Synthesis some of heterocyclic Compounds of Meldrum's Acid and study of The biological Activity

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ABSTRACT
This paper involves synthesis of some heterocyclic compound derivative from Meldrum's acid ,by reaction of Meldrum's acid , indol and p-hydroxy benzaldehyde and catalyst L-proline in acetonitrile to produce Meldrum's acid derivative (P),compound (P) ethanolysis to give ester derivative (P_1),the compound (P_1) reacted with hydrazine hydrate to give hydrazide derivative compound (P_2) ,hydrazide derivative reacted with p-hydroxy benzaldehyde in absolute ethanol to give Schiff base derivative(P_3), Schiff base derivative using to prepare some new heterocyclic compounds by multi step reactions and reactant with different solvent and materials to prepare four ,five and seven ring membered . The prepared compounds were characterized by FT-IR ,H^1NMR,^{13}CNMR .All the prepared compounds were studied the antibacterial activity .
Keywords : indo , comp , character .

I.INTRODUCTION

2,2-dimethyl -4,6-dioxo-1,3-dioxane or Meldrum's acid fig.(1),The structural simplicity of Meldrum's combined with is unique properties has made this a versatile reagent inorganic synthesis[1] , Meldrum's acid is a loftily interesting sort of compounds biological and pharmaceutical properties [2] . The C (5) position of MA supplies an improved and metal-free approach to construct C-C linkages in organic molecules. The unusually high acidity (pKa of 4.83-4.936 in H_2O) of active methylene in MA at C (5) supplies direct access to the formation of a C-C framework[3]. Multicomponent reaction is a one-step reaction that joins two or reactants to form an end product[4],MCRs have been used as a multilateral synthetic method for the synthesis of complex molecules[5] .Indol is one of the most many –sides heterocyclic nuclei ,specific as a pharmacophore in a large number of natural and synthetic biologically active molecules[6],indole nucleus are formed interesting plants[7].Some indol derivatives has been found with broad spectrum of antimicrobial activity [8].

II.MATERIALS AND METHODS

The chemicals compounds have high purity as supplied by sigma and GCC company, Melting point of the compounds recorded by electro thermal 9300,melting point engineering LTD ,All measurements synthesis compounds were recorded by :FTIR spectra ,fourier transform infrared shimadzu(8400),H^1NMR and C^1NMR –spectra in (ppm) in DMSO solvent by AVANCE AQS-300MH_Z ,Iran, Thin layer chromatography used silica gel in (Benzene :methanol) solvent.

Experimental

Synthesis of the compound (P)

By reaction between of indol (1.17gm.0.01 mol) in CH3CN (10)ml ,Meldrum's acid[9](1.14 gm ,0.01ml) ,p-hydroxy benzaldehyde (1.22gm,0.01mol) and L-proline (0.06gm ,0.0005mol), The mixture was stirred at 25-30C^0 for 47 hours ,The product was dissolved in absolute ethanol and recrystallized.

Synthesis of ester derivative of compound (P_1)

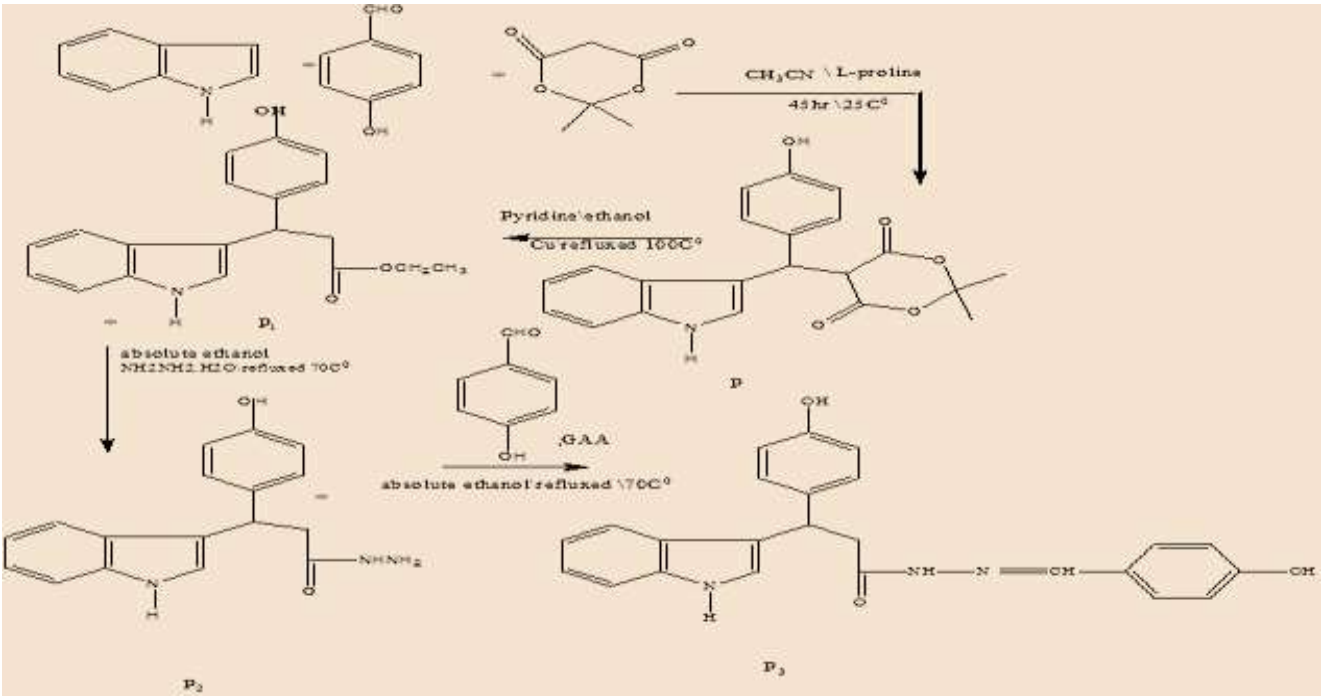
The compound derivative was prepared by mixture of the Meldrum's acid derivative (1equiv) and copper (0.2equiv) was dissolved using a mixture of (10:1) pyridine \ethanol (0.1m) solution[10], The mixture was refluxed to 100C^0 for 3 hours. Removal of the cu powder the product was recrystallized from ethyl acetate \ n-hexane.

Synthesis of hydrazide[11] derivative of compound(P_2)

The compound derivative (P_2) (1 gm ,0.01mol) reacted with hydrazine hydrate (0.5 gm,0.01mol) in absolute ethanol. the mixture was heated and stirred under refluxed to 78 C^0 for 21 hours ,the product recrystallized from ethanol absolute .

Synthesis of Schiff base derivative[12] of compound (P_3)

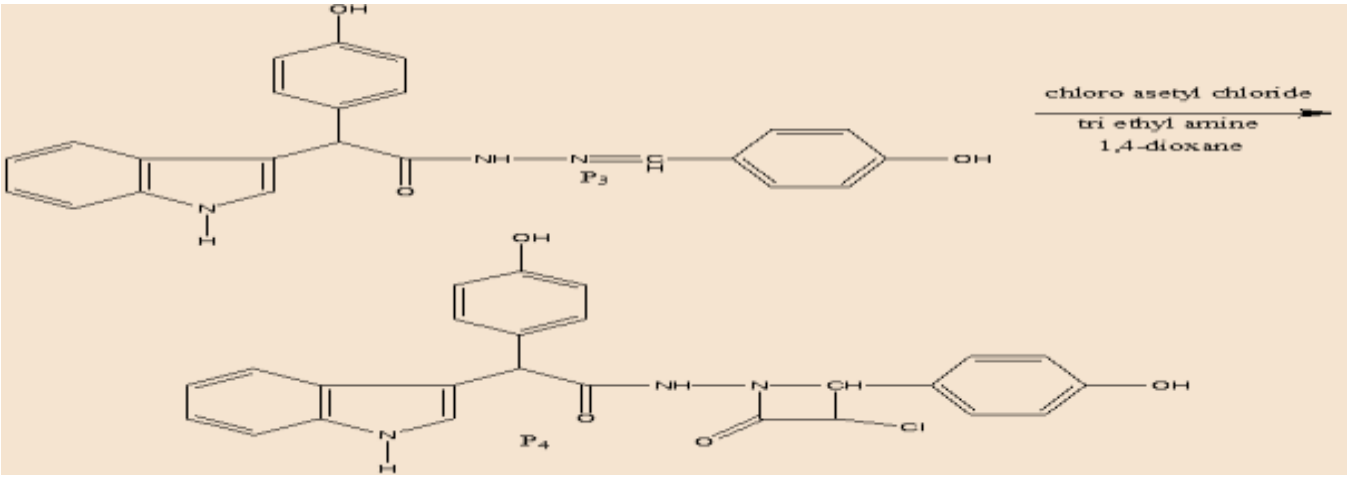
Schiff base compound was prepared by reaction between p-hydroxy benzaldehyde (0.3 gm,0.002 mol) and hydrazide compound (S_2) (0.6gm,0.002) as catalyst in the glacial acetic acid 2-3 drops, The mixture was heated under refluxed to 78C^0 for 15 hours to produce compound(P_3) which recrystallized from ethanol.



Scheme (1): synthesis of compounds (P to P_3)

Synthesis of β-lactam derivative[13] (P_4)

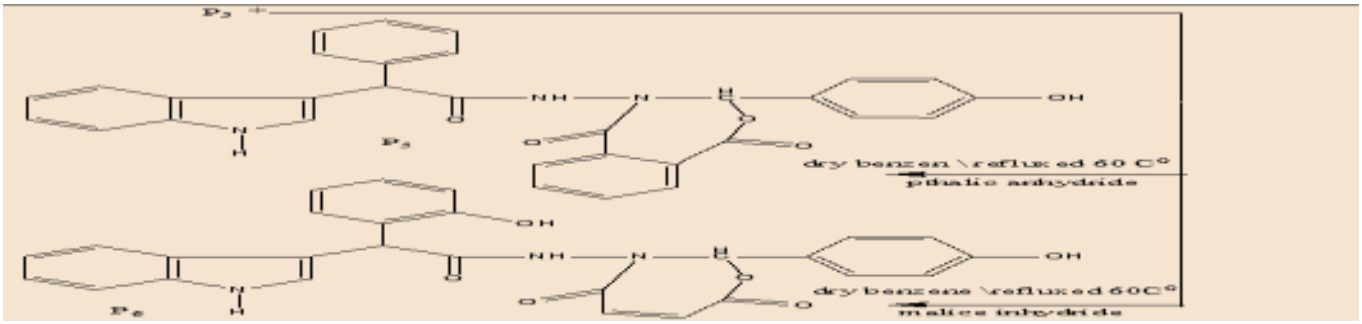
The compound (P_4) was prepared by reaction between the compoundP_4 (0.001 mol ,0.5 gm) and tri ethyl amine(0.001 mol) and chloro acetyl chloride (0.001) in 1,4-dioxane ,The mixture was stirred at1(15-20)C^0 for 20 hours,to produce the compound P_4 , The products ,which crystallized from absolute ethanol.



Scheme (2): synthesis of the compound (P_4)

Synthesis of the oxazepine derivatives[14] (P_5 ,P_6).

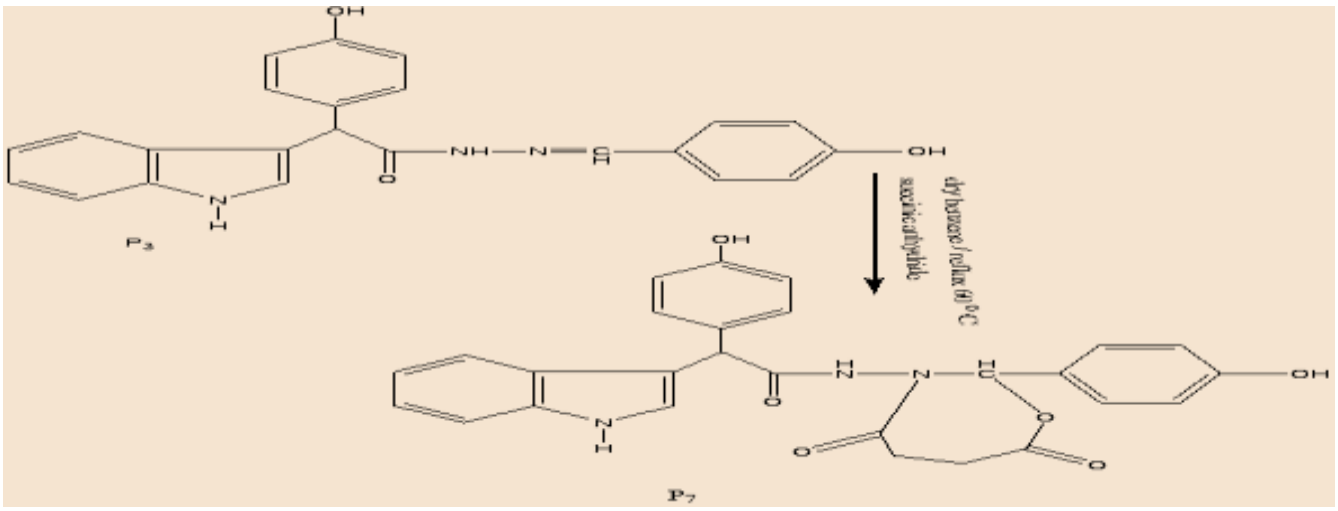
The compounds (P_5-P_7) were prepared by reaction between Schiff base derivative (P_3) (0.01 mol) with(0.01 mol) for (phthalic and malice), anhydride respectively in the dry benzene the mixture were refluxed at 60 C^0 for 30 hours, Scheme (3).



Scheme (3): synthesis of the compounds (P_5,P_7)

Synthesis of oxazepane derivative (P_7)[15]

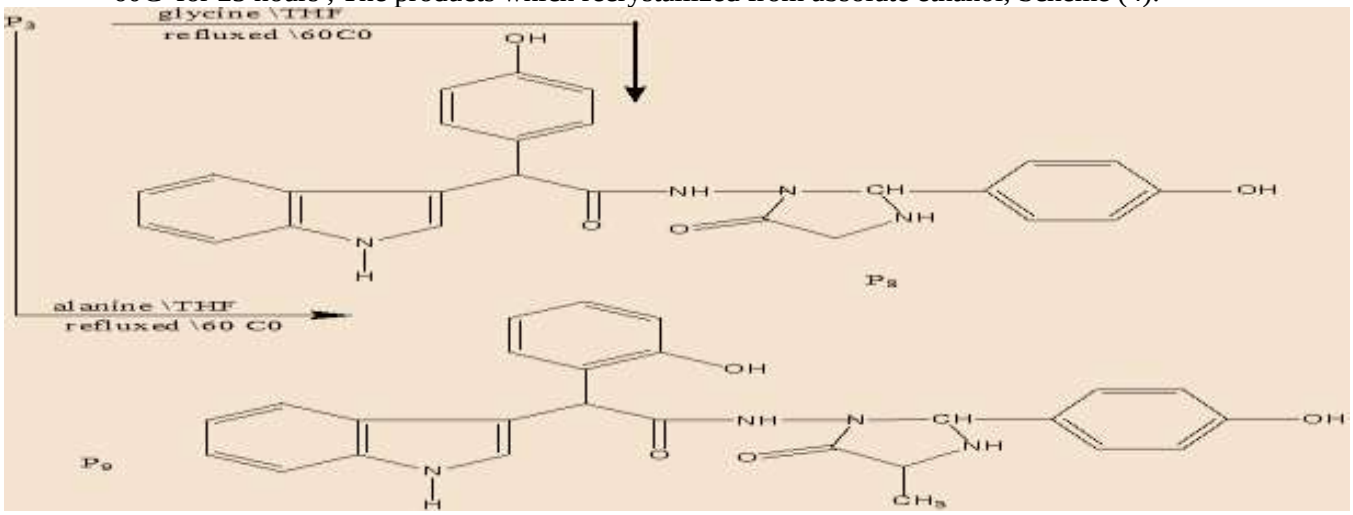
A compound of Schiff base derivatives(P_3) (0.01 mol) and succinic anhydride (2mol) were dissolved in dry benzene (20ml) under reflux in oil bath 60^0C. A precipitate was formed. That are filtered under cool condition to afford oxazepane and recrystallization of the product take place by ethanol.



Scheme (3): synthesis of the compound(P_7)

Synthesis of the compounds (P_8,P_9)[16]

The compounds (P_8-P_9) were prepared by the reaction between Schiff base derivative compound P_3 (0.01mol) with amino acid (glycine and alanine) (0.01 mol) respectively in tetra hydro furan and the mixture was refluxed at $60C^0$ for 25 hours , The products which recrystallized from absolute ethanol, Scheme (4).



Scheme (4): synthesis of compounds (P_8 ,P_9)

2-4 Study of the biological activity of the compound by paper technique disks[17].

Antibacterial activity was measured by using filtering paper type (whiteman NO.1) to prepared (120) pills after purification, after that ,the pills put in the test tube average (5) pills for every tube and added (1 mml) from syntheses compounds solution .were used weight of (5mg,10 mg,20mg) from the synthesis compounds.

III. RESULTS AND DISCCUSION

P : 5- [(4-hydroxy –phenyl) –(1H-indol-3-yl) methyl)] 2,2-dimethyl –[1,3] dioxane -4,6-dione , M.P(92-94) C^0 ,yield % 77,FT-IR(KBr) cm^{-1} ν3414 (OH) , ν 3200 (NH_{indol}), ν3057 ($CH_{aromatic}$) , ν2935-2806($CH_{aliphatic}$), ν1749,1687(C=O) $_{ester}$, ν 1298(C-O).

P_1 : Ethyl- 3-(1H-indol -3-yl)-3-(4-hydroxy phenyl) propanoate,M.P(93-95)C^0,yield % 77, FT-IR(KBr)cm^{-1}, ν3433(OH) , ν 3226(NH_{indol}) ν3064 ($CH_{aromatic}$) , ν2926-2856($CH_{aliphatic}$), ν 1732 (C=O,ester), ν1564-1602(C=C)$_{aromatic}$, ν1280(C-O),^{1}H-NMR(DMSO), δ11.1(s,1H) ,OH $_{phenol}$ 10.3 (s,1H),NH_{indol}, δ 6.8-7.7(m,aromatic ring), δ3.576-3.542(m,CH_2O)$_{ester}$,1.9(d,2H) , δ 1.1(T,3H)$_{ester}$^{1}CNMR(DMSO), δ174C for(C=O) $_{ester}$, δ156C for $(OH)_{phenol}$, δ116-142 C for aromatic ring , δ15 C for($CH_3)_{ester}$[18] , δ 60 C for $(CH_2)_{ester}$. ,

P_2 : 3-(4-hydroxy phenyl)-3-(1H-indol -3-yl)propionic acid hydrazide,M.P(188-190)C^0,yield % 82, FT-IR(KBr)cm^{-1},3454,3425(NH_2), ν3332(NH_{amide}) ν1641(C=ONH), ν1618-1529(C=C)$_{aromatic}$, ^{1}H-NMR(DMSO) , δ 11.7(s,OH), δ 10.2(s,NH_{indol}), δ 9.2(s,1H,C=ONH)[19], 6.3(s,2H,NH2) $_{amide}$, δ6.9-7.7(m, aromatic ring) ^{1}CNMR(DMSO), δ170 C for $(C=O)_{amide}$, δ 125-133 C for aromatic ring .

P_3 : 3-(4-Hydroxy-phenyl)-3-(1H-indol-3-yl)-propionic acid (4-hydroxy-benzylidene)-hydrazide,M.P(223-225)C^0 ,yield %76 , FT-IR(KBr) cm^{-1} ,ν3448(OH), ν 3423 (NH_{amide}),ν3077($CH_{aromatic}$) , ν2995-2850($CH_{aliphatic}$), ν1640(C=ONH $_{amide}$), ν1624($C=N_{schiff\ base}$)[20],ν1589(C=C)$_{aromatic}$,^{1}H-NMR(DMSO), δ11.7(s,OH), δ8.6 (s,1H,N=CH)$_{shiff\ base}$, ^{1}CNMR(DMSO), δ171 C for $(C=O)_{amide}$, δ158 C for $(C=N)_{imine}$, δ155 C for (OH) δ 126-142 C for aromatic ring.

P_4 :N-[3-chloro -2-(4-hydroxy –phenyl)-4-oxo –azetidine -1-yl] -3-(4-hydroxy phenyl)3-(1H-indol-3 yl)-propionamide,M.P(250-253)C^0 ,Yield 76% FT-IR(KBr) cm^{-1} ν3448-3421, (OH), ν 3082(NH_{indol}), ν 3062($CH_{aromatic}$) , 1674(C=O)$_{Lactum}$,1620-1573 (C=C)$_{aromatic}$, ν 800-600(C-Cl), ^{1}H-NMR(DMSO), δ11.7(s,1H,OH) δ8.8-8.9(d,1H,N-CH)$_{lactam\ ring}$, δ 6.9-7.9 (m,aromatic ring) , δ3.4 (s,1H,CHCl), ^{1}CNMR(DMSO), δ185Cfor (C=O)$_{Lactam\ ring}$, δ 171C for $(C=O)_{amide}$, δ 159C for(N-CH)$_{lactam\ ring}$ δ 154 C for (C-OH)$_{phenol\ ring}$, δ116-133Cfor Aromatic ring , δ43C for (C-Cl).

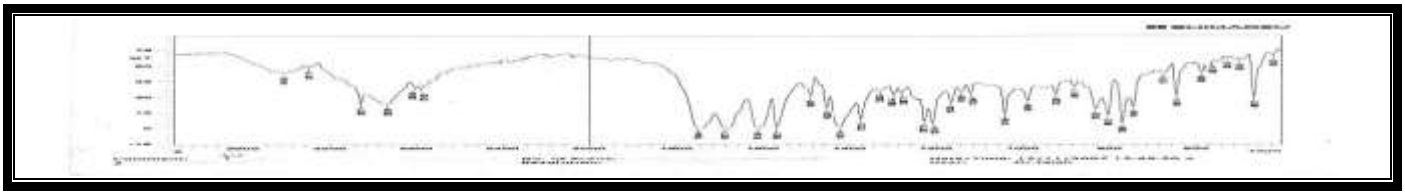
P_5: 3-(4-hydroxy –phenyl) - N-[7-(4-hydroxy –phenyl)-5-9-dioxo -5,9 dihydro -6-oxa –benzene cyclohepten -8-yl] -3- (1H-indol -3-yl)-3- phenyl –propionamide , M.P(318-320)C^0 ,Yield %80 , FT-IR(KBr) cm,ν 3410 (OH), ν1724 (O-C=O)lacton,ν1662(N-C=O)lactam,ν1643(N-C=O) ,ν1600(C=C)$_{aromatic}$,^{1}H-NMR(DMSO), δ11.4(s,1H,OH), δ10.1(sm1H,NH)$_{indol}$, δ 9.3(s,1H,NH)$_{amide}$, δ8.9(s,1H,N-CH)$_{oxazepine\ ring}$, δ7.4-7.8(m, aromatic ring), ^{13}CNMR(DMSO), δ179,174 C for C=O lactone and lactam respectively , δ158 C for (N-CH) $_{ring\ oxazepine}$, δ125-133 C for aromatic ring

P_6: N-[2 –(2-hydroxy –phenyl) 4,7-dioxo -4,7-dihydro -[1,3] oxazepane -3-yl-(1H-indol-3-yl)-3-phenyl –propionamide, M.P(304-306)C^0 ,Yield%83, FT-IR(KBr) cm,ν3404(OH), ν1724(O-C=O)lacton,ν1710(N-C=O)lactam,ν1622 (C=C)$_{alkene,}$ ν (C=C)$_{aromatic}$, ^{1}H-NMR(DMSO), δ11.7 (s,1H,OH), δ 10.1 (s,1H,NH)$_{indol}$, δ6.9-6.92 (d ,CH=CH)$_{alkene}$[21], δ 7-8.1(m ,aromatic ring). ^{1}CNMR(DMSO), δ 179,173 C for (C=O) lactone and lactam respectively , δ160 C for (C=O) $_{amide}$, δ 33,26 C for C CH_2C=O,CH_2O, δ125-133(aromatic ring).

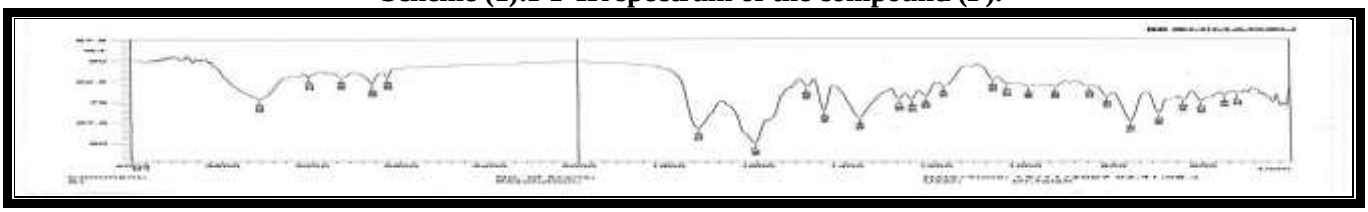
P_7 : 3-(4-hydroxy phenyl)- N-[2 –(4-hydroxy –phenyl) 4,7-dioxo -4,7-dihydro -[1,3] oxazepene -3-yl-(1H-indol-3-yl)-3-phenyl –propionamide, M.P (377-379) ^{0} C, Yield % 83 FT-IR(KBr)cm^{-1},ν3429 (OH), ν 3226(NH_{amide}), ν3059($CH_{aromatic}$), ν1695(O-C=O)lacton,ν1670(N-C=O)lactam ^{1} ,H-NMR(DMSO), δ11.5 (s,1H,OH) , δ 10.00(s,1H,N H)$_{indol}$, δ8.5, δ 1.8,1.2 (s,2H) for lactone and lactam respectively, (1H,N-CH) , ^{1}CNMR(DMSO), δ 179,173 C for (C=O) lactone and lactam respectively , δ160 C for (C=O) $_{amide}$, δ 33,26 C for C CH_2C=O,CH_2O, δ125-133(aromatic ring).

P_8: 3-(4-Hydroxy-phenyl)-N-[2-(4-hydroxy-phenyl)-5-oxo-imidazolidin-1-yl]-3-(1H-indol-3-yl)-propionamide ,M.P(355-357)^0 C ,Yield %78 ,FT-IR(KBr)cm^{-1} , ν3408(OH), 3330 $(NH)_{Imidazolidine}$, ν1726(C=O)$_{Imidazolidine}$, ν1662(C=O) amide H-NMR(DMSO), δ11.7(s,1H,OH), δ 9.9 (s,1H,NH)$_{Imidazolidine}$, δ6.4 (s,2H, CH2)$_{Imidazolidine}$,7.2-8(m ,aromatic ring) ,^{13}CNMR(DMSO), δ 177C for (C=O) $_{Imidazolidine\ ring}$, δ 160(N-CH), δ 107-137(aromatic ring) , δ148C for (C-OH), δ54 C for (CH_2).

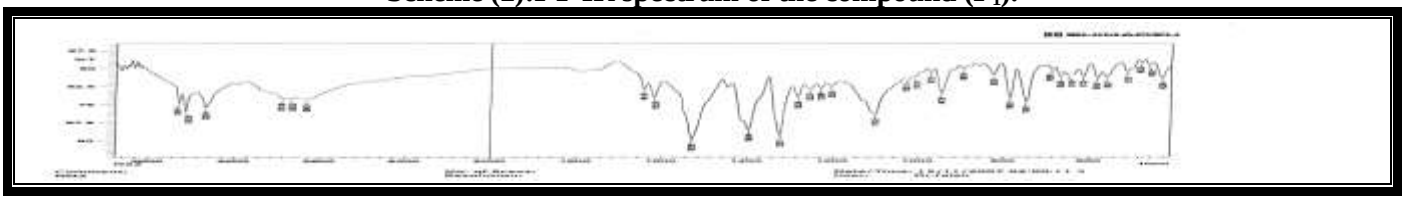
P_9 : 3-(4-Hydroxy-phenyl)-N-[2-(4-hydroxy-phenyl)-4-methyl-5-oxo-imidazolidin-1-yl]-3-(1H-indol-3-yl)-propionamide,M.P(370-372) C,Yield %85, FT-IR(KBr)cm^{-1},ν3415,(OH), ν 3202 (NH $_{Imidazolidine}$ ν3024 ,ν1639(C=O)$_{amide}$, ^{1}H-NMR(DMSO), δ8.9 ($CH_{aromatic}$),ν2916-2851 ($CH_{aliphatic}$) ,ν1676(C=O)$_{Imidazolidine}$ (1H,NH)$_{Imidazolidine}$ δ8.1(s,1H,N-CH), ^{13}CNMR(DMSO) , δ 176 C for (C=O) $_{Imidazolidine\ ring}$,163C for (C=O) (N-CH).



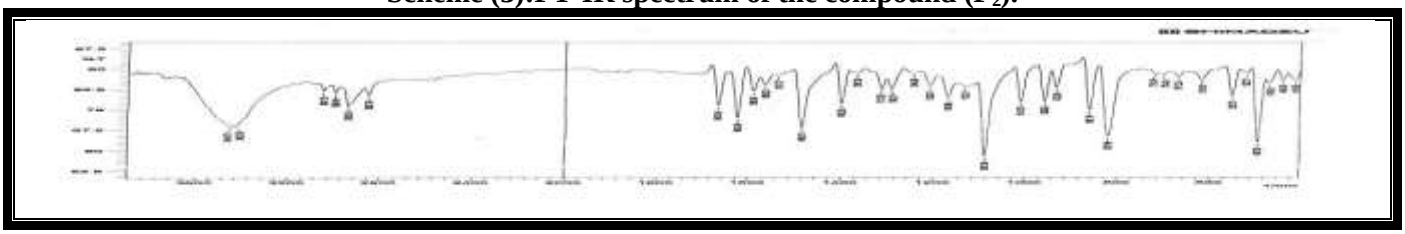
Scheme (1):FT-IR spectrum of the compound (P).



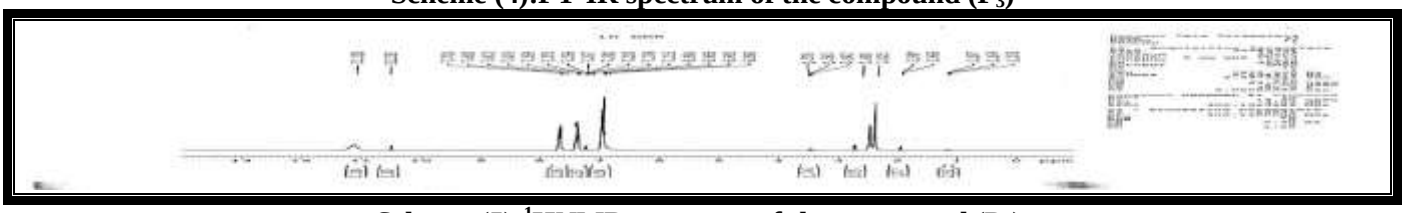
Scheme (2):FT-IR spectrum of the compound (P_1).



Scheme (3):FT-IR spectrum of the compound (P_2).

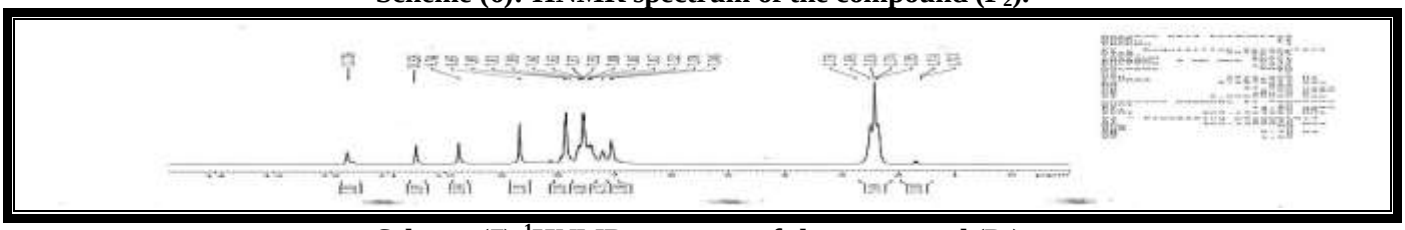


Scheme (4):FT-IR spectrum of the compound (P_3)

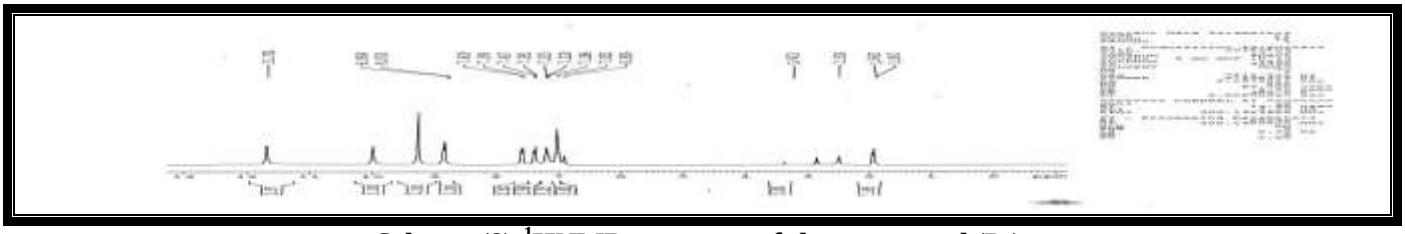


Scheme (5):^{1}HNMR spectrum of the compound (P_1).

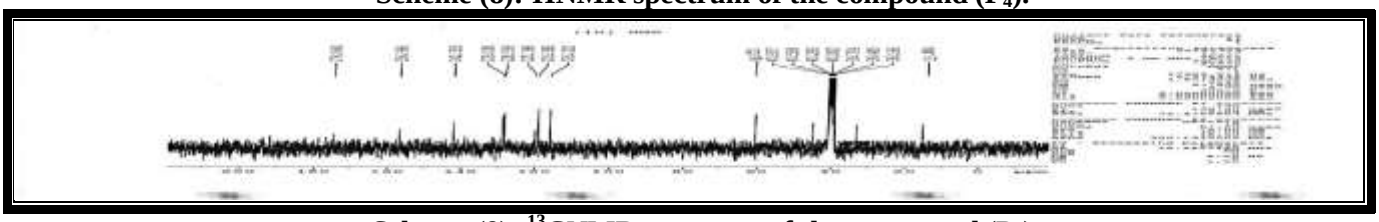
Scheme (6):^{1}HNMR spectrum of the compound (P_2).



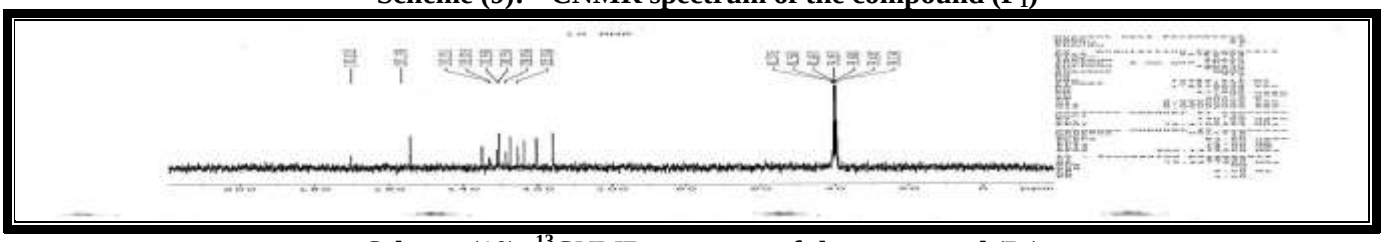
Scheme (7):^{1}HNMR spectrum of the compound (P_3).



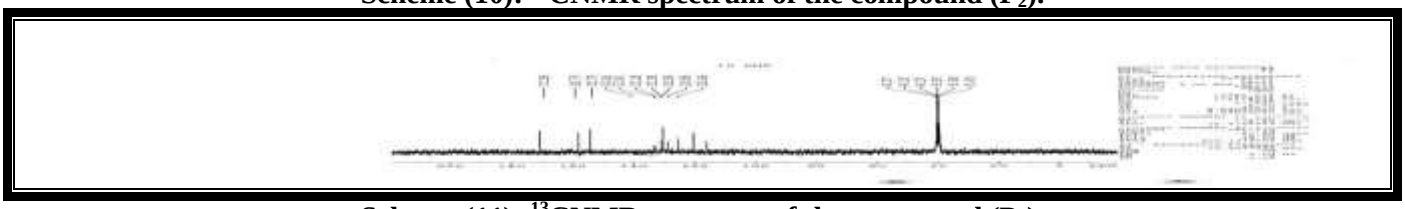
Scheme (8):^{1}HNMR spectrum of the compound (P_4).



Scheme (9): ^{13}CNMR spectrum of the compound (P_1)



Scheme (10): ^{13}CNMR spectrum of the compound (P_2).



Scheme (11): ^{13}CNMR spectrum of the compound (P_3).

Table 1:physical properties of synthesis compounds

NO	M.F	M.P	R_F	color	yield %	solvent
P	$C_{21}H_{19}NO_5$	92-94	0.8	yellow	77	Aceto nitrile
P_1	$C_{19}H_{19}NO_3$	93-96	0.6	yellow	77	Ethanol\pyridine
P_2	$C_{17}H_{17}N_3O_3$	188-190	0.75	Red	82	ethanol
P_3	$C_{24}H_{13}N_3O_3$	223-225	0.93	yellow	76	ethanol
P_4	$C_{25}H_{21}N_3O_4$	250-253	0.91	yellow	76	1,4-dioxane
P_5	$C_{32}H_{22}N_3O_6$	318-320	0.82	Yellow	80	Dry benzene
P_6	$C_{28}H_{23}N_3O_6$	304-306	0.75	yellow	83	Dry benzene
P_7	$C_{28}H_{25}N_3O_6$	377-379	0.79	yellow	83	Dry benzene
P_8	$C_{24}H_{24}N_4O_4$	353-355	0.81	Yellow	78	Tetra hydro furan
P_9	$C_{24}H_{26}N_4O_4$	370-377	0.73	yellow	85	Tetra hydro furan

Table 2: Antibacterial Activity of synthetic compounds

Type of bacteria / Comp.NO.	inhibition zone(mm) 5mg 10mg 20mg (mg\mol)			
	klebsiella pneumonia	***Staphylococcus***	***Enterococcus faecalis***	***pseudomonas aeruginosa***
P	**-,5,8**	**-, -, 6**	**-,-,6**	**-,-,6**
P_1	**-,-,5**	**-, -, 5**	**-,-,8**	**-,-,8**

P_2	**-**	**-, - ,4**	**-,-,10**	**-,-,8**
P_3	**-, -, 8**	**-, 5, 8**	**-,-,-**	**-,-,6**
P_4	**10, 12, 25**	**10, 15, 40**	**-,10,15**	**-, -, 10**
P_5	**-**	**-,-,10**	**-,8,10**	**-,-,7**
P_6	**-**	**-**	**-**	**-,10,15**
P_7	**-, -, 5**	**-, 5, 10**	**-,-,10**	**-,6,8**
P_8	**-,-,8**	**-,-,22**	**-,6,12**	**-,-,8**
P_9	**-,-,10**	**-,-,10**	**-,-,8**	**-,-,8**

REFERENCES

1. Caroline R.M.Doca, Fabriciof Naciuk and others ., ***J.Braz .Chem.Soc.,*** 28,2,**(2017).**
2 .E lmaira K , Nader N. Pesyan ,T. and Ertan S , .,***j.chin. Chem. Soc***.,62.(**2015**).
3.Haroon M ,Aamer S. and others .,***Crystals,***7(211) :1-4,**(2017**).
4.Riat S. ,Agarwal D. and M.C.Agarwal ,***I nternational Journal of Scientific Research and Growth,***1(6):174-193,**(2017).**
5. Caroline R.,Fabricio F. and others .,***J.Braz.Chem.Soc.,*** 28(2):285-298 ,**(2017).**
6. Grazilla T. ,Gloria Z. and others ., ***Molecules ,*** 22,1747,(**2017).**
7. Adriana V. ,Pedro De-La-Torre and Margarita I., ***Journal of Chemistry*** ,**ID 841893** :1-8 ,**(2017).**
8. Tomio S. ,Mai I. and Keimel O., ***International of Chemical EngineerinG and Application ,*** 8(3) ,**(2017).**
9. .Meldrum,*J.Chem.Soc.,* 93,598-601**,(1908).**
10. Oikawa Y.;Hirasawa H .,Yonemistus O.Tetrahedron Lett.,19,1759-1762.(**1978).**
11. Haydr Ghainum and Hasan Thamr ,***J.Chem.Pharm.Res.,***9(1),93-99**,(2017).**
12. Muhammad Nawaz T ,Naghmana Kausar and others.,*Am-Euras.J.Agric &Environ .Sci*., 15(12) : 2479-2483,**(2015).**
13. Ranza A.Elrayess,Nagat Ghareb and others., *Life Science Journal*,10(3),1784-1793,**(2013).**
14.Safa T. ,Hasan T., ***Int. Journal of Chem.Tech Research ,***9(9) :360-367,**(2017).**
15. Muna S. Al-Rawy, Jumbud H and Dhuha F.,***Iraqi National Journal of Chemistry,*** 55,264-274,**(2014).**
16. Vivek G and A. Pandurangan., *American Journal of Advanced Drug* ,1(4):413-421,**(2013)**.
17. K.Bauer ; *J.Amer.Clin.Path*,45,493,(**1966).**
18. Luay Abu-Qatouseh ,Mohammad Abu-Sini and others .,***Molecules*** ,22,71,(**2017).**
19.Bhushan Nazirkar ,Udaysingh Patil and others .,***Der .Pharma.Chemica.,*** 9(3) :45-53,**(2017).**
20. Ruwaida Asyikin ,Meng Guan and Hashimatul Fatma , ***Malaysian Journal of Analytical Sciences .,***21(5) :1168-1175 ,**(2017).**
21. Safa .Thaier and Hasan Thamr , ***Inter.Jour.Of Chem Tech Reser.,***9(9):360-367,**(2016).**