I.R analysis and some biological applications for some Schiff base compounds prepared between (4- di methyl amino benzaldehyde). and some amino acids (Trptophan, Phenylalanine, Asparagine, Glycine and Tyrosine)

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ABSTRACT

According to the results which obtained in this study the design and synthesis of Schiff compounds were produced b simple and rapid reaction, the results showed that some of Schiff base compounds gave antibacterial and anti-fungi activities , compounds(1,2,3 and 5) exhibit antimicrobial activity, On the other side the compounds of (1,2,3,4 and 5 displayed significant activity against Bacillus. The similar compounds (1,2,,3 and 5) provided inhibition zone against Rhizopus Fungi. Also the results indicated that the high concentration of 100 %showed high inhibition zone comparing with the other applied concentration. The same compounds of (1,2,,3 and 5) gave inhibition zone against Rhizopus Fungi and molecular docking model was performed for the synthesized compounds using Autodock Vina against the protein (PDB: 1JIJ). However, the obtained results including (compounds 1 to-5) showed low binding energy against the target protein, In addition, in silico prediction of physicochemical, ADMET and drug-like properties were determined representing that compounds are capable candidates for the advance of new drugs with improved activity and better safety profile.

Introduction

Schiff's bases are a type of chemical substance that is widely used. (Arulmurugan *et al*., 2010). Hugo Schiff was the first to report them in 1864. Schiff's bases are amines with carbonyl groups that condense into Schiff's bases. The azomethine group, with the generic formula RHC = N-R1, is the major structural hallmark of these compounds, with R and R1 being alkyl, aryl, cyclo alkyl, or heterocyclic groups. The chemical compound with the general structure of $R_2C = NR'$ (R' H). They are a type of amine that can be classified as secondary ketimines or secondary aldimines depending on their structure. The name is frequently used interchangeably with azomethine, which refers to secondary aldimines (i.e. $RN=CR_2$), (Eliot,2004).

There are several different naming methods for these compounds. An anil, for example, is a Schiff base produced from an aniline, where R3 is a phenyl or a substituted phenyl, and bis-compounds are commonly referred to as salen-type

compounds. Schiff bases are made by nucleophilic addition of an aliphatic or aromatic amine to a carbonyl molecule, resulting in a hemiaminal. by a dehydration to generate an amine. In a typical reaction, 4,4'-diaminodiphenyl ether reacts with o-vanillin (Jarrabpour,2004). The major component of Ehrlich's reagent is para-dimethylaminobenzaldehyde. It is a powerful electrophile that forms a blue-colored adduct with the electron-rich -carbon (2-position) of indole rings (Kovar *and* Laudsum, 1989). It can be used to find out if there are any indole alkaloids present. Because of steric hindrance, which prevents the reaction from proceeding, not all indole alkaloids produce a colored adduct. Ehrlich's reagent is also used to detect urobilinogen in fresh, cool urine and as a stain in thin layer chromatography. The urobilinogen will not be detected if a urine sample is permitted to oxidize in the air to create urobilin. When a few drops of reagent are added to 3 ml of urine in a test tube, the color changes to dark pink or crimson. The amount of urobilinogen in the urine sample determines the degree of color change (Watt and Chrisp, 1952). The reaction of p-dimethylaminobenzaldehyde with hydrazine produces p-dimethylaminobenzalazine azo-dye, which has an unique yellow color. As a result, it's utilized to determine hydrazine in aqueous solutions using spectrophotometry at 457 nm. para-dimethylaminobenzaldehyde (the word -benz- comes from the Arabic Laban (frankincense from Java). Asimov points out that the name may be pronounced to the tune of the well-known dance "The Irish Washerwoman," and tells a story about how a receptionist of Irish descent mistaken the syllables for the jig's original Gaelic phrases when she heard him sing them that way(Carroll , 1963) It's a simple aldehyde that produces colorful Schiff base adducts with amines, pyrroles, and indoles, and it may be used to screen proteins for residues containing these functional groups, as shown in **Fig. 1**.

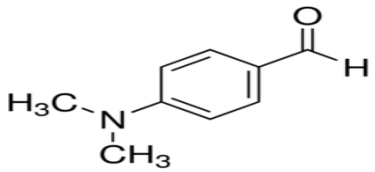


Fig. 1. Structure of (4-Dimethylamino) benzaldehyde.

The Ehrlich reaction, which is a test for the presence of indoles in a sample, frequently uses (dimethylamino)benzaldehyde. The presence of tryptophan residues on proteins is also indicated by this reaction with indole. The major component of Ehrlich's reagent is para-dimethylaminobenzaldehyde. It is a powerful electrophile that forms a blue-colored adduct with the electron-rich -carbon (2-position) of indole rings. It can be used to find out if there are any indole alkaloids present. Because of steric hindrance, which prevents the reaction from proceeding, not all indole alkaloids produce a colored adduct (Manviman and Dhanuskodi ,1980). Ehrlich's reagent is also used to detect urobilinogen in fresh, cool urine and as a stain in thin layer chromatography. The urobilinogen will not be detected if a urine sample is permitted to oxidize in the air to create urobilin. When a few drops of reagent are added to 3mL of urine in a test tube, the color changes to dark pink or crimson. The amount of urobilinogen in the urine sample determines the degree of color change (perr ,1995).

Importance of Amino acids in synthesis of Schiff base are compounds with an amine group, a carboxylic acid group, and an additional chain that differs amongst amino acids. This phrase refers to amino acids with the general formula H NCHRCOOH, where R is an organic substituent, and is particularly relevant in biology .At physiological pH values, amino acids with uncharged amino groups can

form Schiff bases, which gives another potential route for metal complexes(Sari *et al*., 2014). When amino acids are esterified and introduced to the molecular structure, they can improve pharmacological and biological properties of molecules by boosting lipophilicity, reducing toxicity, and increasing bioavailability. Furthermore, amino acids and the molecules that combine with them are significant in understanding the mechanism of transamination in biological systems (Fei- Ran *et al*., 2014).

Amino acids are molecules that have a carboxyl and an amino group, as well as a side chain that differs amongst amino acids. Many types of amino acids are referred to as -amino acids. Monomers are the building blocks of proteins (Al-Salmai *et al*.,2015). Because these groups are present in amino acids, they contain potential donor sites such as (COOH) and (NH2), which could coordinate with metal ions . An imine was created by reacting aldehyde and ketones with primary amines of the types RNH_2 and $ArNH_2$. Schiff's bases are named after Hugo Schiff, who described the synthesis of N-substituted imines in 1864. Schiff base ligands are important in the formation of Schiff base complexes because they have the ability to form stable complexes with metal ions (Abrahimi *et al*., 2014) Due to their applicability in biological, clinical, analytical, and pharmacological research, Schiff bases have also been intensively explored (Abd-Elzar ,2001 and Selvakumar *et al*., 2007).Numerous studies have been conducted to prepare various compounds using Schiff base reactions; the majority of these studies are concerned with using Schiff base compounds for a variety of applications such as antibacterial or antifungal activity, as well as using Schiff base compounds to prepare new compounds; some of these studies and their results are summarized as follows:

Jarina *et al*., (2006) Synthesized , Characterized and studied the anti-oxidant activity of some schiff base compounds included Chloro benzaldehyde Phenylhydrazone and Para Dimethyl aminobenzaldehyde Phenylhydrazone. (Parashuram ,2009) investigated the kinetics and mechanisms of oxidation of 4-hydroxy -3-methoxy benzaldehyde (Vanillin) by Bi (V) in Aqueous Alkaline medium ,they found The title reaction was investigated in aqueous alkaline medium. A first dependence in Bi (V)) concentration and a order in both Vanillin and alkali were obtained at the concentration studied. The effect of added products and the ionic strength of the reaction medium have no significant effect on the reaction rate. Effect of temperature on the rate of reaction has also been studied and Eyring's activation parameters have been evaluated. A mechanism based on the experimental results in proposed and the rate law is derived. Aliyu and Ado, (2011) Studied the properties of Schiff base compounds derived from 2-amino benzoic acid and salicylaldehyde. The Schiff base compounds were used to prepared some of complexes of Mn (II) and Ni (II) with Schiff base derived from salicylaldehyde and 2-amino benzoic acid have been prepared and characterized by gravimetric, potentiometer, molar conductance and infrared analyses. Rashad *et al*., (2012) Investigated new nano-structured Ni(II) Schiff base complex: synthesis, characterization, optical band gaps, and biological activity. The nickel oxide NiO nano powder was obtained from the metal complexes after calcinations. The Schiff base complexes and NiO powders were characterized in detail. The complexes were depicted high activity towards microorganism and breast carcinoma cells.

(Noorjahan Begum and Sreeramulu, 2014) studied the Spectroscopic characterization and biological evolution of ortho vanillin pramipexole Schiff base.the synthesis of Schiff base ligand resulted from the condensation of Pramipexole(N6-propyl-4,5,6,7-Tetrahydro-,1,3-benzothiazole-2,6-diamine) with O-Vanillin (2-hydroxy-3-methoxy benzaldehyde). The compounds were synthesized and characterized using different physic chemical studies as elemental analysis, FTIR, 1H NMR, conductivity, magnetic properties, thermal analysis, and their biological activities. In addition the authors have been screened the compounds for biological activity. The study found that the compounds have shown activity against the organisms like *Escherichia coli*, *Klebsiella* and *Bacillus* subtitles.

Al-Salami *et al* ., (2017) prepared Schiff bases compounds derived from amino acids (Alanine,valine and phenyalanine) with 4- Chlorobenzaldehyde reactions. The Schiff bases compounds were characterized by I.R and Thermal analysis(TGA).The prepared compounds gave good inhibition zones against some species of bacteria. Sree *et al*., (2020) studied the biological activity of some Schiff base compounds by used arginine with 2- hydroxyl- 3- methoxy benzaldehyde , the compounds were subjected to anti-bacterial studies by diffusion method, the results showed significant activity against some of selected bacterial and fungal strains under investigated.

This study tries to create chemical compounds by combining some amino acids (Trptophan, Phenylalanine, Asparagine, Glycine and Tyrosine) by Schiff base reactions using (4- di methyl amino benzaldehyde).The main aims of this study can be design and syntheses compounds of some Schiff base which prepared by reactions between 4-Dimethylaminobenzaldehyde with different amino acids (Trptophan , Phenylalanine, Asparagine, Glycine and Tyrosine and analysis by I.R spectra In addition, using software programs to calculate some of physicochemical properties of organic compounds and study some of biological application of the syntheses Schiff base compounds on some species of bacteria and Fungi.

Experimental Part:

Chemical procedure:

All chemical used in this study were laboratory grade including : (4- di methyl amino benzaldehyde) , and different types of amino acids including (Trptophan , Phenylalanine, Asparagine, Glycine and Tyrosine) in addition to some solvents and solutions: KOH, C_2H_5OH and CH_3COOH,beside Nutrient agar, Subverted agar for antimicrobial activity .The amino acid Schiff bases were prepared as follows: KOH (20 mmol,) was dissolved in methanol (50 cm^3) and (10 mmol) of each the selected amino acids was added. The mixture was stirred magnetically at room temperature , when the mixture became homogeneous, a solution of 4- di methyl amino benzaldehyde (10 mmol) in ethanol (50 cm^3) was added , After two minutes the solution was evaporated to 20% of its original volume and (1 ml) of CH_3COOH was added immediately. After two hours yellow crystals appeared. The crystals were filtered and washed with ethanol. They were recrystallized from hot methanol to give yellow crystals .

Infrared spectra analysis :-

The infrared spectra of the Schiff base compounds were taken in potassium bromide discs using the I.R (Type thermo FT-IR 380Nicolet company) spectrophotometer covering the range from 500 to 4000 cm^{-1}, at central lab of Faculty of Science , Alexandria University.

Antibacterial tests:-

Bacterial cultures:-

Plate cultures of nutrient agar (OXID) media were used for culture of bacteria . the medium was prepared by dissolving of powder in 1liter of sterile distilled water . Then the medium was sterilized by autoclaving at 121 ^{0}C for 15 minutes. The bacteria were cultured and incubated at 37^0 C for 24h.

Antibacterial assay:-

The antibacterial tests were assayed according to the diffusion method. The strains of bacteria used were Gram-positive bacteria (*Bacelli*) and negative –gram (*E.Coli*). All strains were isolated from patients in medicine academe .The identity of all the strains was confirmed. A bacterial suspension was prepared and added to the sterilized medium before solidification under aseptic condition. Schiff base compounds (0.1g from complex in 1litter) were placed on the surface of the culture and incubated at 37C^0 for 24h. After incubation the average of inhibition zones recorded (μm).

Anti-fungi test:

Plate cultures of separated agar medium were used for culture of fungi. the medium was prepared by dissolving 32g of powder in 1liter of sterile distilled water. Then the medium was sterilized by autoclaving at 121 oC for 15 minutes. The fungi were cultured and incubated at 28^0 C from 2 to 3 days. The anti-fungi tests were assayed according to the diffusion method. used were fungal species yeast (*Asparagillus* and *Rhizophus*). All strains were isolated from patients in medicine academe .The identity of all the strains was confirmed. A fungi suspension was prepared and added to the sterilized medium before solidification under aseptic condition. Different concentrations of Schiff base complexes were placed on the surface of the culture and incubated at 28 ^{0}C for 2 - 3days . After incubation the average of inhibition zones recorded as (mm). In this study the compounds obtained were given numbers (**1-5**) for the products of reactions between (4- di methyl amino benzaldehyde) with amino acids of (Trptophan , Phenylalanine, Asparagine, Glycine and Tyrosine), respectively.

Results and Discussion:

The compounds which obtained from the reactions between and the amino acids which used in this study are given in the schematic of the reactions in the Figures of **(4–8)**. All the reactions were occurred according to the Schiff base method. The schematic of each reaction between (4-(dimethylamino) benzaldehyde) with the selected amino acids (Trptophan , Phenylalanine, Asparagine, Glycine and Tyrosine) in this study can be given as following :

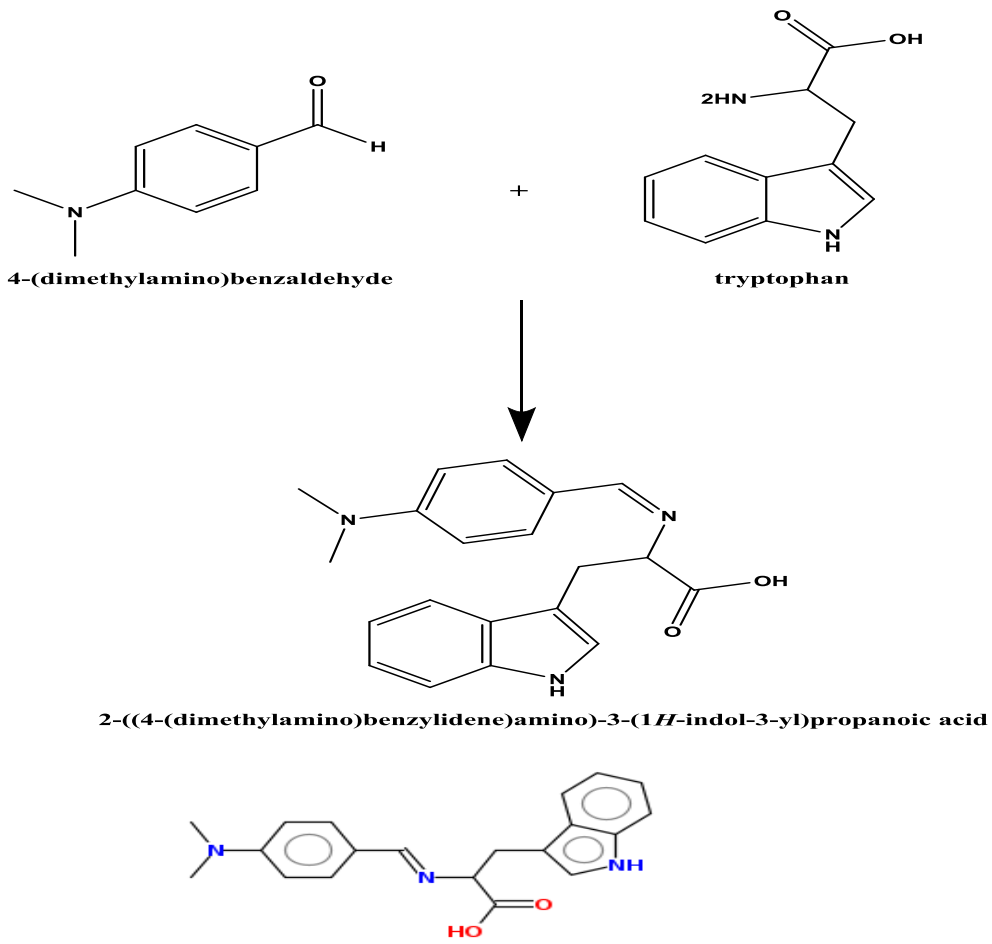


Figure. 2. The reaction between (4-(dimethylamino)benzaldehyde) and tryptophan (Compound 1).

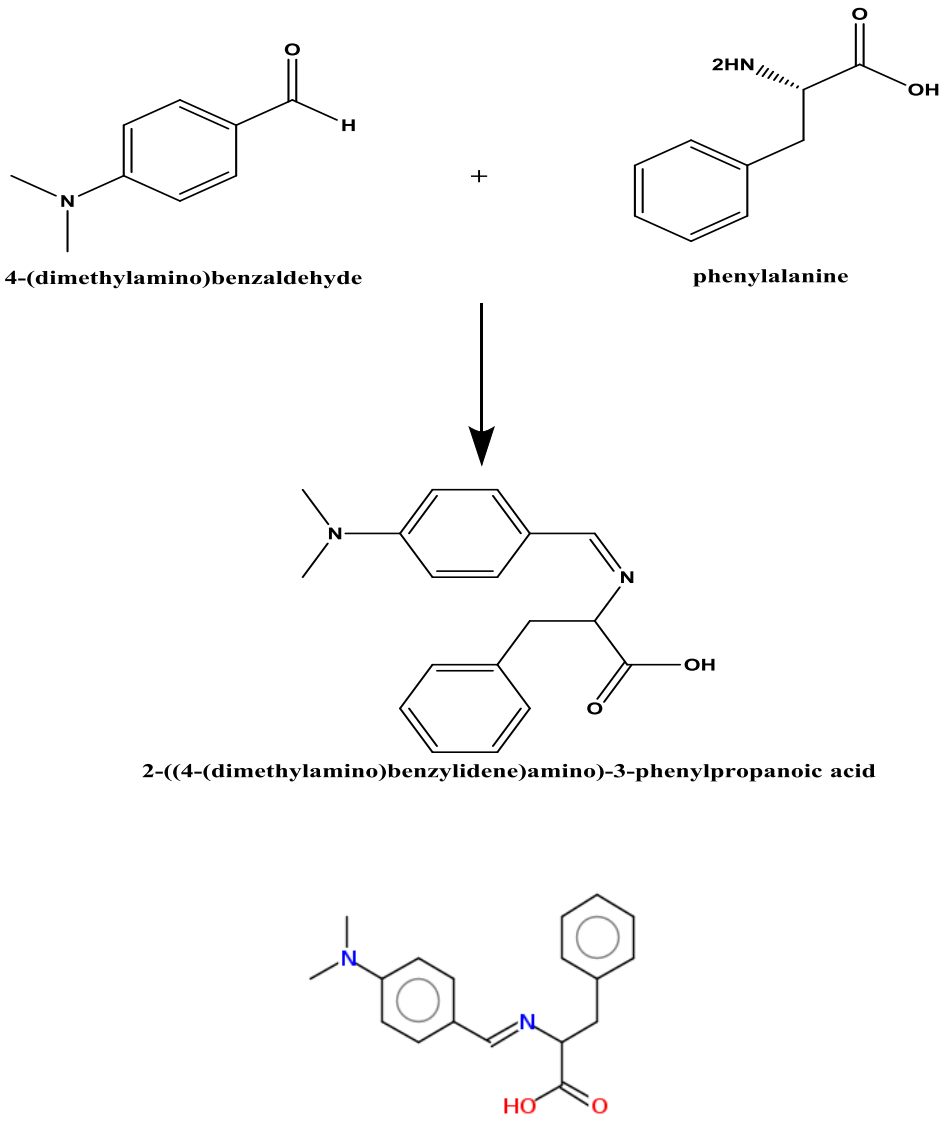


Fig. 3. The reaction between 4-(dimethylamino) benzaldehyde and phenylalanine (Compound 2).

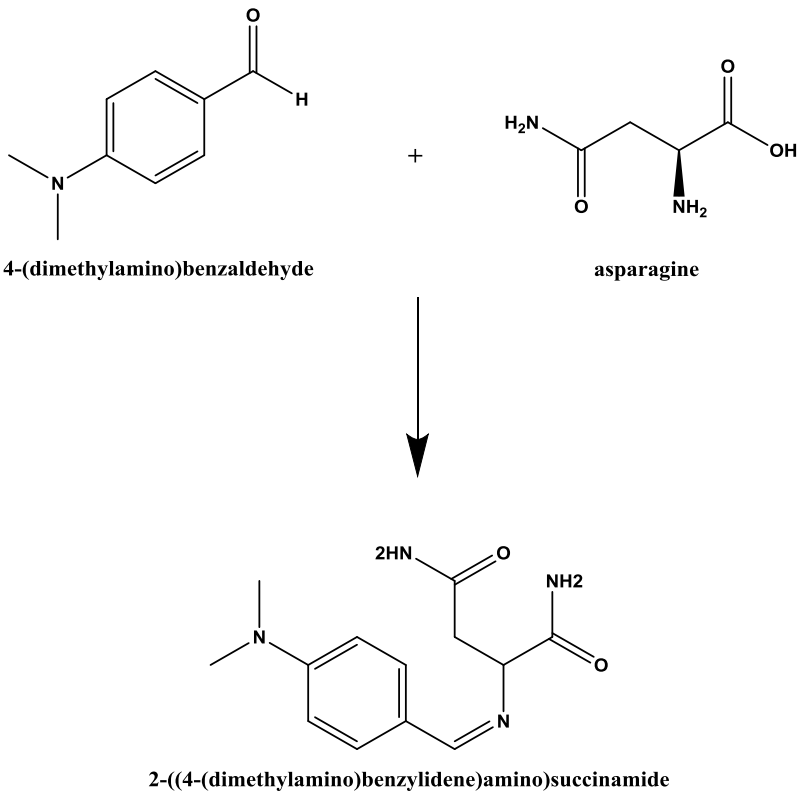


Fig. 4. The reaction between 4-(dimethylamino)benzaldehyde and Asparagine (Compound 3).

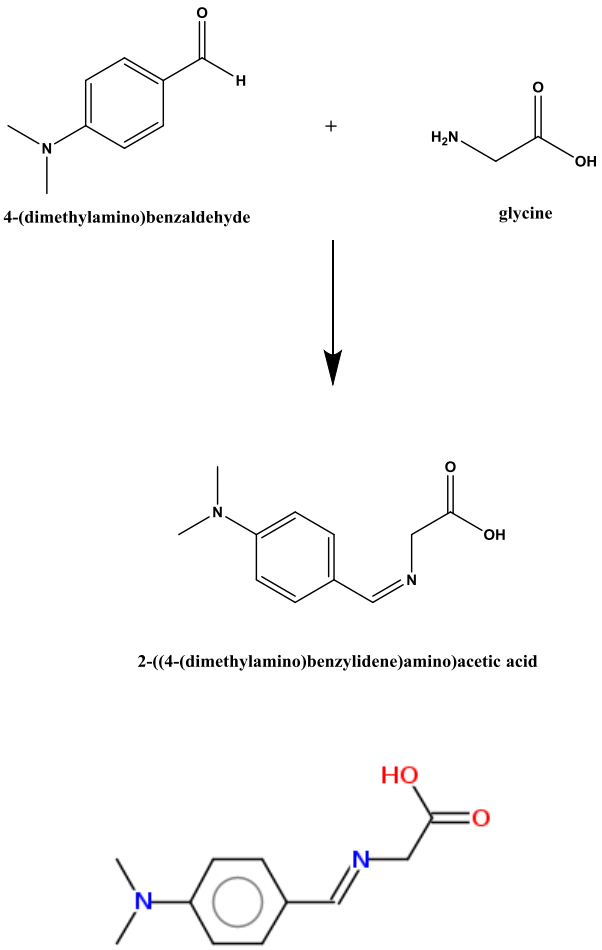
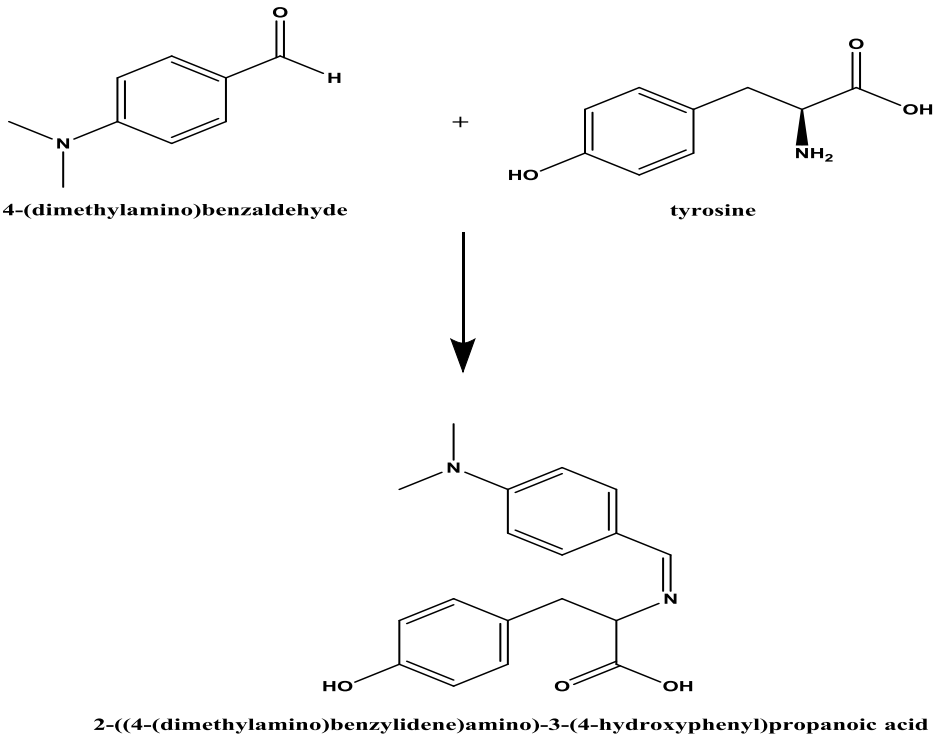


Fig. 5. The reaction between Reaction between 4-(dimethylamino)benzaldehyde and Glycine (Compound 4).



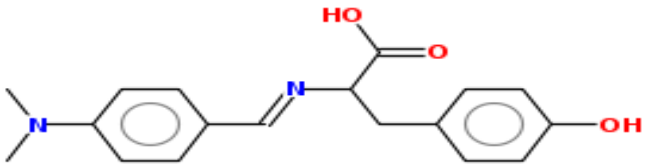


Fig. 6. The Reaction between 4-(dimethylamino)benzaldehyde and Tyrosine (compound 5).

IR spectra studies:-

The (I.R) spectra technique is one of the important methods to study the characterization of the compounds produced between the reactants. The IR spectra were used to describe the structure of the prepared Schiff base, the IR spectra assignment of the Schiff base compounds according to the was achieved by comparing with their vibration frequencies with those of each prepared compounds:

In this study the comparative purposes and in order to facilitate the spectral assignment of Schiff base compounds, the IR spectrum of the new compounds of Schiff base for each reaction between the selected amino acids:(Trptophan , Phenylalanine, Asparagine, Glycine and Tyrosine) with 4-(Di methylamino) benzaldehyde were recorded. The obtained data are presented in ,Table **1** and Figures of **(7-11)**.

Table(1): Fundamental the IR spectra of 4-(Di methylamino) benzaldehyde with (Trptophan , Phenylalanine, Asparagine, Glycine, Tyrosine) Schiff base compounds:

Compounds / Groups	Schiff base (1)	Schiff base (2)	Schiff base (3)	Schiff base (4)	Schiff base (5)
OH	3400	3410	3880	3970	3320
C=O	1710	1640	1620	1725	1610
C=N	1590	1580	1540	1575	1580
C = C	1440	1450	1410	1400	1430
CH_3	1360	1380	1365	1380	1350
CH_2	1410	1400	1405	1370	1420
CH(Aromatic)	3150	3100	3050	3210	3115
CH(Aliphatic)	2890	2820	2720	2830	2825
C-C	850	875	900	890	820

The fundamental I.R spectra of the compounds can be describing as following :

1. Most of prepared compounds have bands located between(3320 - 3410 cm^{-1}) are assigned to OH Group, The relative changing of OH group position indicates the effect of this group by chemical structure of each amino acid and 4 dimethyl amino benzaldehyde (Que *et al* ., 1999).
2. The presence of (C=N) bands for all prepared compounds indicates to produce of Schiff base by the reaction between (NH_2 and C=O) groups , where this band were appeared at (1590 , 1580, 1540, 1575 and 1580 cm^{-1}) for the reactions of the amino acids of (Trptophan ,Phenylalanine, Asparagine, Glycine and Tyrosine) with 4-(Di methylamino) benzaldehyde , respectively.
3. The I.R spectra exhibit presence of (– C=O) bands for all the prepared compounds, indicates to presence of carboxylic acid group of amino acids , These bands are recorded at (1710, 1640 , 1620 , 1725 and 1610 cm^{-1}) for the reactions of the amino acids of (Trptophan ,Phenylalanine, Asparagine, Glycine and Tyrosine) with 4-(Di methylamino) benzaldehyde , respectively. The relative variations of C=O positions of this band are suggesting to coordination through oxygen atom of hydroxyl group (Osman and Amer , 1983).
4. The bands (CH_3), appeared in the range of (1350 - 1380 cm^{-1})assigned to presence of methyl group of 4-(Di methylamino) benzaldehyde , Also the I.R spectra showed presence of CH_2 bonds in all the prepared compounds and located at the range of (1370 -1420 cm^{-1}) and stay in the same position.
5. The C- C of Schiff base bands are located at the range of (820 – 90 cm^{-1}) in all Schiff base compounds .
6. The (CH) aromatic bands are recorded in all Schiff base compounds and located at (3150,3100 , 3050, 3210 and 3115 cm^{-1}) for the reactions of the amino acids of (Trptophan ,Phenylalanine, Asparagine, Glycine and Tyrosine) with 4-(Di methylamino) benzaldehyde , respectively assigned to benzene ring of 4-(Di methylamino) benzaldehyde.
7. The (NH_2) band appear at 3300 Cm^{-1}in Schiff base compounds which containing additional NH_2 group as basic amino acid (Asparagine), the (NH) Schiff base bands located at 1500cm^{-1}.

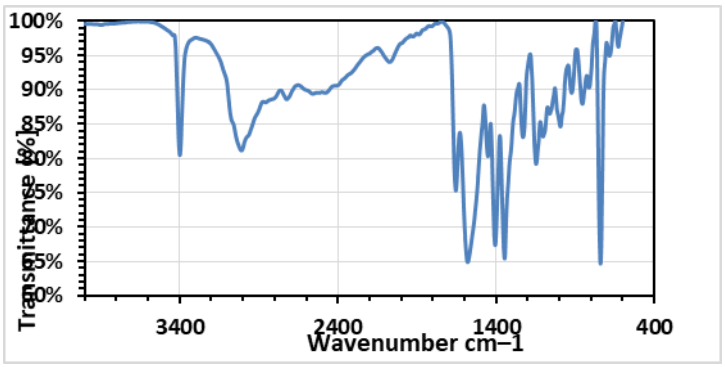


Fig. 7. Fundamental the IR spectra of 4-(Di methylamino) benzaldehyde with Tryptophan Schiff base compound.

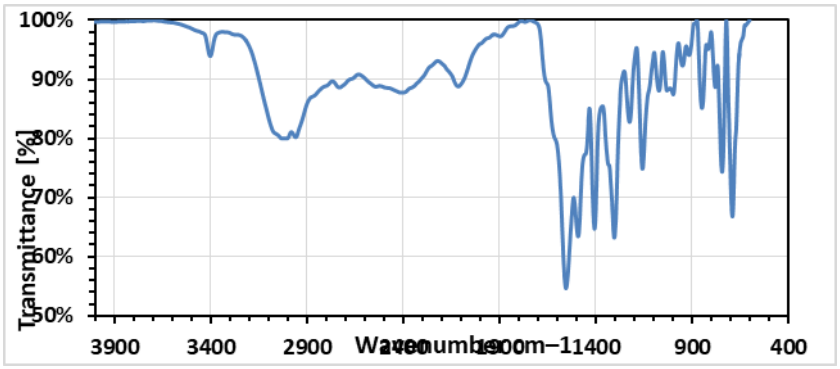


Fig. 8. Fundamental the IR spectra of 4-(Di methylamino) benzaldehyde with Phenylalanine, Schiff base compound.

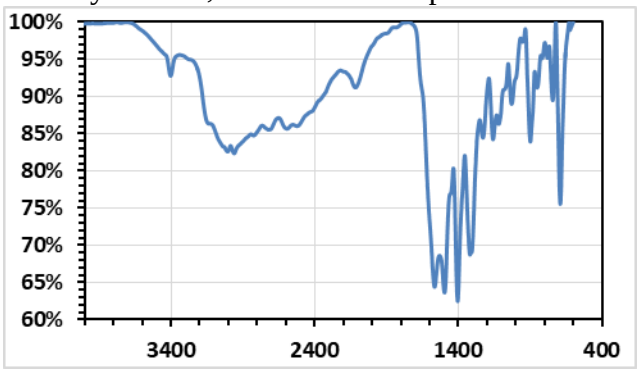


Fig. 9. Fundamental the IR spectra of 4-(Di methylamino) benzaldehyde with Asparagine, Schiff base compound.

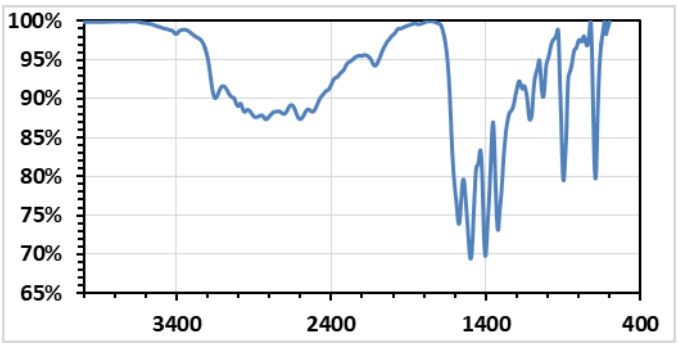


Fig. 10. Fundamental the IR spectra of 4-(Di methylamino) benzaldehyde with, Glycine Schiff base compound.

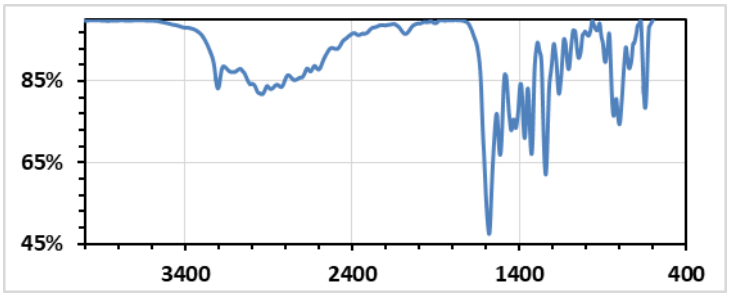


Fig. 11. Fundamental the IR spectra of 4-(Di methylamino) benzaldehyde with Tyrosine Schiff base compound.

Antimicrobial Studies

Antibacterial Activity:

The antimicrobial and antifungal activities were carried on two types of each organism. The antimicrobial activity of Schiff bases representative of *Bacilli* (***Mycobacterium phlei***), Gram-positive bacteria and Gram-negative bacteria (***Escherichia coli***) , and representative fungi species (***Asparagllus and Rhizopus***). By applying the agar diffusion method by cp plate technique (1tap) using try pticase soy agar for bacteria. The products were dissolved in DMSO at concentrations of (25, 50 ,75 and 100 %) were aseptically transferred to preformed cups (100mg/cup) in the dried inoculated .Triticale soy agar plates (Alifano, 1996). All culture plates put on its surface from all concentrations of the solution compounds which prepared, thereafter the plate were incubated inverted at 37C^{o} for 24 h in case of bacteria and at 25 ^{0}C for 48h in case of fungi after incubation, the inhibition zones were recorded in mm. Diameter less than 10 mm indicates no effect (Collins, 1964).The Minimum inhibitory concentration (MIC) was determination of the active compounds. Then 100 ml of each dilution for bacterial species tested against serial dilution was transferred in cups preformed in nutrient agar inoculated with suspension of 10ml microbial cells on the surface of agar plates and incubated at 37 ^{o}C for 24 - 48 hours. After incubation the lowest concentration producing inhabitation was recorded as minimum effective concentration. The results of antimicrobial investigation showed that some of Schiff base compounds of the tested product relived significant antimicrobial effect against on bacteria activity as well as fungi species , also the results indicated that there are

different effecting according to the applied concentrations. In Tables (**2** and**3**), respect to the Minimum inhibitory concentration (MIC), the tested compounds showed comparable antimicrobial activity. With respect to MIC, in general, the antimicrobial activity for the tested products was mostly gave the similar values for Gram-negative and Gram- positive bacteria. In addition to Schiff base of compounds(1,2,3 and 5) exhibit antimicrobial activity for some of the tested organisms comparing to the other compound (4). On the other side the compounds of (1,2,3,4 and 5) exhibit anti bacteria activity against *Bacillus*.

Table (2): Antimicrobial activities of the tested compounds against *E.Coli* (inhibition zone in mm).

Compound Concentrations	Compounds					
No.	***E.Coli***	**1**	**2**	**3**	**4**	**5**
25 %		-	-	1	-	-
50%		2	-	2	-	1
75%		3	3	3	-	2
100%		5	7	5	-	6

Table (3): Antimicrobial activities of the tested compounds against *Bacillus* (inhibition zone in mm).

Compound Concentrations	Compounds					
No.	***Bacillus***	**1**	**2**	**3**	**4**	**5**
25 %		-	-	-	-	-
50 %		2	-	2	-	-
75 %		4	-	5	-	1
100 %		7	3	6	2	6

The inhabitation zones of the compounds of the selected bacteria are shown in the Figures of (**12 - 22**) , and given as following , respectively .

%75

3mm

%100

5mm

%50

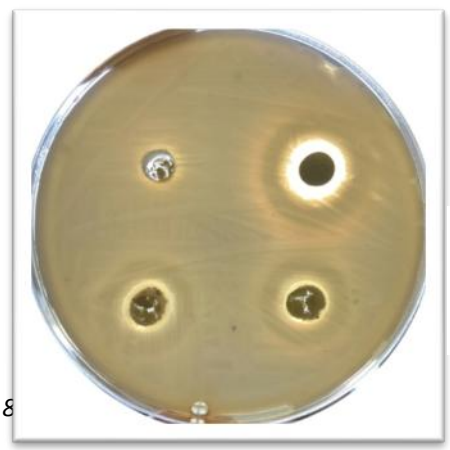
2mm

Fig. 12. Effect of compound (1) concentrations on *E.coli*

Fig. 13. Effect of compound (2) concentrations on *E.coli***.**

Fig. 14. Effect of compound concentrations on *E.Coli.*

(3)



%75

2mm

Escherichia.coli **5**

Fig. 15. Effect of co rations on *E.Coli*

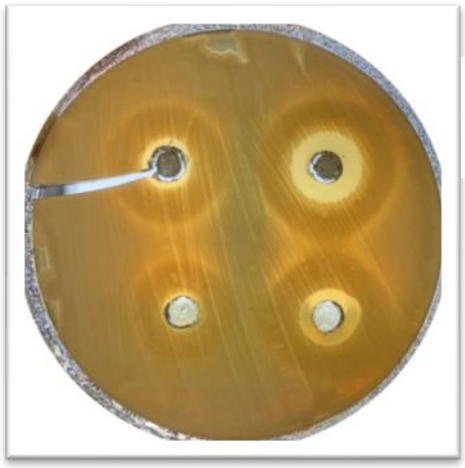


Fig. 16. Effect of compound (1) concentrations on *Bacilli*.

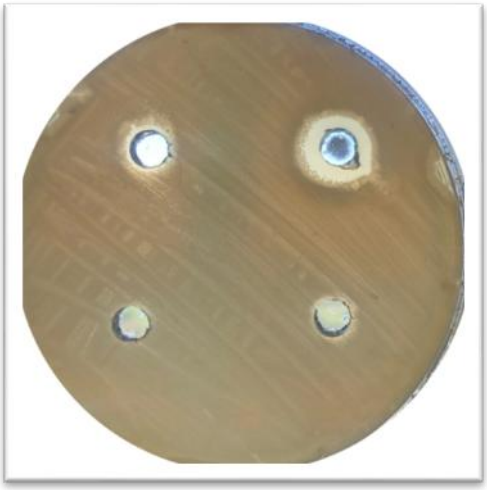


Fig. 17. Effect of compound (2) concentrations on *Bacilli*.

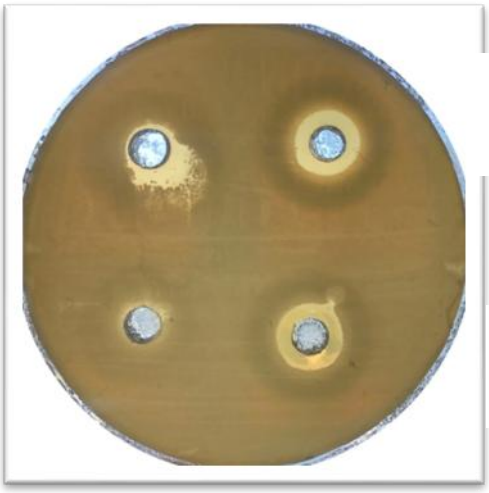


Fig. 18. Effect of compound (3) concentrations on *Bacilli*.

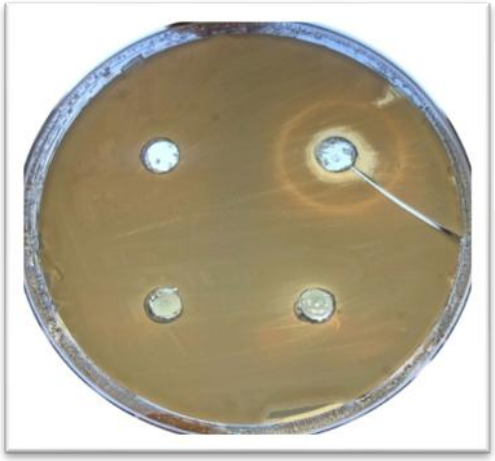


Fig. 19. Effect of compound (4) concentrations on *Bacilli*.

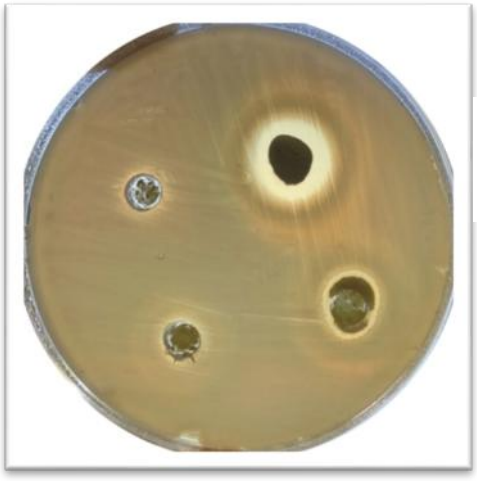


Fig. 20. Effect of compound(5) concentrations on *Bacilli*.

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