Article

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Synthesis, Antibacterial Evaluation and Study Molecular Docking of New derivatives from sulfapyridine

Maryam Methaq Najm and Hanan Faleh Mohsein

Department of Chemistry, College of Education for Girls, University of Kufa

Abstract:

Sulfa pyridine is a sulfa-derived antibiotic. It works to inhibit the activity and reproduction of bacterial cells, by inhibiting the production of some enzymes that bacteria need for their growth and activity. Therefore, in this research, we decided to increase the effectiveness of the Sulfa pyridine compound by adding some groups such as azomethine, as well as preparing some derivatives of thiazolidinone and derivatives , thiazine, hydroquinazolone, and oxazepine, Then evaluating the effectiveness of some prepared derivatives against two types of gram-negative and gram-positive bacteria, such as *E. coli and Staphylococcus aureus* and molecular docking study against skin cancer .

Key word : Sulfa pyridine , Schiff base , Thiazolidinone , hydroquinazolone

Introduction :

Sulfa pyridine, also known as sulfanilamide, is an antibiotic drug belonging to the sulfonamide class. It played a significant role in the early days of antibiotic therapy before the discovery of penicillin. Sulfa pyridine is effective against a wide range of bacteria by inhibiting their growth and reproduction through interference with folic acid synthesis, an essential process for bacterial survival[(1)]. While sulfa pyridine was historically used to treat various infections caused by susceptible bacteria, its usage has significantly declined over the years due to the development of more effective and less toxic antibiotics. Common applications included urinary tract infections,

respiratory tract infections, and skin and soft tissue infections[2]. Schiff bases are considered an important and distinctive class of organic compounds [3] after the German chemist and physicist (Hugo Schiff) was the first to prepare them in 1864. Their name was derived from his name [4] since they contain in their composition the azomethine group (-C=N-) [5-7]or the so-called imine, which is a very effective functional group as expected for a double covalent bond, as well as its ability to react reversibly through the process of rapid hydrolysis [8]. These bases are usually prepared by condensing primary amines with active carbonyl groups such as aldehydes and ketones [9] where they are linked the carbon atom is double bonded to nitrogen [10]. Heterocyclic compounds are a sort of organic compounds in which some or all of the atoms within the molecule are linked together in rings that contain at least one atom of an element other than carbon, utilized as intermediates in the production of other important heterocyclic rings which are normally distributed in nature[11]. The biological activity of some heterocyclic rings, such as nitrogen and sulfur, have made them important for a long time in the healthcare industry[12] anti-tumor, anti-inflammatory, etc.[13] and antibacterial [14] ,anti-HIV [15] ,antidiabetic [16] ,analgesic [17]. Molecular Docking tool for automated docking, as it is considered a way to predict how one molecule will be appropriately bound to another molecule when it is bound to form a compound, to find the best overlapping binding molecules and to know the extent of the binding affinity to them, as in the action of a drug with a target protein or a lock and key This could include the affinity of the link.

This technique takes into account biologically relevant molecules such as proteins, lipids or Nucleic acids or carbohydrates are powerful catalysts for signal transmission and synthesis A relationship in the interference of molecules and the signals resulting from them, such as whether or not they are in opposition and whether the docking depends On the strength and type of the resulting signal, its flexibility, and knowledge of the free energy (G bind), and therefore Molecular docking is a program in which drug development and design are done with the help of computer It became one of the most widely used methods after its first algorithms were modified in the 1980 Through it, it is possible to predict the formation of small molecular bonds for an organic molecule (a compound with the environment of the target protein, which helped save researchers effort, time, and costs[18,19].

2. Experimental

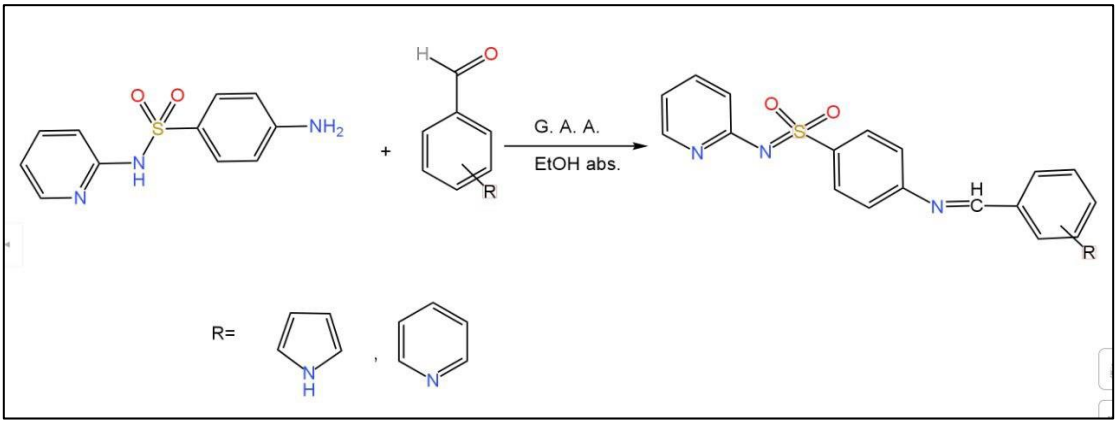
2.1. materials and instruments

All starting materials and solvents utilized in this study were purchased from commercial suppliers and used without any purification. The melting points of the synthesized compounds were accomplished by using an electro thermal capillary apparatus and were uncorrected. The infrared spectrum (FT-IR Shimadzu model) was measured using in the range (600-4000cm^{-1}). 1H-NMR spectra of the prepared compounds were recorded using a (Bruker-Ultra Shield 300 MHz Switzerland) NMR spectrometer (**Iran**).

2.2. Experimental Part

Preparation of Schiff bases compounds Y_3 ,Y_4 [20]

To a stirred solution of 2-(4-pyridyl)benzaldehyde or Indol-3-carbaldehyde (0.002 mole) in Absolute Ethanol (25 ml) add (2-3) drops of G.A.A. Sulfa pyridine (0.002 mole) slowly add and mixture was reflux (15hrs.) after complete of reaction removing the excess of solvent and cooling the residue .The product recrystallized from Absolute Ethanol . (Equation 1.)



Equation 1: preparation of Schiff bases Y_3 ,Y_4

Preparation of hydroquinazoline derivatives Y_3A,Y_4A [21]

In a round bottom flask contain 1,4dioxane (15 ml) dissolved of 2-amino benzoic acid(0.0002mole) in was added to the Schiff bases (0.0002mole) with a few drops of DMF. This solution was heated under reflux for (16 hrs.) The solvent was removed and recrystallized from Absolute Ethanol . (Scheme 1)

Preparation of thiazine derivatives Y_3B,Y_4B [21]

In round flask contain dry benzene (15 ml) dissolved of 2-mercapto benzoic acid (0.0002mole) and was added the Schiff bases (0.0002mole) with a few drops of DMF

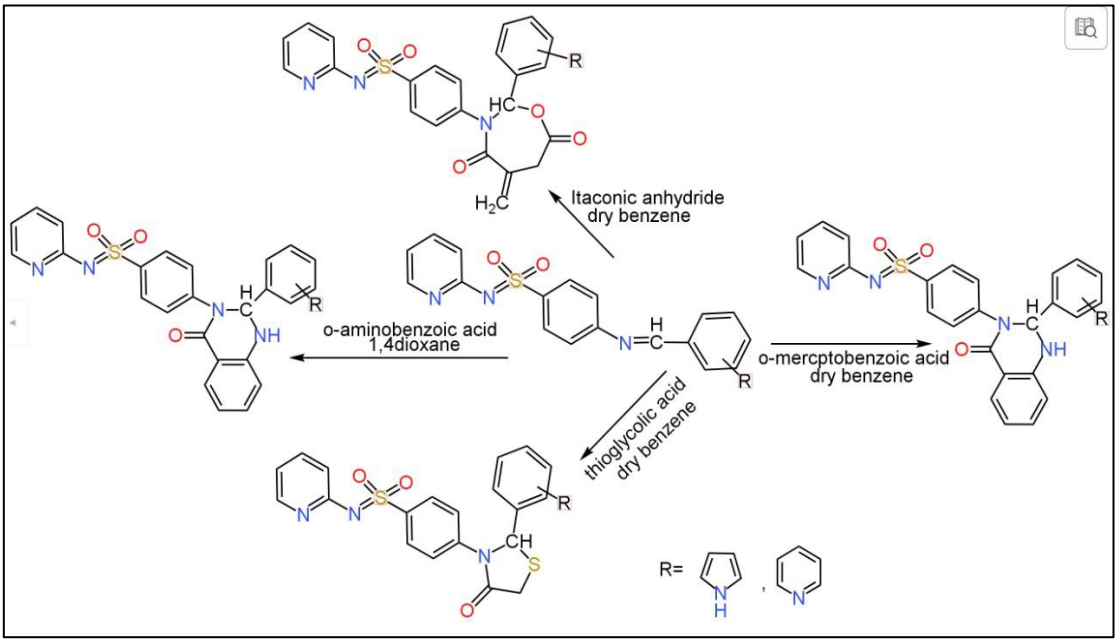
and add (5)drops from Et_3N. This solution was heated under reflux for (18 hrs.) The solvent was removed and recrystallized from Absolute Ethanol . (Scheme 1)

Preparation of oxazapine derivatives Y_3F,Y_4F [21]

In dry clean crucible add benzene (2 ml) dissolved of Schiff bases (0.008 mole) and was added the Itaconic anhydride (0.008 mole) . This solution was subjected to microwave irradiation at 120W about (20-24) min. The solvent was removed and recrystallized from Absolute Ethanol . (Scheme 1)

Preparation of Thiazolidinone derivatives Y_3C,Y_4C [22]

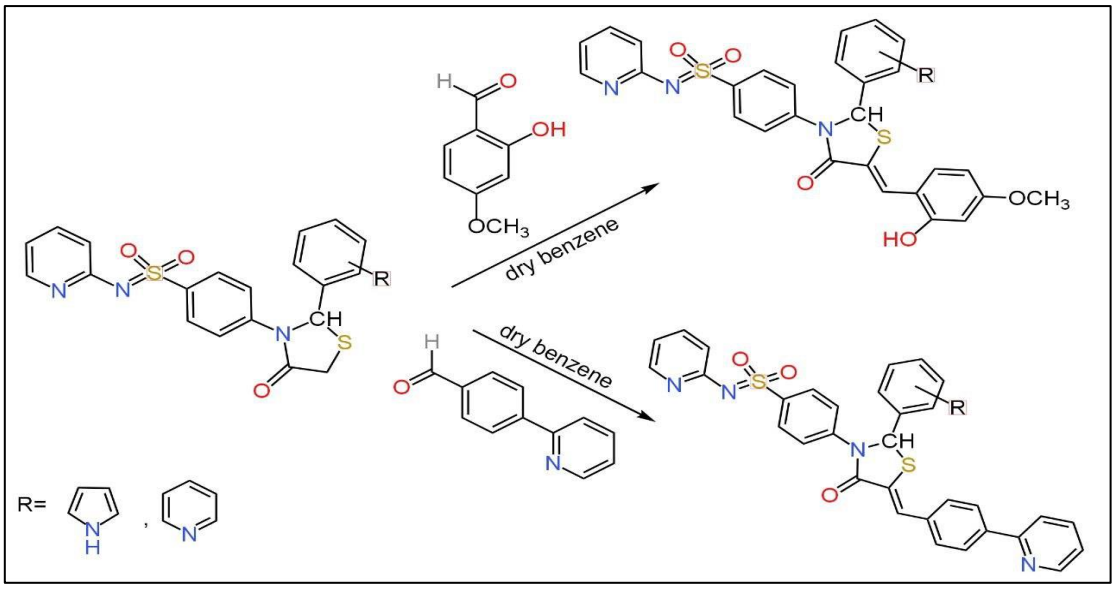
(0.001mol.) of the Schiff bases was dissolved in 15 ml of acetone and add (0.001 mol.) of thioglycolic acid. The reaction mix was reflux (16hrs.). The completion of the reaction was confirmed by TLC. The reaction mix was cooled and the product was dried and recrystallized to give the pure product. (Scheme 1)



Scheme 1: preparation of heterocyclic derivatives

Preparation of chalcones derivatives Y_4C_1,Y_4C_2 [22]

In a round bottom flask, put a mixture of thiazolidinone derivative Y_4C (0.002 mole) and an aromatic aldehyde (0.002 mole) (vaniline,2-(4-pyridyl)benzaldehyde) in Absolute Ethanol(20ml) was reflux (35hrs.) with piperidine (1-3) for 35h. .The solvent was removed and recrystallized from Ethanol Absolute .(Scheme 2)



Scheme 2: preparation of chalcone derivatives Y_4C_1, Y_4C_2

Results and discussion:

Sulfa pyridine was chosen as a starting material for the synthesis of new Schiff bases compounds (Y_3,Y_4) through reaction with 2-(4-pyridyl)benzaldehyde or Indol-3-carbaldehyde respectively, **Equation 1**.

The Schiff bases compounds were identified by the appearance of stretching band of azomethine group at (1627,1635) cm^{-1} and stretching band of a secondary aromatic amine (NH) Sulfone amide in (3414,3415) cm^{-1} and (C=C)aromatic (1529,1583) cm^{-1}, and stretching band of SO_2 at(1274,1244) cm^{-1} respectively. At the same time, there were identified in Y_3, a stretching band of a secondary amine at(3228) cm^{-1}. 1HNMR spectrum for(Y_3,Y_4)characteristic signals at ppm: (s, 1H,CH=N)8.71,8.32 ,(s,1H,NH)11.52 ,11.37 ,(mH for benzene ring) (7.45-8.15) respectively and (d,1H, CH-N) indolcyclic 6.93-6.96 ,(s,1H,NH) indole ring 10.32 .13C-NMR spectrum for (Y_3,Y_4) characteristic signals at ppm: C (CH=N) 158.25 , 161.87, C (Aromatic rings)111.11-132.00,C(-C=N) indocyclic 161.48,163.64, DMSO (solvent) 40.04

This research uses new derivatives of Schiff bases to prepare (hydroquinazoline and thiazine derivatives) were react the Schiff bases' with (*o*-aminobenzoic acid and *o*-mercptobenzoic acid) as well as the amide group (-N-C=O) is appeared in the range (1637-1680cm-1) while the compounds were determined using 1H-NMR . There was a signal at (10.20) ppm of the (1H-NH) of six membered derivative Y_4A and a signal at (6.96,6.55)ppm of the (1H-CH) of six membered derivativesY_3B and Y_4A respectively. The derivatives were also determined by 13C-NMR spectra; one signal of the six membered (C=O) occurred in the range of (163.99-176.26 ppm), while a signal from the solvent employed (DMSO) appeared at the site (40 ppm).Oxazepine

derivatives prepare were react the Schiff bases with itaconic anhydride as well as the lactone group (-O-C=O) is appeared in the range (1699-1707cm-1) while lactame group (-N-C=O) is appeared in the range (1629-1637 cm-1) . Thiazolidinone derivatives prepare were react the Schiff bases with thioglycolic acid as well as the amide group (-N-C=O) is appeared in the range (1697-1718 cm-1) while the compounds were determined using "1H-NMR". There was a signal at (4.40,4.73) ppm of the (1H-CH-N) and a signal at (3.33,3.95)ppm of the (2H-CH_2-C=O) of Thiazolidinone ring.

Chalcone derivatives prepare were react thiazolidinone derivative Y_4C with different aromatic aldehydes the FT-IR spectrum clearly show characteristic absorption band at (1650,1697 cm-1) is for carbonyl group of chalcon ,bands in region (1631,1635cm-1) is for (C=C) alkene . 1H-NMR spectra of compounds showed the signal at (5.18,5.51)ppm integrated for(1H,CH=C-) ,and a signal at (4.55,4.80) ppm of the (1H-CH-N) respectively and a signal at 3.77ppm of the (3H,OCH_3) for Y_4C_1 derivative. The derivatives were also determined by 13C-NMR spectra a signal at (175.75,177.42) ppm for (C=O) and signal at (69.48,80.46)ppm for (CH-N) of thiazolidinone ring .

Table 1: Physical Properties of prepared compounds

No of Comp.	Name	M.F	M.wt	M.P	R_f	Yield%	Color
Y3	(*E*)-*N*-(pyridine-2-yl)-4-((4-(pyridine-2-yl)benzylidene)amino) benzenesulfonamide	$C_{23}N_4O_2SH_{18}$	414	268-270	0.76	78.7	Light Yellow
Y4	(*E*)-4-(((1*H*-indol-3-yl)methylene)amino)-*N*-(pyridine-2-yl)benzenesulfonamide	$C_{20}N_4O_2SH_{16}$	376	210-212	0.91	80.3	Yellow Crystal
Y3A	4-(4-oxo-2-(4-(pyridine-2-yl)-1,4-dihydroquinazoline-3(2*H*)-yl-*N*-(pyridin-2-yl)benzenesulfonamide	$C_{30}N_5O_3SH_{23}$	533	250-257	0.84	66.5	Light Yellow
Y3B	4-(4-oxo-2-(4-(pyridine-2-yl)-2*H*-benzo[e][1,3]thiazin-3(4*H*)-yl-*N*-(pyridin-2-yl)benzenesulfonamide	$C_{30}N_4O_3S_2$ H_{22}	550	279-281	0.55	86.4	Dark Yellow
Y3C	4-(4-oxo-2-(4-(pyridine-2-yl)thiazolin-3-yl)-*N*-(pyridine-2-yl) benzenesulfonamide	$C_{25}N_4O_3S_2H_{20}$	488	296-295	0.90	74.5	Yellow
Y3F	4-(5-methylene-4,7-dioxo-2-(4-(pyridine-2-yl)phenyl)-1,3-oxazepan-3-yl)-*N*-(pyridine-2-yl) benzenesulfonamide	$C_{27}N_4O_5SH_{22}$	514	208-210	0.73	59.3	Light Yellow
Y4A	4-(2-(1*H*-indol-3-yl)-4-oxo-1,4-dihydroquinazoline-3(2*H*)-yl-*N*-(pyridin-2-yl)benzenesulfonamide	$C_{27}N_5O_3SH_{21}$	495	290-292	0.82	88.7	Dark Brown

Y4B	4-(2-(1*H*-indol-3-yl)-4-oxo-2*H*-benzo[e][1,3]thiazin-3(4*H*)-yl-*N*-(pyridin-2-yl)benzenesulfonamide	$C_{27}N_4O_3S_2$ H_{20}	512	137-139	0.77	60.9	Light Brown
Y4C	4-(2-(1*H*-indol-3-yl)-4-oxothiazolidin-3-yl)-*N*-(pyridin-2-yl)benzenesulfonamide	$C_{22}N_4O_3S_2H_{18}$	450	260-262	0.62	92.9	Yellow Crystal
Y4F	4-(2-(1*H*-indol-3-yl)-5-methylene-4,7-dioxo-1,3-oxazepan-3-yl)-*N*-(pyridine-2-yl) benzenesulfonamide	$C_{25}N_4O_5SH_{20}$	488	200-202	0.93	89.5	Yellow
Y4C1	(*E*)-4-(5-(2-hydroxy-4-methoxybenzylidene)-2-(1*H*-indol-3-yl)-4-oxothiazolidin-3-yl)-*N*-(pyridin-2-yl)benzenesulfonamide	$C_{30}N_4O_5S_2H_{24}$	584	255-257	0.68	70.2	Light Orange
Y4C2	(*E*)-4-(2-(1*H*-indol-3-yl)-4-oxo-5(4-(pyridine-2-yl)benzylidene)thiazolidin-3-yl)-*N*-(pyridin-2-yl)benzenesulfonamide	$C_{34}N_5O_3S_2H_{25}$	615	249-251	0.73	79.8	Orange

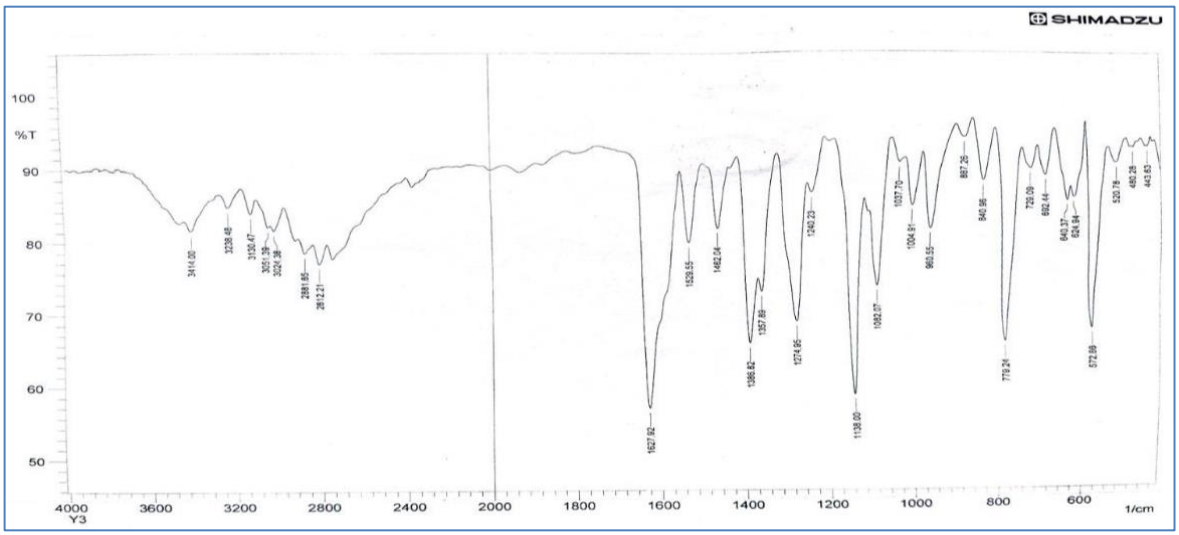


Fig.1:FT-IR Spectra of Comp.Y3

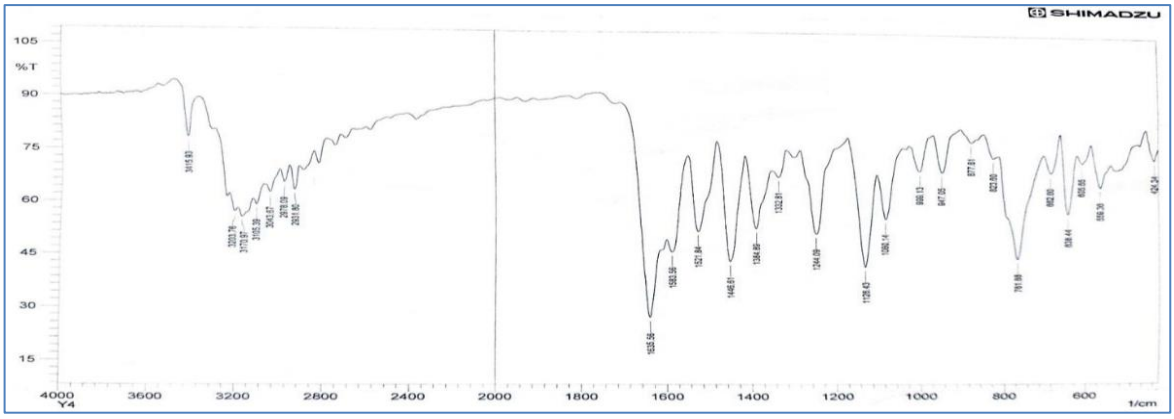


Fig.2:FT-IR Spectra of Comp.Y4

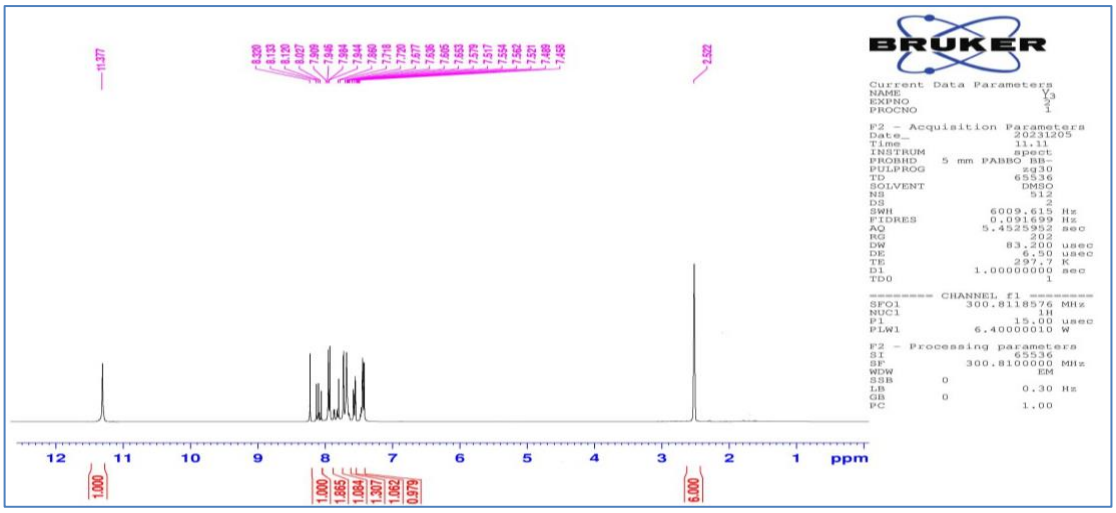


Fig.3:1H-NMR Spectra of Comp.Y3

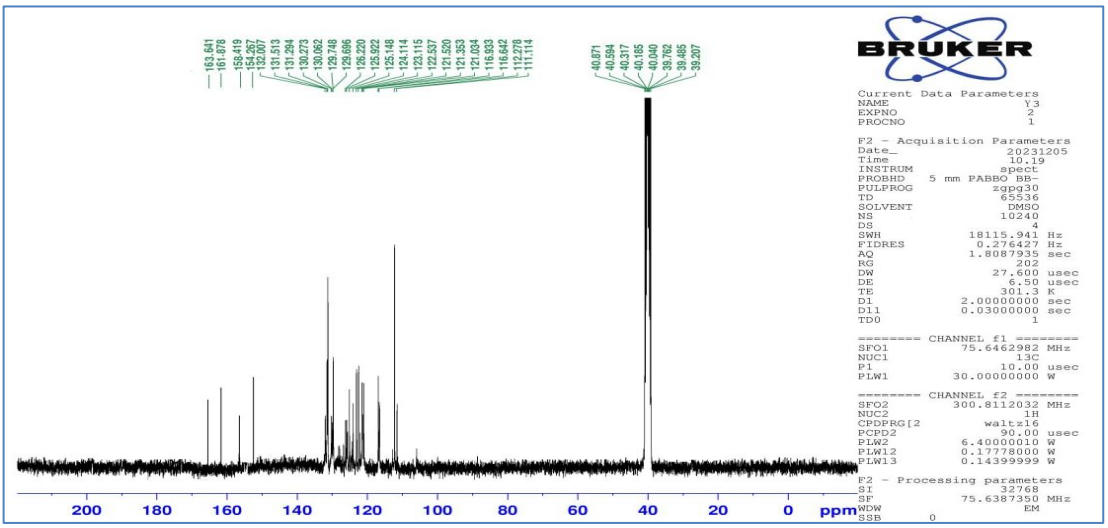


Fig.4:13C-NMR Spectra of Comp.Y3

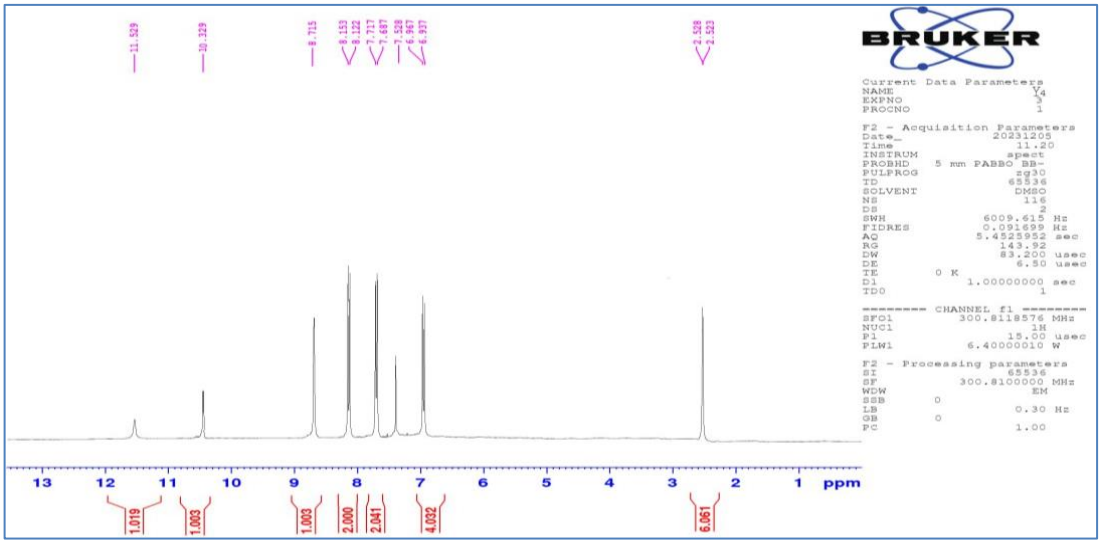


Fig.5:1H-NMR Spectra of Comp.Y4

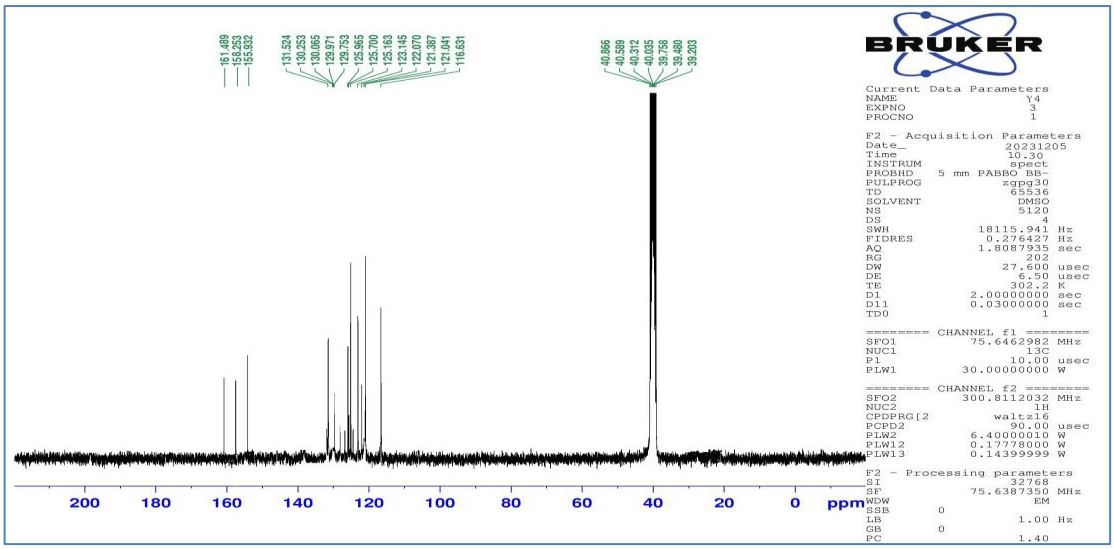


Fig.6:13C-NMR Spectra of Comp.Y4

Antibacterial Activity :

The biological activity for the compounds (Y4A ,Y4B) via using (DMSO) solvent and studying its effect on two types of bacteria which are G+ (*Staphylococcus Aurous*) for and G-(*Escherichia Coli*)with solutions of (125µg/ml) , (250µg/ml) , (500µg/ml) and (1000µg/ml).The effect of the solvent alone was measured and subtracted from the product . The amount of inhibition of the heterocyclic prepared compound (Zone of inhibition) in the ruler and the table 2. show that the vital amount of inhibition.

Table 2. The biological effectiveness of the heterocyclic compounds

Comp.	Concentration	*E.Coli*	*Staph.Auous*
Y4A	**1000µg/ml**	24	23
	500µg/ml	23	21
	250µg/ml	22	20
	125µg/ml	21	19
Y4B	**1000µg/ml**	24	22
	500µg/ml	22	20
	250µg/ml	21	19
	125µg/ml	20	18

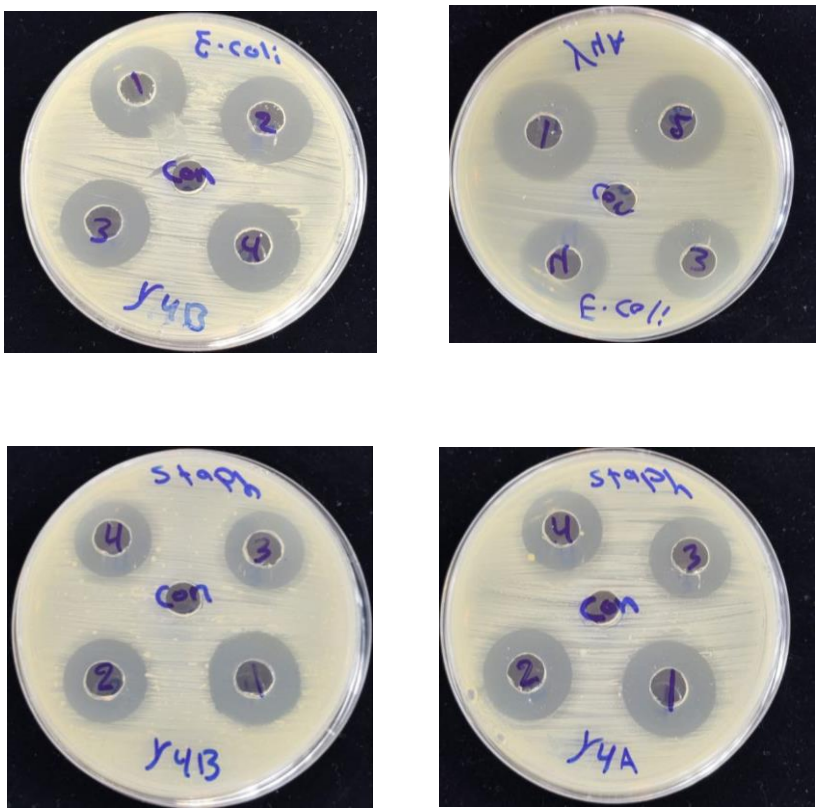


Fig.7:Antibacterial Activity of Compound Y4A,Y4B

Molecular Docking Studies :

The molecular docking of two compounds and one of the skin cancer proteins was studied using the Auto Dock program. The results obtained showed that the compound Y4C2 gives the lowest binding energy (ΔG) and is therefore the candidate compound .as an inhibitory compound for skin cancer

S (Kcal/mol)	RMSD (Å)
-7.8390	1.8585

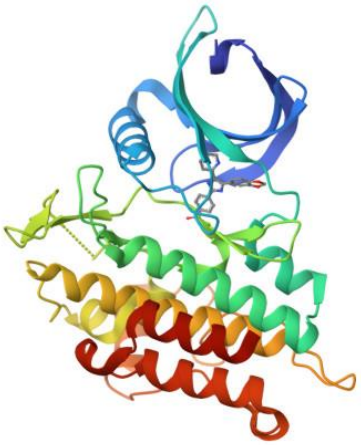
Ligand Interactions Report

Thu Feb 22 02:06:15 2024 (MOE 2015.10)

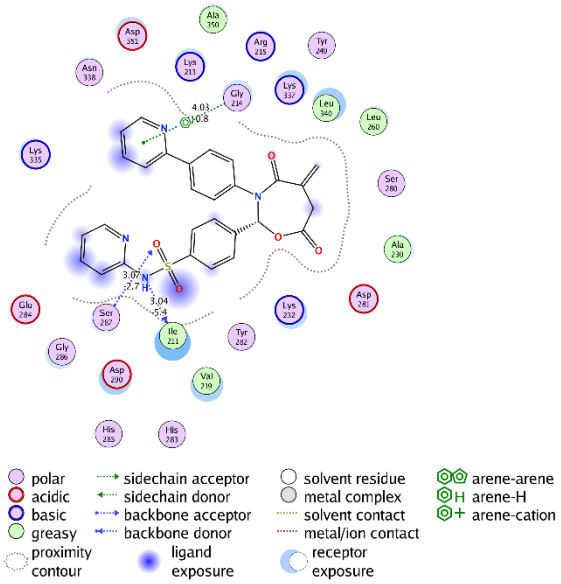
3TZM: TRANSFERASE/TRANSFERASE INHIBITOR / 3TZM

Ligand	Receptor				Interaction	Distance	E (kcal/mol)
N 48	O	ILE	211	(A)	H-donor	3.04	-5.4
O 1	N	SER	287	(A)	H-acceptor	3.07	-2.7
6-ring	CA	GLY	214	(A)	pi-H	4.03	-0.8

Ligand Interactions



Protein ID (3TZM)



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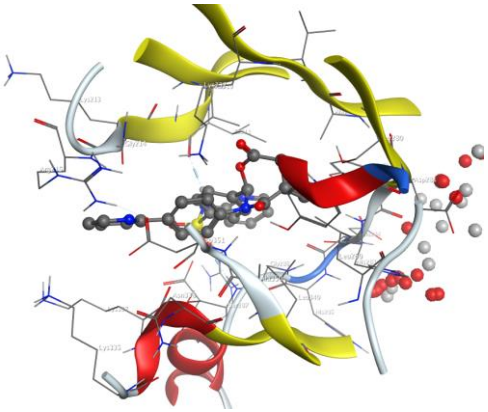

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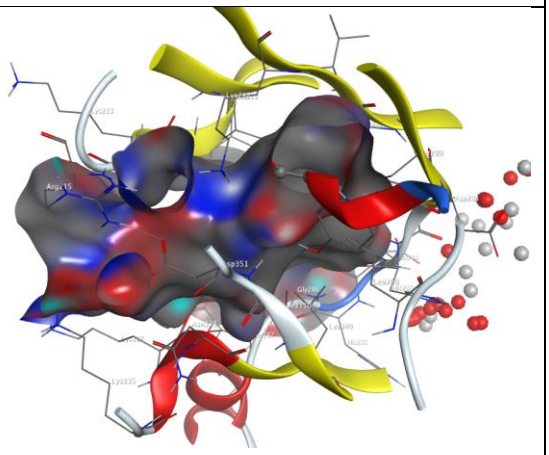


Map

S (Kcal/mol)	RMSD (Å)
-8.6272	1.5530

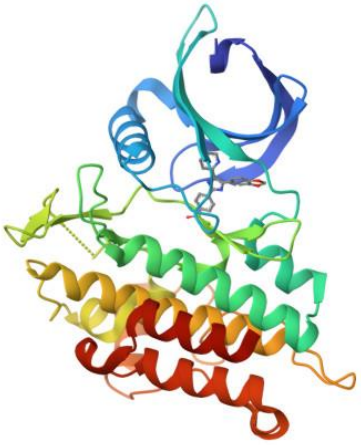
Ligand Interactions Report

Thu Feb 22 01:58:08 2024 (MOE 2015.10)

3TZM: TRANSFERASE/TRANSFERASE INHIBITOR / 3TZM

Ligand	Receptor				Interaction	Distance	E (kcal/mol)
N 57	OE2	GLU	319	(A)	H-donor	2.90	-11.4
O 69	N	ALA	361	(A)	H-acceptor	2.91	-2.6
6-ring	NH1	ARG	357	(A)	pi-cation	3.61	-1.0
6-ring	NH2	ARG	357	(A)	pi-cation	4.09	-0.9
5-ring	CB	ASP	366	(A)	pi-H	4.20	-0.6

Ligand Interactions



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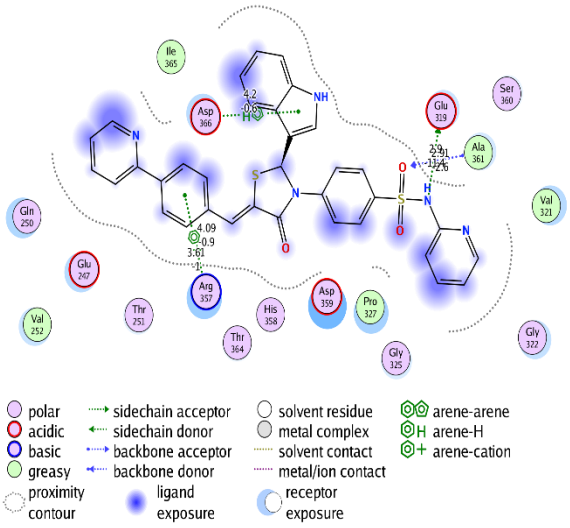

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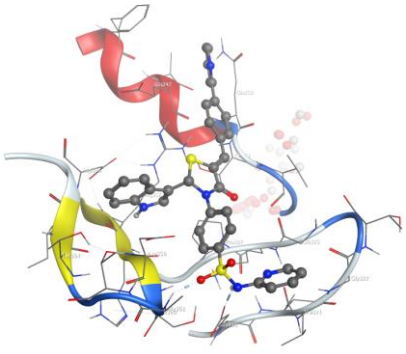

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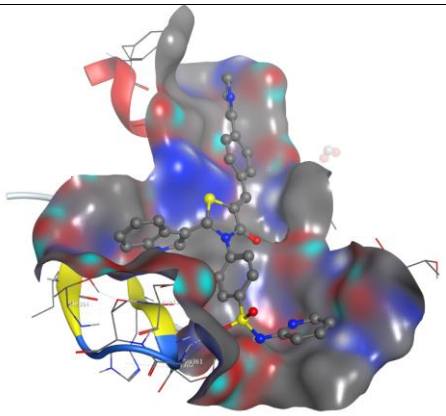

Map

Conclusion:

In this study, several new heterocyclic derivatives were prepared from the reaction of sulfa pyridine with different aromatic aldehydes. The work included preparing two Schiff bases as a first step. It was found that these derivatives are stable at room temperature. While one of these derivatives was oily, the others had high melting points. All these derivatives were confirmed by analysis of spectroscopic data: FTIR, 1H-NMR and 13C-NMR. In addition, biological evaluation confirmed that some of them had good anti-skin cancer and anti-bacterial properties.

Acknowledgement:

The authors express their appreciation to everyone who provided them with a helping hand, as well as to the people who worked with them in the Department of Chemistry/College of Education for Girls/University of Kufa/Iraq .

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