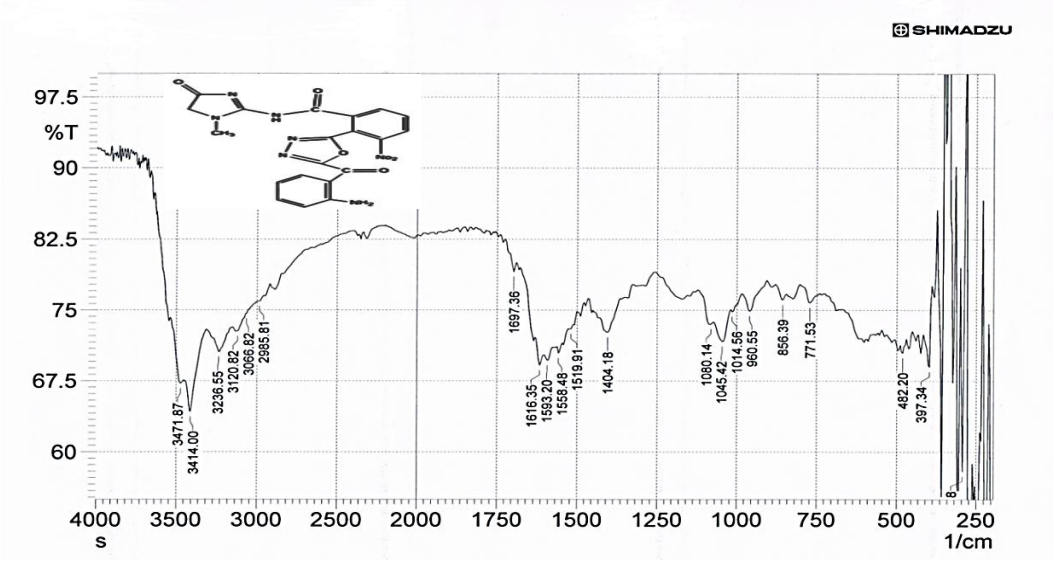


Fig5- FTIR spectrum data of (comp.25)

^{1}H-NMR spectrum of comp.(6-10) showed signal at δ: 1.05-1.07 (S, 2H, CH_2Creatinine)ppm. signal at δ: 1.8(S, 3H , CH_3-N)ppm, δ: 2.1 (S,4H,CH_2- Succinic) ,figure-6.

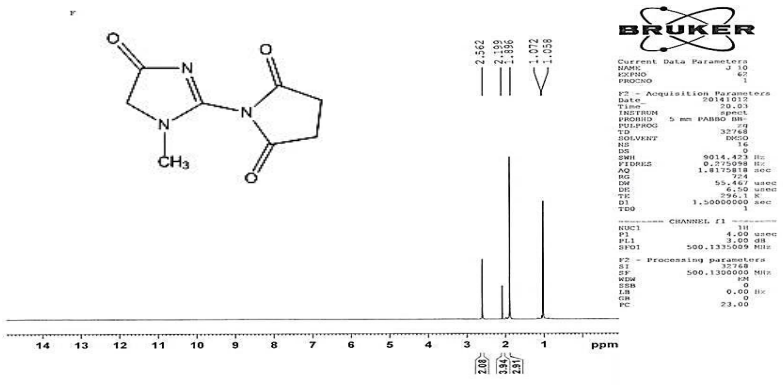


Figure 6 -^{1}H-NMR for the (comp. 6)

.^{1}H-NMRspectrum of (comp.21) showed signal at δ: 7.2-7.9 (m,4H, Aromatic)ppm, signal at δ:5.39 (S,1H, NH)ppm. And signal at δ:2.33-2.10 (S,2H, CH_2 Succinic)ppm ,signal at δ: 1.8(S,3H,CH_3-N)ppm signal at δ: 1.6 (S,3H,CH_3-Ph) ppm, signal at δ: 1.07-1.05(S,2H,CH_2Hetro) ,figure-7 .

^{1}H-NMRspectrum of (comp.22) showed signal at δ: 7.5-7.9 (m,4H, Aromatic)ppm, signal at δ:5.39 (S,1H, NH)ppm. And signal at δ:5.50 (S,1H,CH Succinic)ppm ,signal at δ: 1.8(S,3H,CH_3-Ph)ppm signal at δ: 1.6 (S,3H,CH_3-N) ppm, signal at δ: 1.07-1.05(S,2H,CH_2Hetro) ,figure-8 .

^{1}H-NMRspectrum of (comp.23) showed signal at δ: 7.3-8.2 (m,4H, Aromatic)ppm, signal at δ:5.32 (S,1H, NH)ppm. And signal at δ:4.2 (S,1H,OH Phenolic)ppm ,signal at δ: 2.7-2.1(S,2H,CH_2Glutaric) ppm ,signal at δ: 1.8 (S,3H,CH_3-N) ppm, signal at δ: 1.07-1.05(S,2H,CH_2Hetro) ,figure-9.

^{1}H-NMRspectrum of (comp.24) showed signal at δ: 7.5-8.04 (m,4H, Aromatic)ppm, signal at δ:5.39 (S,1H, NH)ppm. And signal at δ: 1.8(S,3H,CH_3-N)ppm signal at δ: 1.6 (S,3H,CH_3-Ph) ppm, signal at δ: 1.05(S,2H,CH_2Hetro), figure-10.

^{1}H-NMRspectrum of (comp.25) showed signal at δ: 7.5-8.07 (m,4H, Aromatic)ppm, signal at δ:5.7(S,2H,NH_2)ppm ,signal at δ:5.39(S,1H,NH)ppm ,signal at δ: 1.8(S,3H,CH_3-N)ppm, signal at δ:1.05(S,2H,CH_2Hetro), figure-11

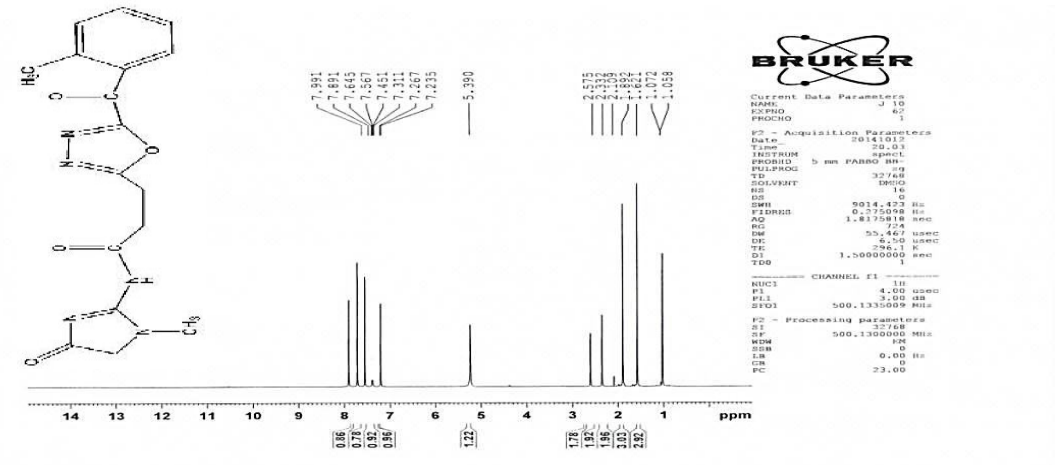


Figure7-[1]H-NMR for the (comp.21)

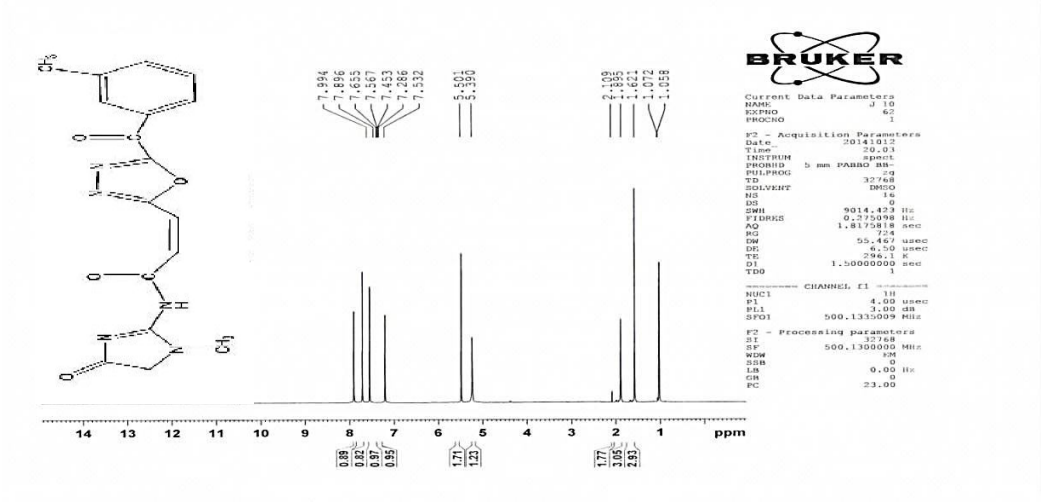


Figure 8-[1]H-NMR for the (comp.22)

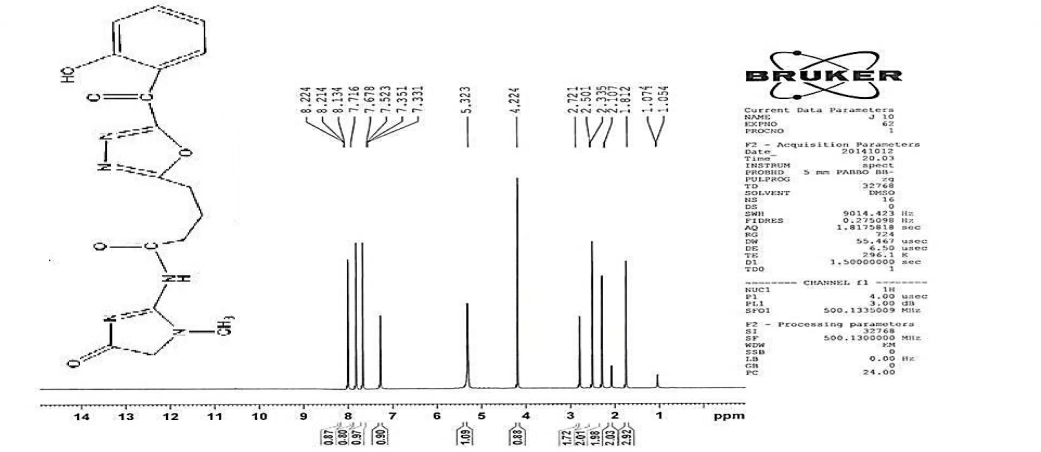


Figure 9-[1]H-NMR for the (comp.23)

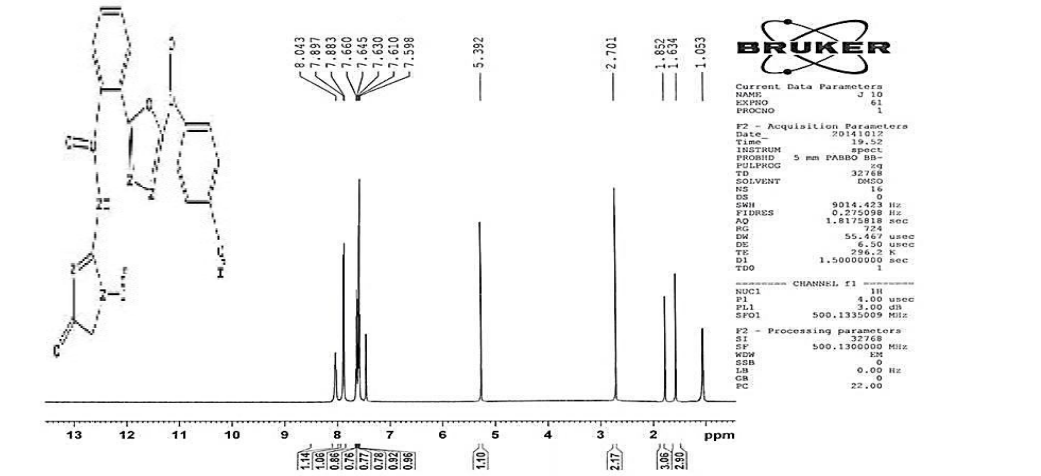


Fig . (10) ^{1}H-NMR for the comp. 2

Figure 10-^{1}H-NMR for the(comp.24)

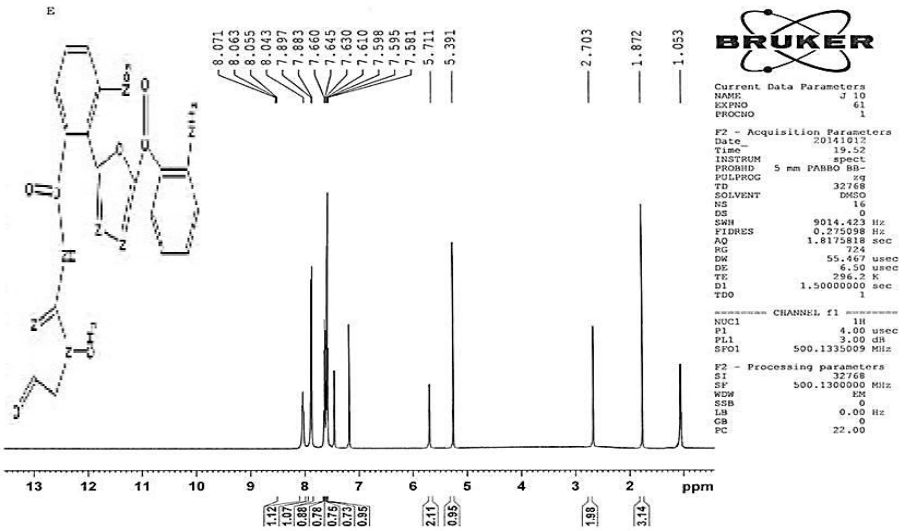


Figure 11-^{1}H-NMR for the (comp.25)

Mass spectral data for compounds (21-25) shown in table 9 ,figure-(12-16).

Table 9- mass spectral data of comp. (21-25)

Mass Spectral Data For Compounds (21-25)					
Comp .No.	21	22	23	24	25
Total MWt	$[C_{17}H_{17}N_5O_4]^{+\cdot}$ 355	$[C_{17}H_{15}N_5O_4]^{+\cdot}$ 353	$[C_{17}H_{17}N_5O_5]^{+\cdot}$ 371	$[C_{21}H_{17}N_5O_4]^{+\cdot}$ 403	$[C_{20}H_{15}N_7O_5]^{+\cdot}$ 449
Fragment 1	$[C_{16}H_{14}N_5O_4]^{+\cdot}$ 340	$[C_{16}H_{12}N_5O_4]^{+\cdot}$ 338	$[C_{16}H_{14}N_5O_4]^{+\cdot}$ 340	$[C_{21}H_{16}N_5O_4]^{+\cdot}$ 388	$[C_{20}H_{13}N_6O_5]^{+\cdot}$ 433
Fragment2	$[C_{10}H_{10}N_4O_3]^{+\cdot}$ 210	$[C_8H_8N_4O_3]^{+\cdot}$ 208	$[C_8H_{10}N_4O_3]^{+\cdot}$ 210	$[C_{13}H_{12}N_4O_3]^{+\cdot}$ 258	$[C_{12}H_9N_5O_5]^{+\cdot}$ 303
Fragment3	$[C_{10}H_7N_2O_2]^{+\cdot}$ 187	$[C_{10}H_7N_2O_2]^{+\cdot}$ 187	$[C_9H_9N_2O_3]^{+\cdot}$ 189	$[C_{11}H_{10}N_2O_3]^{+\cdot}$ 216	$[C_9H_9N_3O_2]^{+\cdot}$ 188
Fragment4	$[C_{10}H_{10}N_4O]^{+\cdot}$ 168	$[C_7H_8N_3O]^{+\cdot}$ 166	$[C_7H_{10}N_3O]^{+\cdot}$ 168	$[C_{10}H_7N_2O_2]^{+\cdot}$ 187	$[C_8H_8NO_2]^{+\cdot}$ 148
Fragment5	$[C_9H_7O_2]^{+\cdot}$ 147	$[C_9H_7O_2]^{+\cdot}$ 147	$[C_8H_5O_3]^{+\cdot}$ 149	$[C_9H_7O_2]^{+\cdot}$ 147	$[C_6H_6N]^{+\cdot}$ 92
Fragment6	$[C_7H_7]^{+\cdot}$ 91	$[C_7H_7]^{+\cdot}$ 91	$[C_8H_5]^{+\cdot}$ 93	$[C_7H_7]^{+\cdot}$ 91	$[C_6H_6N]^{+\cdot}$ 92
Fragment7	$[C_6H_4]^{+\cdot}$ 76	$[C_6H_4]^{+\cdot}$ 76	$[C_6H_4]^{+\cdot}$ 76	$[C_7H_7]^{+\cdot}$ 91	$[C_6H_4]^{+\cdot}$ 76
Fragment8	$[C_2N_2O]^{+\cdot}$ 68	$[C_2N_2O]^{+\cdot}$ 68	$[C_2N_2O]^{+\cdot}$ 68	$[C_6H_4]^{+\cdot}$ 76	$[C_2N_2O]^{+\cdot}$ 68
Fragment9	$[C_5H_4]^{+\cdot}$ 64	$[C_5H_4]^{+\cdot}$ 64	$[C_5H_4]^{+\cdot}$ 64	$[C_2N_2O]^{+\cdot}$ 68	$[C_5H_4]^{+\cdot}$ 64

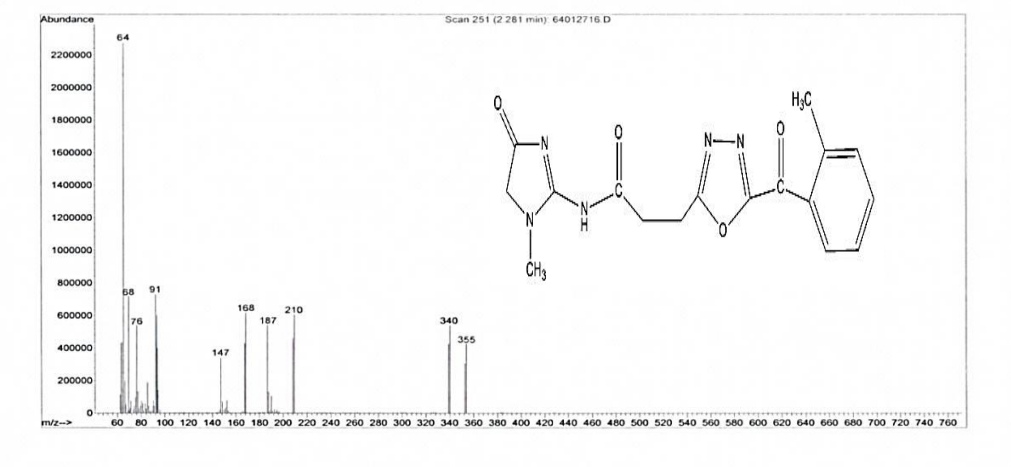


Figure 12-mass spectra of (comp.21)

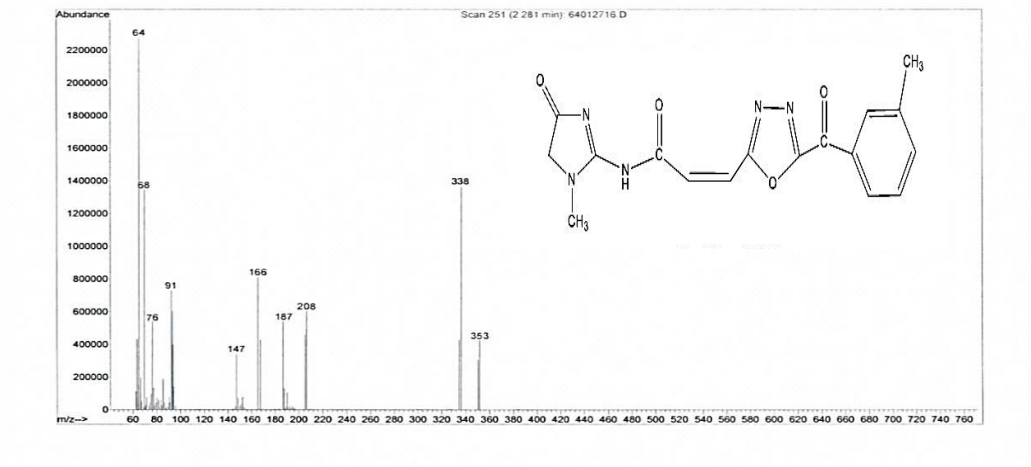


Figure 13-mass spectra of(comp.22)

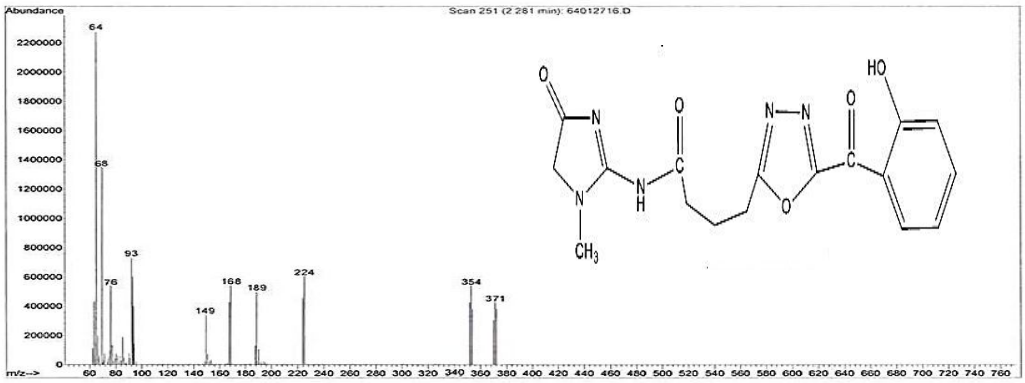


Figure 14-mass spectra of (comp.23)

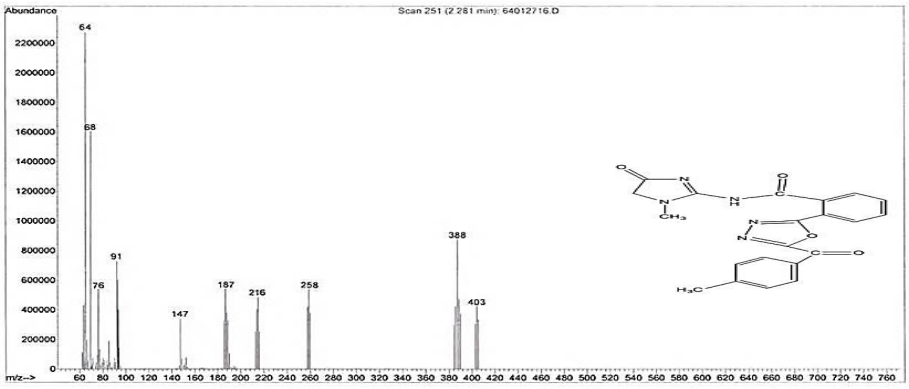


Figure 15- mass spectra of (comp. 24)

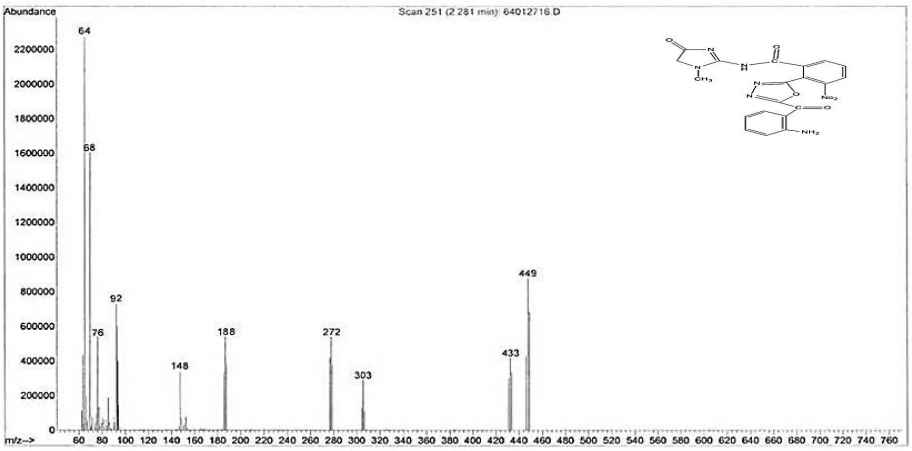


Figure 16-mass spectra of (comp. 25)

Where an example fragment scheme for compound 23 shown in fig.17

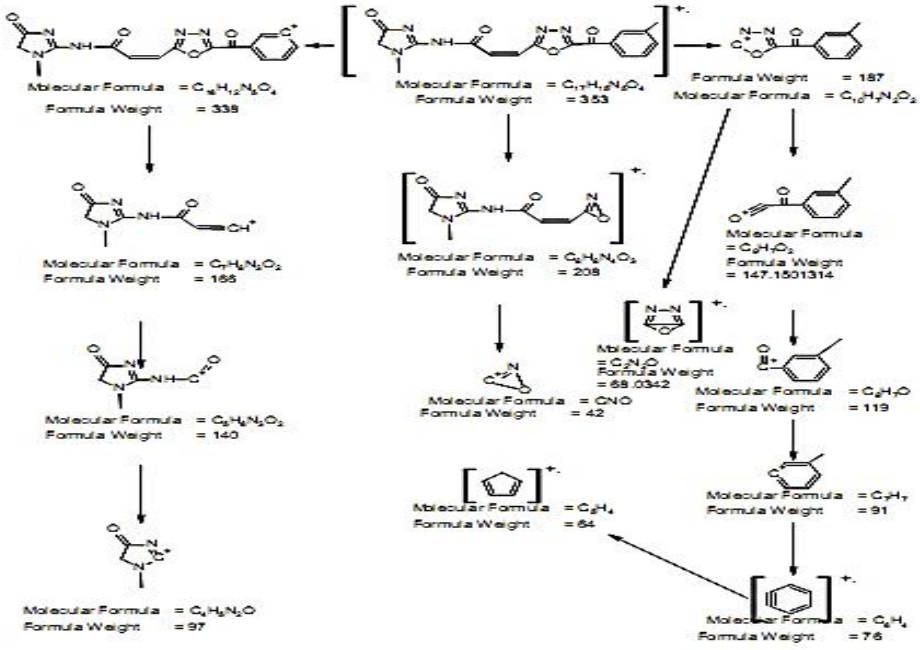


Figure 17-mass fragment of (comp. 22)

Antimicrobial Activity

Antimicrobial activity of 1,3,4-Oxadiazole derivative were studied with two types of pathogenic bacteria, which have been isolated from clinical isolates after diagnosis and demonstrate qualities and was subsequently the development of bacteria in the center of Mueller-Hinton Agar and degree of 37 C ° process and these pathogenic bacteria two categories. The first class was a positive for the bacteria dye Cram (Gram positive)1- .Staphylococcus Aureus.And second Class -negative bacteria to dye Cram (Gram negative)2- .Escherichia coli Positive results are obtained of those effective inhibitory compounds showed Direction bacteria under study, and compared the results of effectiveness with the antibiotic (Ciprofloxacin) known commercially (Siprodar) was our choice for this counter, because it is one of the life of antibiotics that affect the cell wall. Table10.

Table 10-antimicrobial activity of 1,2,4-oxadiazoles derivatives

Compound Number	*Escherichia coli* *Gram negative bacteria*	*Staphylococcus Aureus* *Gram positive bacteri*
	Inhibition zone(mm)	Inhibition zone(mm)
21	++	+++
22	++	++>
23	+++	+++>
24	+++	+++>
25	++++	++++

Key to symbols = Inactive = (-) inhibition Zone < 6 mm
Slightly active = (+) = inhibition Zone 6-9 mm
Moderately active = (++) inhibition Zone 9-12 mm
Highly active = (+++) inhibition Zone 13-17 mm
Very high activity = (++++) inhibition Zone > 17 mm

References

1.Basavapatna, N. Prasanna K, Kikkeri N., Lingappa M., and Kikkeri P. H.**, 2013,**synthesis &in vitro antimicrobial evaluation of new 1,3,4-oxadiazole bearing 5-chloro-2-methoxyphenyl moiety. *International journal of medicinal chemistry,* Vol(2013),pp:1-6

2.Srivastav, S.P. ,S.N.**2011.**various approaches for synthesis of oxadiazole derivative . *International journal of Research in Ayurveda& Pharmacy*,2(2) ,pp:459-468.

3.Vinay, K.,Sahu R., Arvind K. S., Deepmaz Y.**2011**. Review article on 1, 3, 4-Oxadiazolederivatives and it's Pharmacological activities.*International Journal of ChemTechResearch* ,3(3), pp:1362-1372.

4.Al-Azawi, A. M., Ahmed S.H., **2010**, Synthesis and evaluation of Biological activity of new cyclic Imides derived from 4-amino phenazone.*Journal of KerbalaUniversity(*Scientific *)* ,8 (1),,pp:387-402.

5.Al-Azzawi, A. M. and Hamd , A. S.**2011**.Synthesis, Characterization and Evaluation of Biological Activity of Novel Cyclic Imides Containing Heterocycles Based on 2,5disubstituted-1,3,4 thiadiazoles**.***Al-Anbar J. Vet. Sci* ,4 (2), pp:152-164

6.Rashidi, N.A. ,Berad B.N **.2013.**Synthesis of some Novel 1,3,4-Oxadiazole derivatives. *Research Journal of Recent Sciences, 2*, pp: 2277-2502.

7.Suaad, M. H. and Zahraa S. S. **2013.**Synthesis and Characterization of Some New 1,2,3-Triazole, Amic Acids, Imides, and Isoimides from Ethyl-p-aminobenzoate and -Study Their Biological Activity.*Journal of Al-Nahrain University ,16 (2)*, pp:59-69.

8.Khan, M.S.Y &Akhtar M.**2003**. synthesis of new 2,5-disubstituted 1,3,4-oxadiazole derivatives and their biological activity .*Indian journal of chemistry ,* 42B(l), pp: 900-904 .

9.Rana, A. A.**2011.** Synthesis of New Schiff's Bases Derived from 4-PhthalimidylAcetophenone. *Journal of Al-Nahrain University,* 14 (3), pp:1-8.

10. Bachwani, M., Sharma V.**2011**.Antimicrobial activities of 1,3,4-oxadiazole :A review . *International journal of Research in Ayurveda& Pharmacy,* 2(6),pp:1738-1742 .

11. Pyridi, T.M., and AL-Majidi S. M. H. **2006**. Modification of poly[styrene-co-Butadiene] rubber to polymer containing pendant amic acid, isoimide and imide isomerization of the polymer containing isoimide to the corresponding imide.*J. Um-salama, Sci*., 3(4), pp:656-669

12. Ali, E. T. ,Lazim K. M. and Tomma J. H.**2011**. Synthesis and Characterization of New Symmetrical Pyromellitdiimide Derivatives and Their Amic Acids, *Ibn al- Haitham j. for pure & appl. sci., 24* (3),PP: 1-12

13. Anil, N. M., Hemmige S. Y., Narayana B., .Sarojini B. K, Kumari N. S. **2010.** Synthesis and Antimicrobial Studies on New Substituted 1,3,4-OxadiazoleDerivatives Bearing 6-Bromonaphthalene Moiety ,*international journal of chemistry ,* 2 (1).pp:38-43 .

14. Rakesh, C., Anshu A., Manoj K. P.,Prabodh C., Der S., Sukumar M. **2010**. Synthesis of novel 1,3,4-oxadiazole derivatives as potential antimicrobial agents, *Acta Pol Pharm*. 67(3):pp247-253.

15. Pyriadi, T. M., Al-Azzawi, A. M. & Al-Obaidi, K. K. **2009**. Synthesis, characterization and polymerization of N-substituted maleimidyl acrylates. *J. Al-NahrainUniversity ,Sci.,* 12(2),pp: 1-14

16.Al-Azzawi, A. M. & Hassan, A. S. **2010.** Synthesis and evaluation of biological activity of new cyclic imides derived from 4-amino phenazone. *J. of Kerbala University*,8(1)pp: 387-402

17.Borchhardt, D. M. &Andricopulo, A. D. **2009**. CoMFA and CoMSIA 3D QSAR models for a series of cyclic Imides with analgesic activity.*Med.Chem.,5,pp: 66-73*.

18. Ivan, H.R.,Tomi ,Alaa H.J. Al-Qaisi , Zyad H.J. Al-Qaisi**.2010**. Synthesis, characterization and effect of bis-1,3,4-oxadiazole rings containing glycine moiety onthe activity of some transferase enzymes . *Journal of King Saud University (Science)* ,23,pp: 23–33.

19. Chava, A. A. &Pai, N. R. **2007**. Synthesis and biological activity of N-substituted -3-chioro-2-azetdines.*Molecules,* 12,pp: 2467-2477.

20. Katritzky, A. R.; Wang, Z. &Offerman, R. J. **1990**. S,S'- and *S,N*-di-substituted derivatives of 1,3,4-thiadiazoledithiones. *J. Heterocyclic Chem*., 27:pp139-142.