Egypt. J. Chem. Vol. **65**, No. 3 pp. 571 - 579 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis, Characterization and Anticancer Assessment of New Nitrogen-Cyclic Compounds

Hanan Faleh Mohsein[a] , Noor Dia Jaffer[b] , Huda Sabah Hassen[c] ,Athmar Ali Kadhim[d]

[a,b,c]Department of Chemistry ,College of Education for Girls , Iraq

[d]Lecture in Chemistry, College of Hilla University, Babylon, Iraq

Abstract

The contemporary work contracts with the production of new chalcone derivation from reaction between 4-aminoacetanilide with vanilline. formerly chalcone compound retorts with Acetoacetanilide, 2,4-dinitrophenylhydrazine, Thiourea, Thiosemicarbazide, o-phenylenediamine and Acetylacetone in absolute ethanol to prepare cyclic compounds derivatives through applying condensation reaction, cyclization reaction for carbonyl compounds with di amine compounds or amine with any other nucleophile compound to yield N-cyclic compound, and the chemical techniques were tested like identification study , bio study for these prepared compounds. Then anticancer Assessment of chalcone derivative , the structure of these derivatives were characterized by (H1-NMR, C13-NMR, H-C NOSY NMR, FT-IR) Techniques , melting points in addition to other physical studies., The date of Spectra measurements appeared exactly structures of prepared compounds through disappearing of some bands and appearance of new bands in formatted compounds represented by Nitrogen- Cyclic compounds.

Keywords: Aminoacetanilide , Chalcone , N-cyclic derivatives, amine, phenyl.

1.Introduction

Chalcons are a class of chemical derivatives termed flavonoids, that are un-saturated carbonyl system[(1)]. They are categorized through their ability to reduce and oxidize, as well as the electron transfer process that are attributed to the lack of charge concertation in their molecules[(2)]. chalcons are found naturally in many natural herbs , plants like vegetables and beans[(3)],also they can synthetically synthesize in the lab by a condensation process called Clasien-Schmidt which catalyzed with a basic medium of a suitable aromatic aldehyde and ketone in the pretense of a polar solvent like ethanol[(4)]. Chalcons have occupied great importance in the recent years for being an intermediate compound in the biosynthesis of other organic cyclic compounds which prepared by closing the cycle of the chalcones[(5)] and for their medical, pharmacological[(6)] and industrial importance[(7)]. They have curative activates against cancer, tumor [(8)], malaria, viruses, fungi[(9)] and gram-negative and gram-positive bacteria[(10)], as well as against candida albicans[(11)]. They have a good anti-oxidant, anti-viral[(12)], anti-inflammatory and anti-ulcerative properties[(13)]. It found that the unsaturated carbonyl system was the responsible for the antimicrobial activity which can be controlled by changing the type and the location of the substituted groups [(14)]. Chalcone also showed a good liquid crystal and properties, they have been used to enhance the crystallization properties and the light transmittance of materials[(15)]. Nitrogen cyclic compounds are characterized by their wide biological ,pharmacological applications and are the basic link for many pharmaceutical drugs and vitamins

2. Experimental Methods:

All applied chemicals were obtained from international companies like (Fluka, BDH and Merck) without any additional purifications. The course of the reaction and the purity of the products were monitored by Thin Layer Chromatography technique (TLC) with a mixture of solvents absolute ethanol and benzene. The measurements of I.R –Spectra carried out in Research ceter in Pharmacy College , while H.NMR and C.NMR –Spectra were carried out in Iran Universities in Center of Measurements. The magnetic stirring device was used to achieve the complete dissolution of the primary materials and the continuous stirring during the reflex reactions.

*Corresponding author e-mail hanan.faleh@gmailcom ; (Hanan Faleh M).

Receive Date: 14 September 2021, Revise Date: 23 September 2021, Accept Date: 01 October 2021

DOI: 10.21608/ejchem.2021.96112.4504

1. Synthesis of the chalcone N-(4-aminophenyl)-3-(4-hydroxy-3-methoxy phenyl) acrylamide (R)[16]
p-amino acetanilide (1.5 gm., 0.001 mole) was completely dissolved in 30 ml absolute ethanol. 5ml of 10 % NaOH was added to the reaction flask, then (1.52 gm. , 0.001 mole) of Vanillin was added with the continues stirring at room temperature for (5 hours).
yield 67.67 %, m. p 125-127°C; 1H-NMR (DMSO): δ 7.19-7.53.61 (m,5H) for aromatic ring, δ 9.63 (s, 1H, NH), δ 3.53 (s, 3H, OCH3) , δ 4.93 (s, 2H) for (NH2), δ 6.48-6.51 (d, 2H) for (CH=CHCO),δ8.54(s,1H,OH);13CNMR(DMSO):114.27,119.94,119.97,120.10,121.32,121.61,124.60,129.09(C)Phenyl ring , 24.13 C,OCH_3, 145.03 C=C alkene , 167.79 C=O ketone . ; IR: (NH2) 3456-3238cm−1 , (O-H) 3371cm−1 , (N-H) 3307cm−1, (C-H, aliphatic) 2902cm−1 ,(C-H, alkene) 3072 cm−1 ,(C=C alkene) 1600 cm−1, (C=O ketone) 1664 cm−1, (C=C aromatic) 1514 cm-1.

2. Synthesis 5-((4-aminophenyl)amino)-4'-hydroxy-3'-methoxy-N-methyl-3-oxo-1, 2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxamide (R1)[17]
(0.49 g , 0.002 mole) aceto acetanilide was added to (0.57 gm. , 0.002 mole) from the chalcone R dissolved in 30ml ethanol, (5 ml) 10 % NaOH was also added. The mixture was refluxed for (17 hours).
yield 60.2 %, m. p 231-233°C; 1H-NMR (DMSO): δ 7.00-7.62 (m,7H) for aromatic ring, δ 10.14 (s, 1H, NH-C=O), δ 3.45 (s, 3H, OCH3) , δ 8.11 (s, 1H) for (C=CH-C=O), δ 4.83 (s, 2H) for (NH2), δ9.95(s,1H,OH); ; 13C-NMR (DMSO): 119.46,123.40,129.08,130.43 (C)Phenyl ring , 24.44 C,OCH3 ,139.82-140.19 C,-C=CH- , 168.74 C=O amide , 193.44C, C=O ketone . 11.46 C,CH2; IR: (N-H) 3394cm−1, (C-H, aliphatic) 2981cm−1 ,(C-H, alkene) 3062 cm−1 ,(C=O amide) 1660 cm−1, (C=O ketone) 1710 cm−1, (C=C aromatic) 1598 cm-1.

3. Synthesis 4-(3-((4-aminophenyl)amino)-1-(2,4-dinitrophenyl)-4,5-dihydro-1H-pyrazol -5-yl)-2-methoxyphenol (R2)[18-20]
(0.57 g , 0.002 mole) of chalcone R soluble in 30ml of ethanol added gradually to (0.39 g , 0.002 mole) of (2,4-Dinitrophenylhydrazine). 5ml from 10% NaOH added and reflexed for (14 hours).
yield 58 %, m. p 158-160°C; 1H-NMR (DMSO): δ 7.19-8.81 (m,8H) for aromatic ring, δ 10.01 (s, 1H, NH), δ 2.03 (s, 1H, N-CH-N) , δ 3.86 (s, 3H) for (OCH3), δ 6.48-6.51 (s, 2H) for (NH2), δ9.57(s,1H,OH), δ 1.97 (s, 2H) for (-CH2) ; ; IR: (NH2) 3352-3277cm−1 , (N-H) 3116cm−1, (O-H) 3296cm−1, (C-H, aliphatic) 2976cm−1 ,(C-H, aromatic) 3068 cm−1 ,(NO2) 1514-1334 cm−1, (C=N Endocyclic) 1647 cm−1, (C=C aromatic) 1558-1618 cm-1.

4. Synthesis 4-(6-((4-aminophenyl)amino)-2-mercaptopyrimidin-4-yl)-2-methoxyphenol (R3)
Thio urea (0.506 gm, 0.00l mol) was refluxed with (0.57 g , 0.002 mole) from the compound R dissolved in (30ml) ethanol with the addition of 10% NaOH (5 ml) and reflex for (12 hours)
yield 69 %, m. p 196-198°C; IR: (NH2) 3442-3300cm−1 , (N-H) 3419cm−1, (O-H) 3367cm−1, (C-H, aliphatic) 2976-3931cm−1 ,(C-H, aromatic) 3068 cm−1 ,(S-H) 2819 cm−1, (C=N Endocyclic) 1658 cm−1, (C=C aromatic) 1554-1602 cm-1.

5. Synthesis ((4-aminophenyl)amino)-5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (R4)[18]
Compound R4 was obtained from (15 hours) reflex between Thiosemicarbazide(0.19 g , 0.002 mole) and the chalcone (0.57 g ,0.002 mole) in (30 ml) ethanol and (5ml) NaOH 10%.
yield 77 %, m. p 118-120°C; 1H-NMR (DMSO): δ 6.54-8.08.61 (m,12H) for aromatic ring, δ 10.20 (s, 1H, NH), δ 1.38 (s, 3H, $N(CH_3)_2$) , δ 3.76 (s, 1H) for (HC-C=O) ; 13C-NMR (DMSO): 116.21,117.82,123.17,122.50,135.44(C)Phenyl ring , 27.21 C,$N(CH_3)_2$,57.43 C,CH-C=O , 149.42 C=O amide , 151.38-154.70 C=O ketone . ; IR: (NH2) 3444-3294cm−1 , (N-H) 3371cm−1, (O-H) 3421cm−1, (C-H, aliphatic) 2927-2866 cm−1 ,(C-H, aromatic) 3066 cm−1 ,(C=S) 1265 cm−1, (C=N Endocyclic) 1662 cm−1, (C=C aromatic) 1598 cm-1.

6- Synthesis 4-(4-((4-aminophenyl)amino)-1H-benzo[b][1,4]diazepin-2-yl)-2-methoxy phenol (R5)[17]
R5 was produced from the adding of o-phenylenediamine (0.22 g , 0.002 mole) to the solution of R compound in (30 ml ethanol) and (5ml, 10 %) NaOH and reflex for (18 hours).
yield 80.76 %, Oily; IR: (N-H) 3381cm−1, (O-H) 3431cm−1, (C-H, aliphatic) 2974-2937 cm−1 ,(C-N) 1066 cm−1 ,(C=C alkene) 1637 cm−1, (C=N endocyclic) 1662 cm−1, (C=C aromatic) 1531-1512 cm-1.

7- synthesis (Z(-5-((4-aminophenyl)amino)-4'-hydroxy-2-(1-hydroxyethylidene)-3'-methoxy-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (R6)[17]
(0.2 g , 0.002 mole) acetylacetone was added to (0.57 g , 0.002 mole) from (R) dissolved completely in 30 ml ethanol, then 10 %(5 ml) NaOH added and the reaction mixture was reflexed for (20 hours).
yield 76.9%, m. p 140-142°C; IR: (N-H) 3281cm−1, (O-H) 3452cm−1, (C-H, aliphatic)

2935-2914 cm−1 ,(C=C alkene) 1639 cm−1, (C=O ketone) 1666 cm−1, (C=C aromatic) 1564 cm-1.

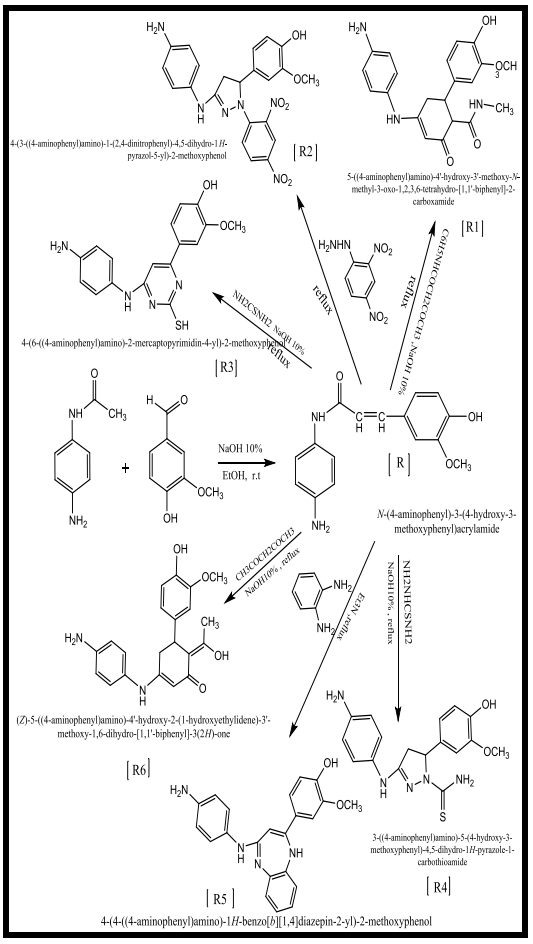
3.Results and Discussion

In our work for synthesis of chalcone compound and reaction with Acetoacetanilide , 2,4-dinitrophenylhydrazine, Thiourea, Thiosemicarbazide, o-phenylenediamine and Acetylacetone to produce heterocyclic derivatives of five ,six and seven membered rings derivatives . involves the following steps: the first step involves the preparation of chalcone compound . the reaction sequence is out lined in Scheme 1, The IR spectra of the N-(4-aminophenyl)-3-(4-hydroxy-3-methoxy phenyl) acrylamide is characterized by the presence of appeared the carbonyl group ,alkene and substituted ring which occurs within the ranges 3072,1664,1600 cm-1, respectively. The α ,β unsaturated carbonyl group decreased the absorption frequency of carbonyl group at 1664 cm^{-1} .

The 1H-NMR of chalcone and heterocyclic compounds R,R1,R2 showed regions , an aliphatic regions including one group of signals at the region δ(3.53,3.45,3.86) ppm ,corresponding to methoxy group. In the 1H-NMR spectra of the aromatic regions ,these are close similarity of the electronic environment of the aromatic protons which led the line collapsed makes an arrow range of the chemical shift and in many cases the spectra lines are superimposed 7 upon each other. In spite of formula similarity, we can notice two doublet at the range of δ(7.19-7.22 ,7.53)ppm ,(7.00-7.05 ,7.26-7.31 and 7.51-7.68,8.21-8.25) ppm corresponding to 4H of chalcone and heterocyclic derivatives which is included (3-2),(3-5),(3-8)

The 13C NMR spectra of chalcone and heterocyclic compound R,R1 showed the resonance at δ167,193 ppm were assigned to the carbonyl groups ,alkene group within the range δ 145,140 ppm and methoxy group within range δ 24.13 ,24.44 ppm. The chemical shift values of aromatic carbon atoms within the range 114.27-129.09 , 119.46-130.43 ppm .

2D NMR HMQC 1H-13C spectra : The 2D NMR HMQC 1H-13C spectra of the 2R and 4R showed a correlation of the methylene
protons signals of 2R ,4R at δ 1.9 ppm , 1.8 ppm with carbon at δ 24.09 ppm 24.89 ,δ 24.09 ppm, which to the assignment of methylene group carbon. The HMQC spectra showed a correlation between proton signals at 2.45-2.3 ppm ,3.51-3.82 ppm carbon signals at δ 41.5 -40.2, 57.3-56.7 ppm .,The aromatic protons from δ6.51,7.19,7.2,7.30,7.81,8.35, 8.63ppm have been correlation with carbon aromatic signals at 115.0,120.8,119.1,130.6,125.4 ppm., Figures (1-16) .



Scheme.1:Synthesis new cyclic compounds

Cell viability And Cytotoxicity assay

Freshney's method was used to grow cancer cell lines as follows:- The cell of the cancer cell line was thawed using a water bath at a temperature of 37°C. Then, the cell of the cancer cell line was transferred to an animal cell culture vessel with a diameter of 25 cm 2 containing RBMI-1640 culture medium and 10% bovine calf serum. Then it was placed in an incubator, the proportion of carbon dioxide in it 5% CO2, at a temperature of 37 °C for 24 hours, after 24 hours of incubation, and when it was confirmed that there was growth in the cell culture and that it was free of contamination. The cells were examined using an inverted microscope To ensure its vitality, free from contamination, and its growth to the required number (500 - 800) thousand cells / ml approximately. The cell was transferred to the growth booth, and then the used culture medium was disposed of by washing the cell using Physiological Salin Solution (PBS). Then a sufficient amount of trypsin enzyme was added to the cell and it was incubated for 30-60 seconds at a temperature of 37°C and monitored until they changed from a monolayer

of cells to single cells. In this case, the enzyme was stopped by adding a new growth medium containing calf serum. cows. Then the cell was collected in centrifugal tube and placed in a centrifuge at a speed of 2000 rpm for 10 minutes at room temperature, for the purpose of precipitating cell and getting rid of the trypsin and the used culture medium. The filtrate was disposed of, and the cell was suspended in a fresh culture medium containing 10% bovine calf blood serum. The number of cell was examined by taking a certain volume of the cell suspension and the same volume of Trypan Blue dye was added to it. To find out the number of cell and their vitality percentage using the Hemacytometer chip and according to the equation:

$C = N*10^4 *F$ /ml

Where as

C= the number of cells in one ml of the solution

N= the number of cells in the slide

F= dilution factor

10^4 = slice dimensions

After that, the percentage of cell viability in the sample was calculated using a Hemacytometer chip according to the equation :

Percentage of live cell viability = (living cells / dead cells)*100

The cell suspension was distributed into new containers and then incubated in a 5% CO_2 incubator at 37 °C for 24 hours .

MTT stain test to check cell vitality:

MTT Assay for Cell Viability

Test Principle:

In this test, the cytotoxic effect of compound R (**N-(4-aminophenyl)-3-(4-hydroxy-3-methoxy phenyl) acrylamide**) was determined. on eye cancer cell for the purpose of demonstrating its toxic efficacy on human body cells and the possibility of using them as anti-cancer drugs.

Work Method:

This method was carried out by preparing[18,21] the cell of the cancer line by following the steps described above. The cell suspension was placed in a 96-hole flat-bottom plate, and incubated in a 5% CO2 incubator at 37 °C for 24 hours, then 100 µl of the cell suspension was added in every hole. Followed by the addition of the prepared concentrations of R (**N-(4-aminophenyl)-3-(4-hydroxy-3-methoxy phenyl) acrylamide**) ., (400, 200, 100, 50, 25, 12.5 µ/ml) to the pits, with a rate of (3) holes for each concentration. The plate was incubated for 24 hours at 37°C. Then 10 ml of MTT solution was added to each hole at a concentration of 0.45 mg/ml. The plate was incubated for 4 hours at 37°C. Then 100 µl of solubilization solution was added to each hole to dissolve the Formazan Crystals. The absorbance of the sample was recorded at a wavelength of 570 nm using an ELASIS device.

Effect of Compound (R) on the growth of Eye cancer cell line (MP46) and normal cells (WRL-68)

The results of the tests showed that the highest inhibition of the compound R for the MP46 cancer cell line was 51.77% at a concentration of 400 Mg/ml, while the lowest inhibition of the compound for the cells of the normal cell line WRL68 was 4.2% at a concentration of 6.25 Mg/ml. Required to kill about half of the cells, as the IC50 of cells of the MP46 cell line (IC50 =22.04), While its value was for the regular cellular line (IC50=268.4), and this result indicates the possibility of using the compound((**N-(4-aminophenyl)-3-(4-hydroxy-3-methoxy phenyl) acrylamide**) as a new treatment against this type of cancer for the line MP46 and the table (1) shows the effect of this compound on eye cancer cells compared to normal cells, while the figure shows the comparison of the half-inhibitory concentration of cancerous and normal cells against the logarithm of the concentration compound .

It is appeared good inhipition in level of tumor compared with previously studies in same field that is due to nitrogen –cyclic compounds and involving of N-atom in their structures.

Table.1:The effect of compound R on the cells of the eye cancer cell line MP46 and compared it with the cells of the normal line WRL-68 for the same concentrations using the MTT test for 24 hours at 37C

Con. (Mg/ml$^{-1)}$	Mean Percentage (%) for each cell line			
	MP46		WRL-68	
	Cancerous line cells of MP46		Normal line cells of WRL-68	
	Cell Viability	Cell Inhibition	Cell Viability	Cell Inhibition
6.25	95.87	4.13	95.80	4.2
12.5	84.45	15.55	95.06	4.94
25	74.61	25.39	95.02	4.98
50	63.27	36.73	89.55	10.45
100	50.69	49.31	84.34	15.66
200	52.89	47.11	74.19	25.81
400	48.23	51.77	62.62	37.38

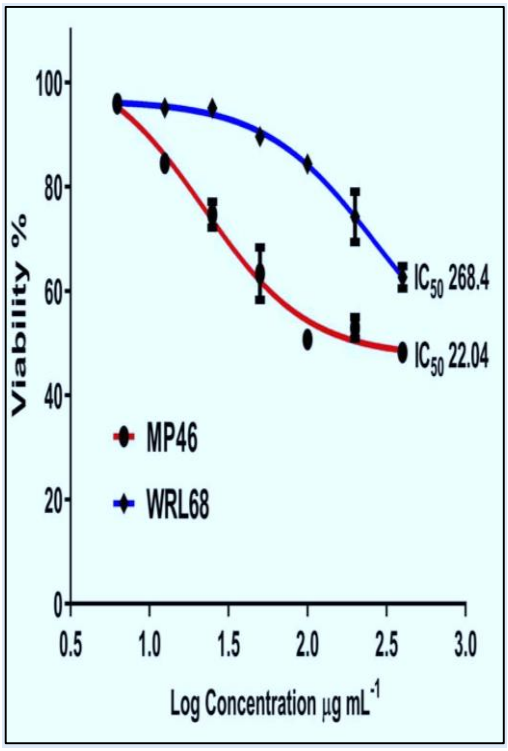


Fig.1:Compare IC50 of Cancer cell line MP46,Normal cell line against logarithm of compound concentration(R)

Table.2:Statistical values of the Mp46 Eye cancer cell line of compound(R)

Dose (Mg/ml)	Mean	No. of values	Std. Deviation
6.25	95.87	3	0.98
12.5	84.45	3	0.58
25	74.61	3	2.52
50	63.27	3	5.08
100	50.69	3	1.75
200	52.89	3	2.09
400	48.23	3	1.18
Total	470.01	21	14.18

Table.3:Statistical values of the WRL -68 Normal cell line of compound(R)

Dose (Mg/ml)	Mean	No. of values	Std. Deviation
6.25	95.80	3	0.48
12.5	95.06	3	1.65
25	95.02	3	1.29
50	89.55	3	0.77
100	84.34	3	1.44
200	74.19	3	4.81
400	62.62	3	2.12
Total	596.58	21	12.56

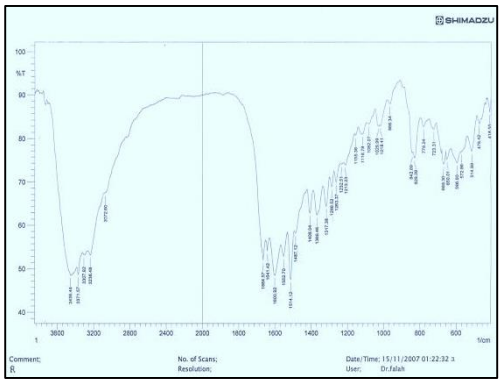
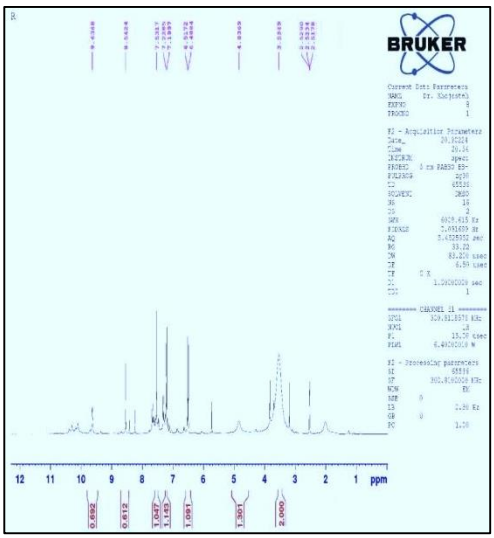


Fig.(2) FT-IR of Comp. R



(3) 1H-NMR of Comp. R

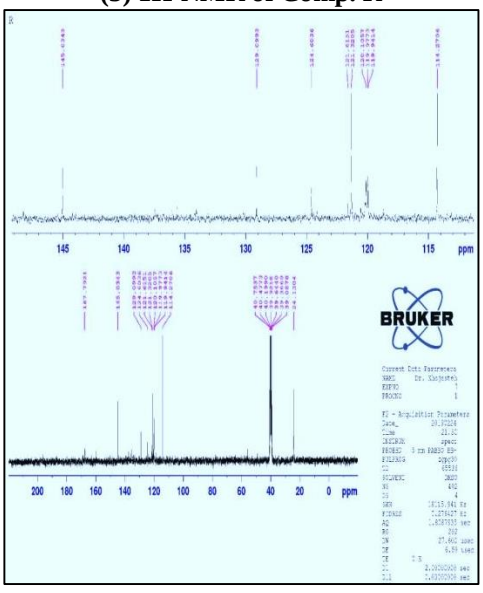


Fig.(4) 13C-NMR of Comp. R

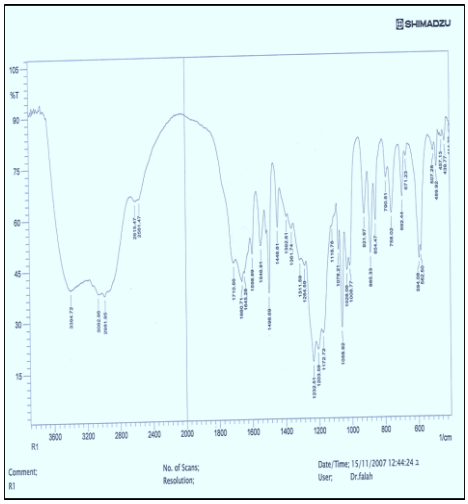


Fig.(5) FT-IR of Comp. R_1

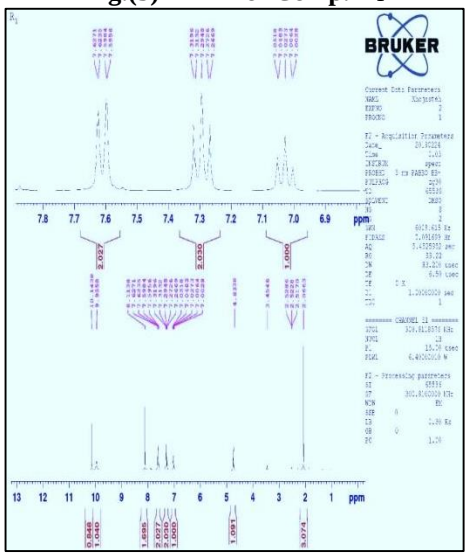


Fig.(6) 1H-NMR of Comp. R1

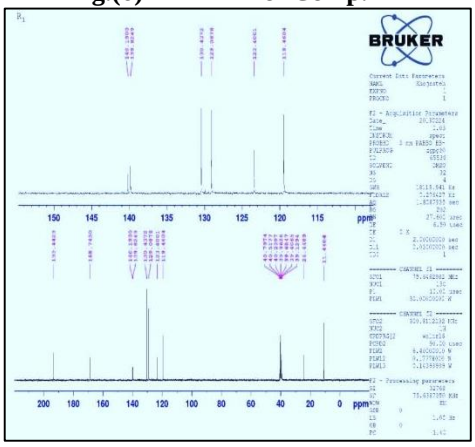


Fig.(7) 13C-NMR of Comp. R1

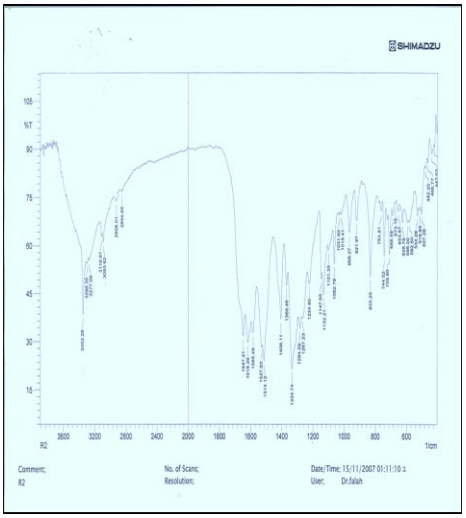


Fig.(8) FT-IR of Comp. R_2

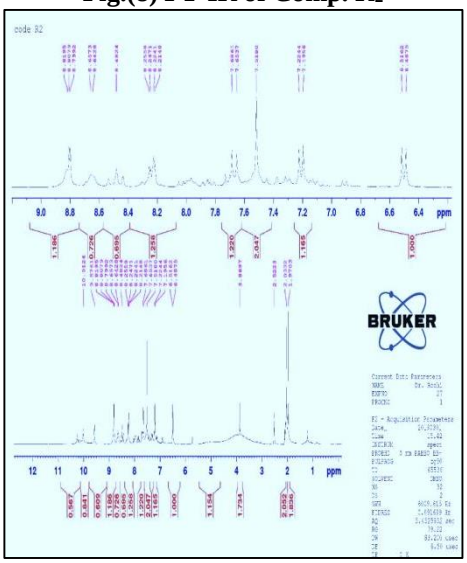


Fig.(9)1H-NMR of Comp. R2

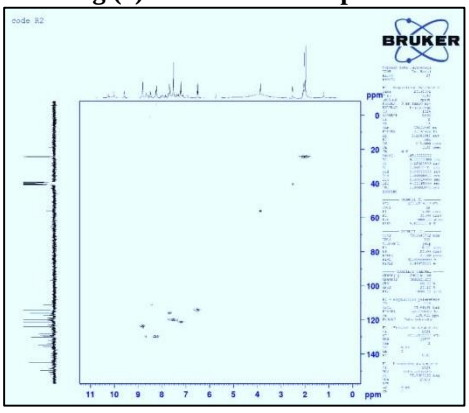


Fig.10:1H-13C NMR of Comp.R2

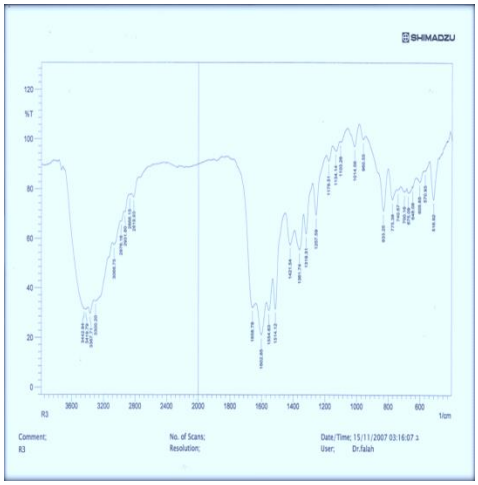


Fig.11:FT-IR of Comp. R_3

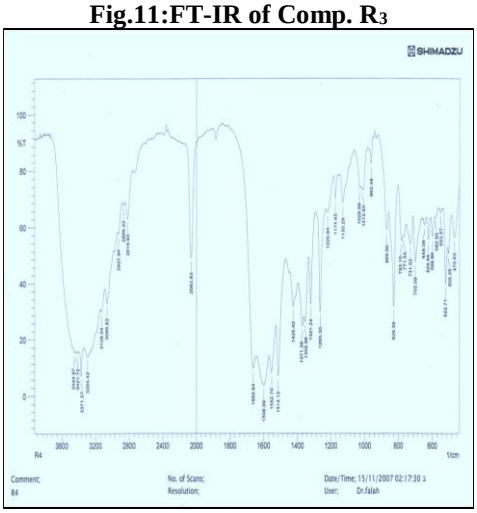


Fig.(12) FT-IR of Comp. R_4

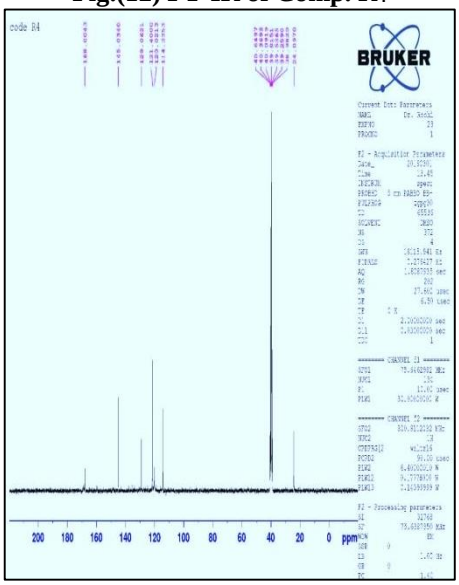


Fig. 13 : ^{13}C-NMR of Comp.R4

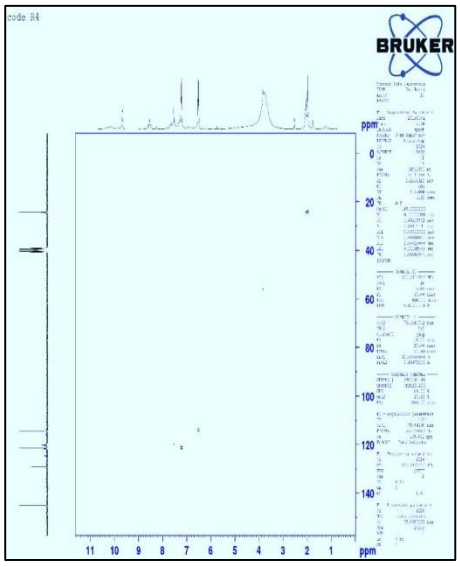


Fig.14:1H-13C NMR of Comp.R4

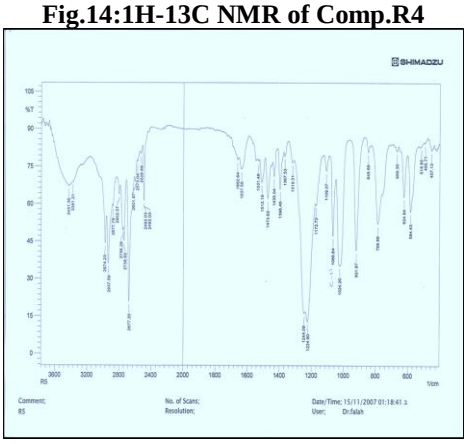


Fig.15:FT-IR of Comp.R_5

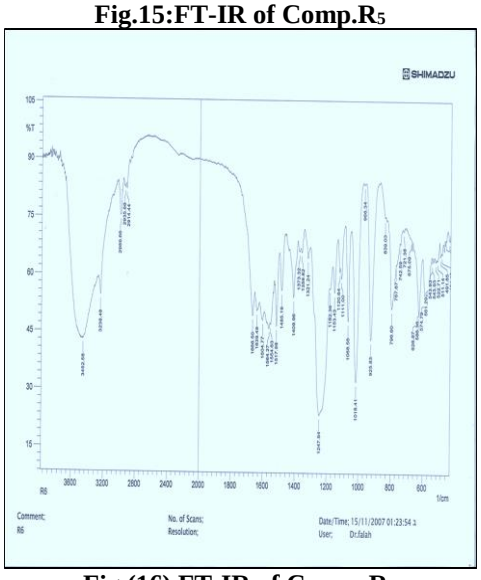


Fig.(16) FT-IR of Comp. R_5

4. Conclussion:

The results of Spectra studies appeared exactly structures of prepared compounds through disappearing of some bands and appearance of new bands in formatted compounds represented by Nitrogen- Cyclic compunds. Also anticancer studying gave good data by inhipition of tumors level in selected cancer cells.

References

1. Lina Saadi, Shaimaa Adna, Synthesis and Characterization of Some Heterocyclic Compounds from Chalcone Derivatives and Studying of their Biological Activity, Journal of Global Pharma Technology, 10(9):179-206, 2017.
2. Ramesh C. Kamboj, Rita Arora, Geeta Sharma, Dinesh Kumar, Chetan Sharma, Radhika Joshi and K. R Aneja, Eco-friendly synthesis and antimicrobial activity of chalcones, Der Pharma Chemica, 2 (3): 157-170, 2010.
3. Muna S. Al-Rawi, Synthesis of Some New Heterocyclic Compounds Via Chalcone Derivatives, Ibn Al-Haitham J. for Pure & Appl. Sci., 28(1): 88-99, 2015.
4. - D. Vasudha, Y. Rajendra Prasad, Afzal Basha Shaik, Addipalli Kanaka Raju, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL CHALCONES OF 2-ACETYL-6-METHOXYNAPTHALENE AS POTENTIAL ANTIMICROBIAL AGENTS, World Journal of Pharmacy and Pharmaceutical Sciences, 4, 06, 2015.
5. Jumbad H. Tomma, Dhuha F. Hussein, Nebras M. Jamel, Synthesis and Characterization of Some New Quinoline-2-one, Schiff bases, Pyrazole and Pyrazoline Compounds Derived from Hydrazide Containing Isoxazoline or Pyrimidine Cycles, Iraqi Journal of Science, 57, 2C:1316-1332, 2016.
6. Yosra Snoussi & Néji Besbes, USE OF ALUMINOSILICATES SUCH AS ACID - ACTIVATED CLAYS AS SOLID CATALYSTS FOR THE REACTIVITY OF THE VARIOUS CARBONYL COMPOUNDS IN HETEROCYCLIC SYNTHESIS, J. Mar. Chim. Heterocycle., 19(3): 46-61, 2020.
7. Noor Dia Jaffer, Production of new monomers from cyclic derivatives and study of their (chemical, physical, thermal characterization and biological effects), RJPT, 12(9): 4149-4154, 2019.
8. Souad Jabbar Lafta, Hayder Jawad and Ahmed Mutanabbi Abdula, SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL EVALUATION AND DOCKING STUDY OF NEW CHALCONE DERIVATIVES CONTAINING 1, 3, 5-TRIAZINANE-1, 3, 5-TRIYL) MOIETY, Int. J. Chem. Sci., 14(1):88-102, 2016.
9. Rajaa Abdul Ameer Ghafil, Nour A Alrazzakb, Nagham Mahmood Aljamali., Synthesis of Triazole Derivatives via Multi Components Reaction and Studying of (Organic Characterization, Chromatographic Behavior, Chem-Physical Properties)., Egyptian Journal of Chemistry. Vol. 63, No. 11, pp. 4163 - 4174 (2020). DOI: 10.21608/EJCHEM.2020.23541.2399 .
10. Rammohan, A., Reddy, J.S., Sravya, G. et al. Chalcone synthesis, properties and medicinal applications: a review. Environ Chem Lett 18, 433–458 2020.
11. M. Irshada, Q. Alia, F. Iram, S. A. Ahamad, M. Saleem, M. Saadia, M. Batoole, A. Kanwala, and S. Tabassum, Aurones and Analogues: Promising Heterocyclic Scaffolds for Development of Antioxidant and Antimicrobial Agents, Russian Journal of General Chemistry, 89(7):1519-1527, 2019.
12. Zahraa F. Khudair, Shaimaa A. Behjet, Synthesis and Characterization of Some New Heterocyclic Derivatives and Studying of their Biological Activity (Anti-Bacteria), International Journal of Pharmaceutical Quality Assurance, 11(1):38-44, 2020.
13. Hasaneen Kudhair Abdullabass, Aseel Mahmood Jawad , Nagham Mahmood Aljamali. Synthesis of drugs derivatives as inhibitors of cancerous cells., Biochem. Cell. Arch, Vol. 20 (2) – October 2020., DocID**:**

https://connectjournals.com/03896.2020.20.5315.

14. Santosh L. Gaonkar & U.N. Vignesh, Synthesis and pharmacological properties of chalcones: a review, Res Chem Intermed, 4(3):6043–6077, 2017.

15. Zainab Ngaini, Chua Mei Chee and Lim Lian Chin, A new type of banana shape bifunctional monomer of ester chalcones, Malaysian Journal of Fundamental and Applied Sciences, 10(2), 53-58, 2014.

16. Aseel Mahmood Jawad, Mostafa N., Salih, Thanaa A., Nadia H, Nagham Mahmood Aljamali. Review on Chalcone (Preparation, Reactions, Medical and Bio Applications), IJCSCR,5(1):16–27, 2019.

17. Hanan Faleh Mohsein., Preparation, Identification with Anticancer Assay of Quinoline Compounds through Meldrum Acid., Journal of Pharma and Drug Regulatory Affairs, Volume-3, Issue-2, 2021, P: 10-14.

18. Rabab Mahdi Ubaid Mahmood , Nagham Mahmood Aljamali., Synthesis, Spectral Investigation and Microbial Studying of Pyridine-Heterocyclic Compounds., European Journal of Molecular & Clinical Medicine , 2020, Volume 7, Issue 11, Pages 4444-4453.

19. H.F. Mohsein ,N.S.Majeed , Th.A.Al-Ameer helal , Research J. and Tech. , 12(7): July . 2019.

20. S.Samshuddin, B.Narayana, B.Kunhanna ,R.Raghavendra , Der Pharma Chemica, 4(4):1445-1457, 2012 .

21. Adnan, S. (2020). Synthesis, Spectral Characterization and Anticancer Studies of Novel Azo Schiff Base And its Complexes with Ag (I), Au (lll) And Pt (lV) ions. Egyptian Journal of Chemistry, 63(12), 4749-4756. DOI:https://dx.doi.org/10.21608/ejchem.2020.2331 2.2438