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SYNTHESIS, DIAGNOSIS, EVALUATION OF BIOLOGICAL ACTIVITY AND STUDY OF MOLECULAR DOCKING FOR FUROSEMIDE DERIVATIVE AND ITS COORDINATION WITH SOME METALS

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Abstract: *This study includes the preparation and characterization of new compound (4-bromo-5-(N-((4-chlorophenyl) (1,1-dioxide-3-oxobenzo isothiazol-2(3H)-yl)methyl)sulfamoyl)-2-((furan-2-ylmethyl)amino)benzoic acid) from the reaction of furosemide, Saccharin and p-bromo benzaldehyde in a molar ratio 1:1:1 in ethanol. All the complexes are prepared from the reaction of Mannich bases with metal nitrate salts of transition metals such as Co, Ni, Cu and Zn in equimolar ratio (1:1) in ethanol solvent. The prepared compounds were characterized by elemental analysis (C.H.N.S), H-NMR, FT-IR, molar conductivity and magnetic sensitivity were determined. The results showed that furosemide derivatives bi-dentate are coordinated by nitrogen and oxygen atoms with metal, giving tetrahedral geometry. The antibacterial activity was studied for ligands and their complexes using the agar diffusion method. All the prepared compounds were studied and applied to two types of bacteria at different concentrations. It was showed, that the obtained complexes demonstrate a higher inhibitory effect on Staphylococcus aureas bacteria than on Pseudomonas aeruginosa bacteria.*

Keywords: *Furosemide, Mannich base, Mannich reaction, para bromobenzaldehyde, Saccharin.*
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1. Introduction

The Mannich bases were obtained by aldehyde condensation with a combination containing active hydrogen (acidic) and a primary or secondary amine or sometimes ammonia via a Mannich reaction [1-4]. The Mannich bases apply to a comprehensive and essential life. Especially those compounds that contain heterogeneous rings in their composition have been used as antibacterial agents [5]. In addition, a huge number of Mannich bases have been obtained [6], which have proven their ability as an antidote to various diseases and are considered essential substances in the preparation of various active molecules. The Mannich bases have one lone pair of electrons on the nitrogen atom that can donate it to another atom forming good important complexes used for medicinal efficacy against fungi and bacteria [7-8].

The Mannich bases has a one lone pair of electrons on the nitrogen atom can donate it to another atom forming a good important complexes used as medicinal efficacy against fungi and bacteria [7-9]**.** Chelating compounds for Mannich bases that contain active carbonyl and amine groups, can coordinate with transition metals to form different geometric structures, such as an octahedral hexahedral coordinate, a tetrahedral shape, or a tetrahedral and square planar coordinate. Due to these properties, numerous researchers have investigated Mannich complexes and examined their pharmacological properties [9-11].

2. Experemental part

2.1. Materials Employed: All chemicals utilized were procured from Fluka and Aldrich Companies.

2.2. Used Instruments

Infrared spectra of the synthesized compounds were recorded using an FTIR-8400S instrument provided by SHIMADZU. The spectra were recorded in the range of 4000-400 cm^{-1} using KBr pellets. (^{1}H, NMR) Nuclear Magnetic Resonance spectra were acquired using a Bruker Spectrometer (500 MHz), respectively, in the d^6-DMSO solvent. The measurements were conducted using an SMP10 Automatic Melting Point apparatus from the British company STUART. The Magnetic susceptibility measurements of certain solid metal complexes were carried out at the laboratory temperature using a Sherwood Scientific instrument. The Faraday method was employed for these measurements.

2.3. Preparation Methods *Synthesis of Mannich Base Aj.*

Mix 3.307 g of furosemide with 2.05 g of sodium saccharin in absolute ethanol in a water bath and then add 1.85 g of 4-bromobenzaldehyde in absolute ethanol drop by drop to the reaction mixture for one hour with continuous stirring for two hours. The mixture color changed from colorless to yellow. The sediment was recrystallized using absolute ethanol after the excess solvent had evaporated. A yellow precipitate was produced with a melting point between 186 and 188° Celsius, and 92 % yield.

Synthesis of Mannich Bases Complexes A_2-A_5

To obtain A_2 complex, 2.26 g of base A_1 dissolved in 5 ml of pure ethanol was added to 0.01 mol of metal nitrate salt dissolved in 3 ml of absolute ethanol, stirred for 3 hours, then raised for two hours and left to dry. As a result, the residue was recrystallized from pure ethanol. All other complexes were obtained by similar methods. **Table 1** shows the physical properties of the prepared complexes A2-A5.

Table 1. Physical properties of the complexes A_2-A_5

No	Complexes	Colour	M. p., (^{o}C)	Yield, %	Cond.Λm Ω^{-1} cm^2 mol^{-1}	μ_{eff} (BM)
A_2	$[Co(A_1)(NO_3)_2]$	Red	230-232	90	8.4	3.47
A_3	$[Ni(A_1)(NO_3)_2]$	Light green	262-264	85	6.2	2.89
A_4	$[Cu(A_1)(NO_3)_2]$	Dark brown	266-268	83	3.2	1.63
A_5	$[Zn(A_1)(NO_3)_2]$	Brown red	245-247	92	5.6	2.83

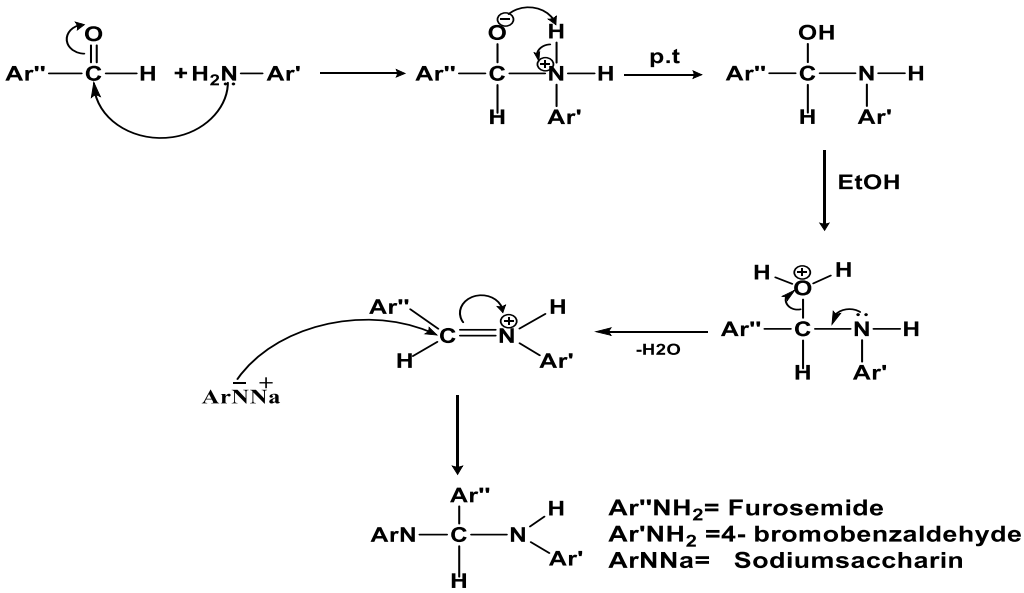
The Biological Activity Study

The biological activity study for the Mannich bases and its complexes are taken against two types of bacteria ***(Staphylococcus Aureus)*** and ***(Pseudomonas*** aeruginosa), using a nutrient medium. The solutions of Mannich base and their complexes were prepared using a DMSO solvent with different concentrations (25, 50, and 100 mg/ml). In this study, we use the agar-well diffusion method and its effect on inhibiting bacteria growth by measuring the diameter of 6 mm circulated on the agricultural medium surface. After this, the dishes were incubated at 37° C for 24 hours. The effectiveness of all compounds was calculated by measuring the inhibition zone diameter.

3. Results and discussion

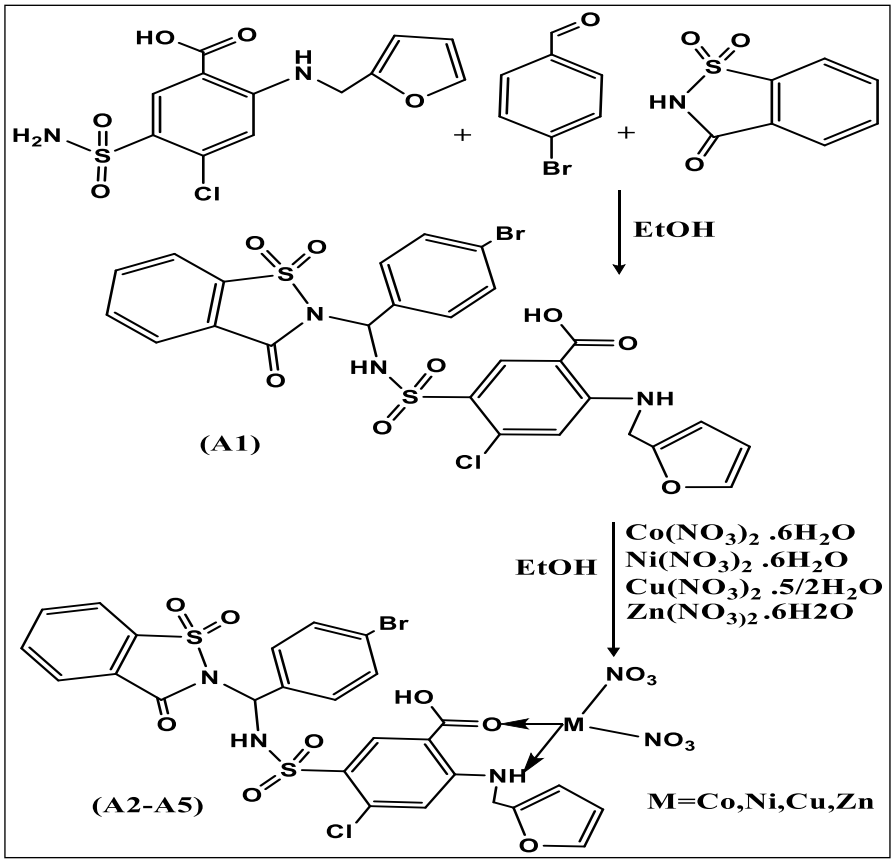
The compound A_1 (4-bromo-5-(N-((4-chlorophenyl) (1,1-dioxido-3-oxobenzo[d]isothiazol- 2(3H)-yl) methyl) sulfamoyl)-2-((furan-2-ylmethyl) amino (benzoic acid) was prepared from the reaction of SodiumSaccharin with 4-bromobenzaldehyde

and furosemide in ethanol as in the following mechanisms below:



Scheme 1. Reaction mechanism scheme

3.1. Infrared Spectra (FT-IR)



Scheme 2. The prepared compounds A1-A5

The spectral peaks for the compound Ai (**Fig.1**) at the frequency 3425 cm^{-1} belonging to

the group of O-H, as well as the appearance of an intense peak at the frequency 3350 cm^{-1} attributed to the group of N-H, and also the formation of a peak at the frequency 3120 cm^{-1} belonging to the group of C-H aromatic, the absence of the double shift belonging to the group of NH_2, which means that the interaction occurred through the group NH2 as well as the appearance of a peak at a frequency of 1705 cm^{-1} attributed to Frequency C = O. The appearance of two peaks belonging to the group SO_2, one of which appears at the site 1321 cm^{-1} and the other appears at the site 1163 cm^{-1}. The appearance of an intense peak at the frequency 1672 cm^{-1} is attributed to the group of C = C of the aromatic ring, as well as the appearance of a peak at the frequency 1442 cm^{-1} belonging to the group of (CH_2), and the formation of a peak at the frequency 752 cm^{-1} belonging to the group of C- Br as shown in **Fig. 1**.

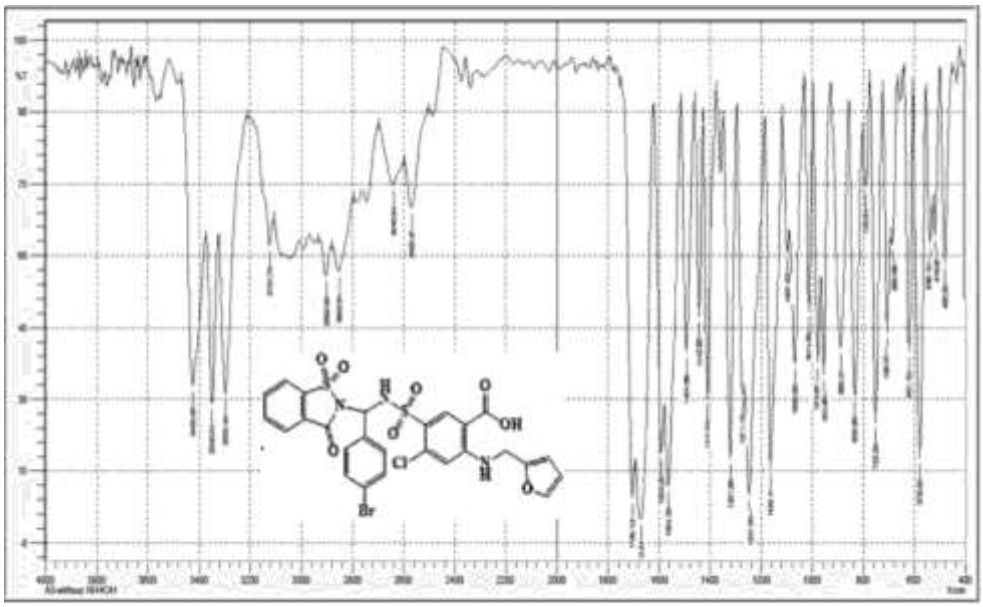


Fig. 1. Infrared Spectrum of the A_1 compound

The appearance of the M-N group absorption beam in the spectra of the complexes and its absence in the ranges of the Mannich bases is a clear indication of the consistency between the metal and the nitrogen atom of the amine group that appeared in the region 516-478 cm^{-1} [12]. **Table 2** shows infrared spectrum peacks (cm^{-1}) for prepared complexes A_2-A_5.

Table 2. FT-IR Spectrum peacks for the prepared complexes A_2-A_5 (cm^{-1}

No	Complexes	O-H	N-H	C=O	SO_2 Sym. Asym.	M-N	M-O	C-Cl
A_2	$[Co(A_1)_2(NO_3)_2]$	3398	3341 3313	1722	1336 1176	516	881	754
A_3	$[Ni(A_1)(NO_3)_2]$	3402	3373 3348	1724	1338 1178	453	663	754
A_4	$[Cu(A_1)(NO_3)_2]$	3400	3325 3284	1724	1336 1178	455	831	752
A_5	$[Zn(A_1)(NO_3)_2]$	3426	3348 3254	1672	1338 1168	478	887	752

FT-IR spectrum of the (A_3) compound (Fig. 2) shows following absorbance peaks: at 3402 cm^{-1} attributed to O-H group; at 3373 and 3348 cm^{-1} for N-H group; at 1724 cm^{-1} for the

C=O group; at 1338 and 1178 cm^{-1} for the SO_2. For the nickel complex the absorbance peaks at 663 cm^{-1} and 453 cm^{-1} reflex the Ni-O and Ni-N bonds, respectively.

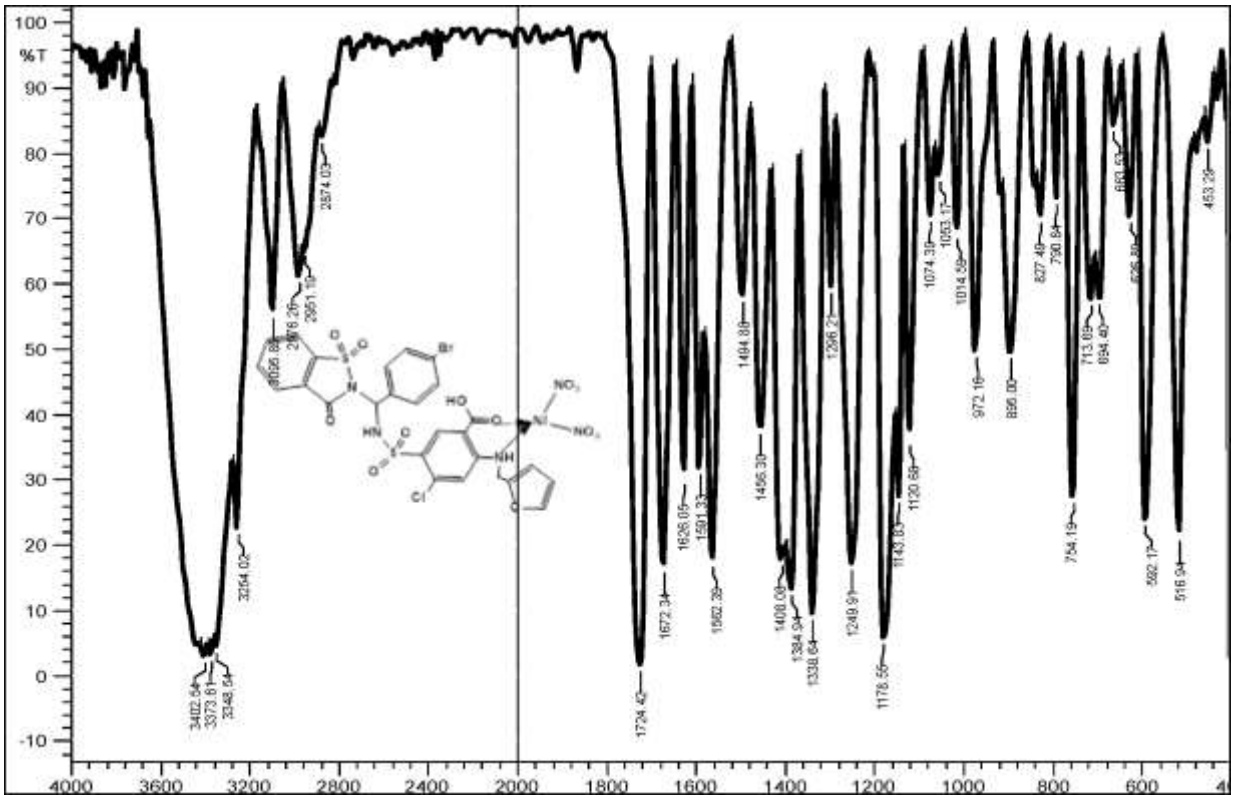


Fig. 2. FT-IR spectrum of the compound A_3

3.2. Nuclear Magnetic Resonance Spectrum (^{1}H-NMR)

The proton N.M.R. spectra of the compounds were measured to support the expected structure of the compound using a solvent DMSO-d^6.

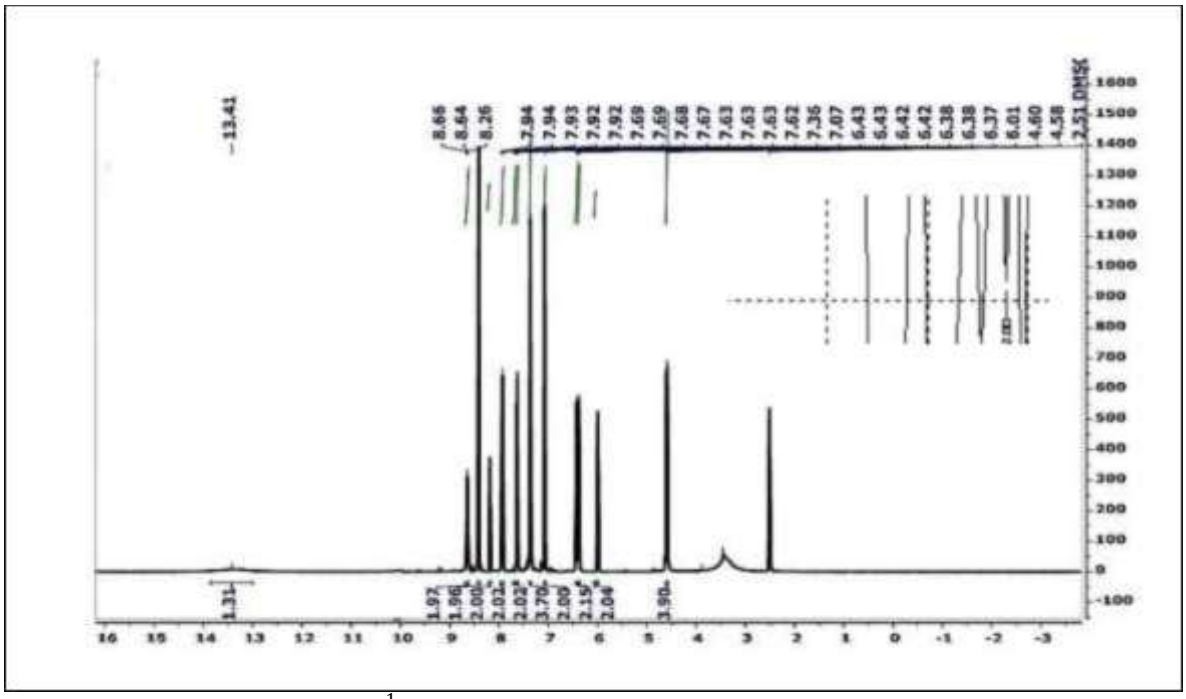


Fig. 3. ^{1}H-NMR spectrum of the compound A_1

The N.M.R. spectrum of ^{1}H-NMR of this compound showed a singlet signal at 4.6 ppm belonging to the (CH_2) group associated with the five-ring of the furosemide, a sign at 6.01 ppm belonging to the CH that connects to the three starting compounds, two signals at the range 6.376.43 ppm belonging to (3H) for the furan ring, a sign at the content 7.3-7.9 ppm belonging to the protons of the aromatic rings of the prepared compound, and a signal at 8.26-8.66 ppm belonging to the two (N-H) groups of f furosemide. Finally, a sign appears at 13.41 ppm belonging to the OH terminal group of furosemide as shown in **Fig. 3**.

3.3 (C.H.N.S) Analysis of elements.

Careful elemental analysis of the prepared compound's was stduded to prove the validity and calculate the practical percentage compared with theoretical percentage for the compounds. All the data were shown in **Table 3.**

Table 3. Elemental analysis of the compounds A_1-A_5

Comp. No.	Formula	Calculated / Theoretical			
		% C	% H	% N	% S
A_1	$C_{26}H_{19}N_3O_8S_2BrCl$	45.81 / 45.86	2.82 / 2.81	6.14 / 6.17	9.44 / 9.42
A_2	$[Co(A_1)(NO_3)_2]$	36.17 / 36.15	2.23 / 2.22	8.18 / 8.11	7.43 / 7.42
A_3	$[Ni(A_1)(NO_3)_2]$	36.17 / 36.16	2.25 / 2.22	8.15 / 8.11	7.44 / 7.42
A_4	$[Cu(A_1)(NO_3)_2]$	35.94 / 35.96	2.24 / 2.21	8.04 / 8.06	7.35 / 7.38
A_5	$[Zn(A_1)(NO_3)_2]$	35.86 / 35.88	2.18 / 2.20	8.01 / 8.05	7.34 / 7.37

3.4 Biological Activity

Table 4 and Figures 4 and 5 show the effect of Mannich bases and their prepared complexes on bacteria, and it was found that the prepared compounds have varying strength effectiveness in inhibiting of the growth of studied bacteria. It was also noted that the inhibitory ability of metal complexes was higher than that of Mannich bases in the development of selected bacteria due to the small invasion shown by bacteria to such metals. It was also noted that the inhibition of the growth of the bacteria type *Staphylococcus aureus* is higher than the inhibition of the development of the bacteria type *Pseudomonas* aeruginosa, and this is due to the structure of the cell wall as the bacteria positive for the dye Cram contain less amino acids than the harmful bacteria for dye Cram. The negative bacteria of the dye gram contain fatty substances higher than the positive gram. The highest inhibition of bacteria was for complex A3 [13], and the lowest inhibition was for the compound A5.

Table 4. Inhibition radius (mm) of Mannich bases and their prepared complexes against the studied bacteria

Comp. No.	*Streptococcus mutants*			*Pseudomonas aeruginosa*		
Conc. (mg/ml)	25	50	100	25	50	100
A_1	14	19	23	11	14	18
A_2	19	23	25	12	18	20
A_3	20	22	26	14	17	22

A_4	21	24	31	19	22	29
A_5	9	14	19	7	11	16
Ampicillin	23	26	32	21	26	32
Amoxicillin	21	24	34	20	25	31

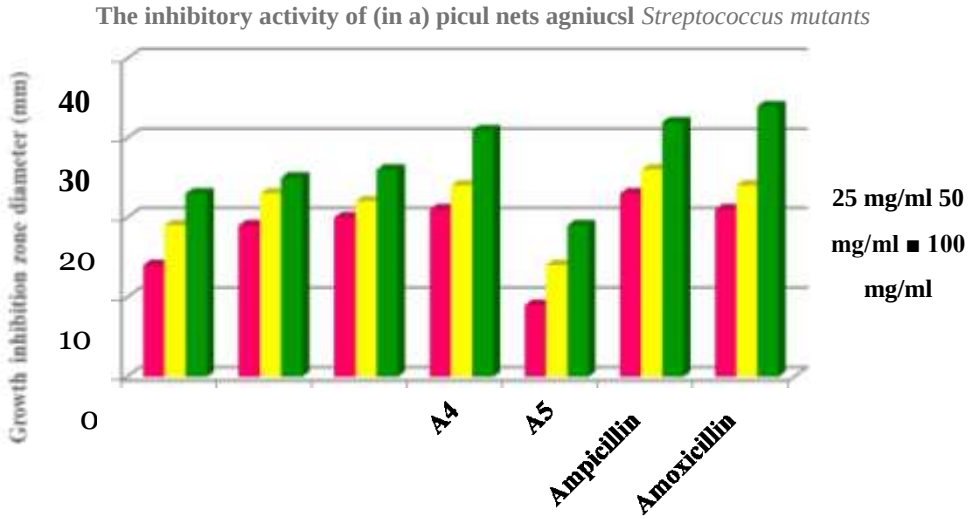


Fig. 4. Biological activity of the ***Streptococcus Mutants.***

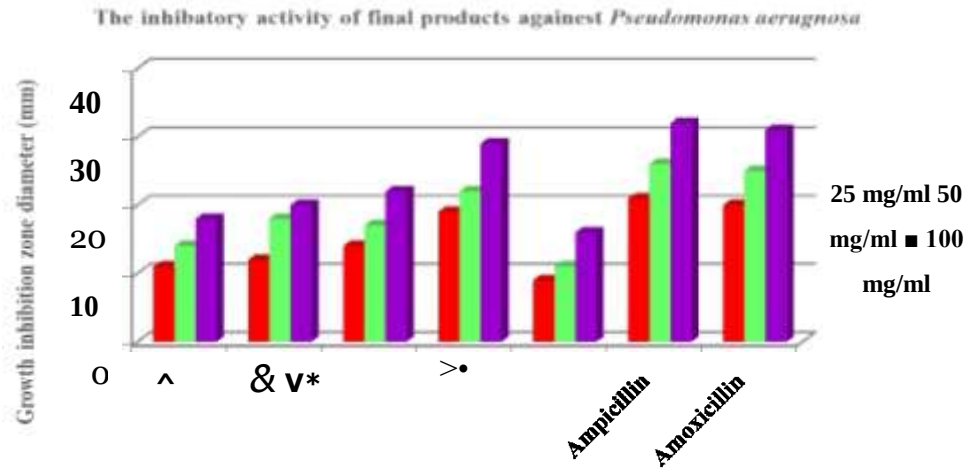


Fig. 5. Biological activity of ***Pseudomonas Aerugnosa***

3.5 Study of Molecular Docking Compounds [14, 15]

Molecular docking of some prepared compounds Ai, A_3, A_4 was carried out on one line of the bacterium Pseudomonas aeruginosa, where the process of energy recovery of the studied carriers was completed in order to obtain the most stable vacuum form (lowest interfering energy). The composition of Pseudomonas aeruginosa bacteria was downloaded from the World Bank Protein Bank (6R3X receptor) and a personal calculator was used. In this case, the binding energies of the compounds were calculated as indicated in **Table 5**. The study of molecular fusion of the obtained organic derivatives made it possible to determine the number and types of bonds through which these obtained derivatives bind to amino acid residues found in the active center through the formation of a series of bonds [16].

Table 5. Values of binding energy, hydrogen bond lengths and amino acid effect between prepared compounds and receptor (6R3X) One line of Pseudomonas aeruginosa

Comp. No	Correlation Energy Docking Score	RMDS	Hydrogen bond			Other amino acids affected by Vandervaalz and other forces	Number of amino acids affected
			Number of ydrogen bond	Associated amino acidosis	Hydrogen bond length		
Ai	-6.286	2.27	3	Arg.517 Met. 553 Arg.68	2.41(A) 1.92(A) 2.04(A)	Val.555, Arg.438 Asp.253, Leu.260 Pro.556,Asn.69 Glu.258,Thr.256 Asn.554	9
A3	-7.389	2.38	3	Tyr.223 Arg.331 Arg489	1.82(A) 2.08(A) 2.40(A)	Ser.249,Arg.335 Asp.332,Leu.221 Glu.255,Met.436 Gly.534,Thr.487 Ala.220,Lys.297 Ser.249,Asn(351,348) Ter(407,523,498,238)	18
A4	-6.631	4.19	3	Arg.489 Arg.335 Arg.331	2.28(A) 2.04(A) 2.00(A)	Val.333,Glu.500 Asn.(501,351) Thr.487,Ala.485 Asp.332,Phe.533 Ser.294,Ter.(532,409, 407,503,487,)	14

The study showed that compound Ai reacts with amino acid residues located in the active center, forming two types of bonds. First, three hydrogen bonds are formed, the first of which connects the amino acid residue Arg.68, located in the active center, with the electron pair of the oxygen atom of the pentaring sulfoxide group, and the second and third connect the amino acid residues Met.553, Arg.517, located in the active center , with the electron pair of the oxygen atom of the hydroxyl group of the carboxylic acid. Furthermore, a number of amino acids are exposed to Van der Waals forces, as shown in Table 5.

It has been discovered that compound A_3 interacts with the amino acid residues found in the active site by forming two types of bonds, specifically three hydrogen bonds. The first hydrogen bond linking the amino acid residue Arg.331, Arg.489 located in the active site with the electron pair of the penta-ring sulfoxide oxygen atom, and the third linking the amino acid residue Tyr.409 located in the active site with the electron pair. For an oxygen atom of the sulfamide group, a Pi- Alkyl type bond residue of the amino acid Arg.331 which resides in active situ with the electron pairs of the aromatic ring, and a number of amino acids affected by Van der Waals forces (see Table 5).

The study showed that the compound (A_4) reacts with the amino acid residues that reside in the active site by forming three hydrogen bonds. One of them linking the amino acid residue Arg.489 located in the active site with the electron pair of the penta-ring sulfoxide oxygen atom, and the second one bonding the amino acid residues Arg.335 located in the active site with the electronic pair of the sulfamide group oxygen atom, and the third one linking the amino acid residues. Arg.331 is in active location with the electron pair of an oxygen atom of the hydroxylic acid carboxylic group. A Pi-Alkyl type bond the residue of the amino acid Val.333 which resides in active situ with the electron pairs of the furan aromatic ring, and a number of amino acids affected by Van der

Waals forces as in **Table 5** above.

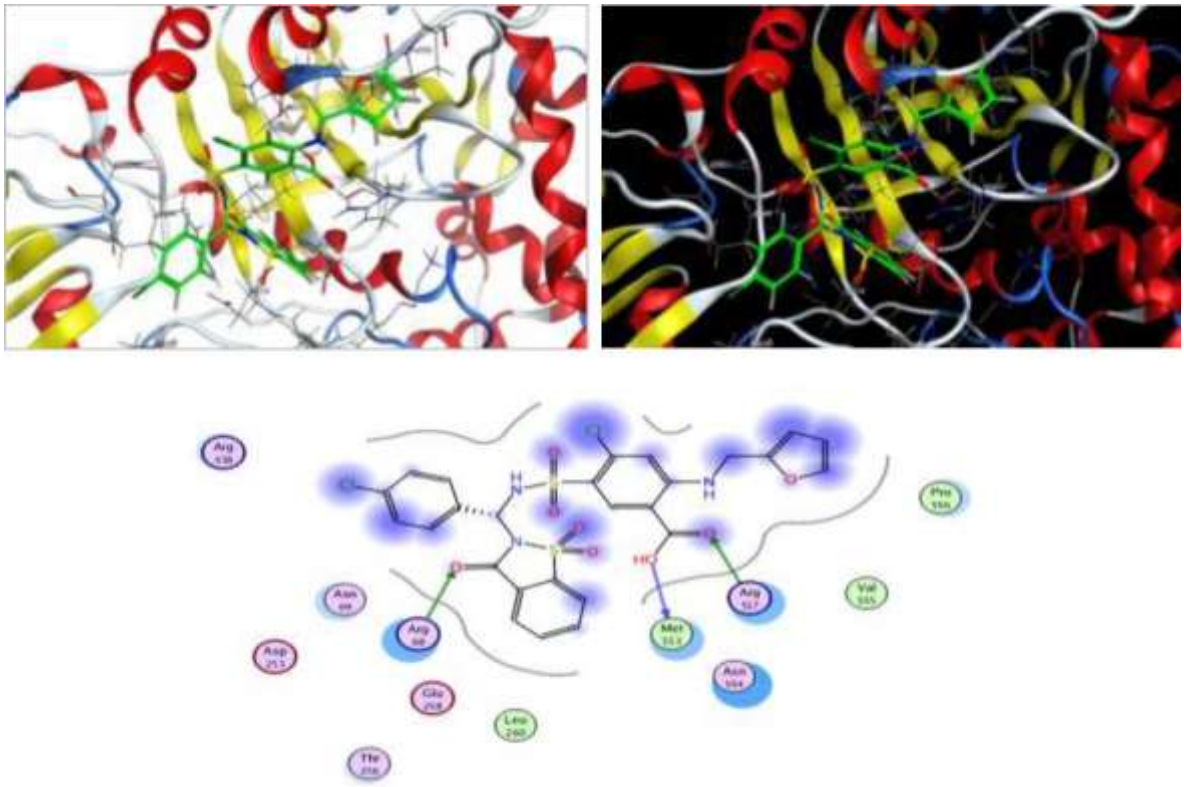


Fig. 6. Interactions Ai with amino acids in 3D and 2D

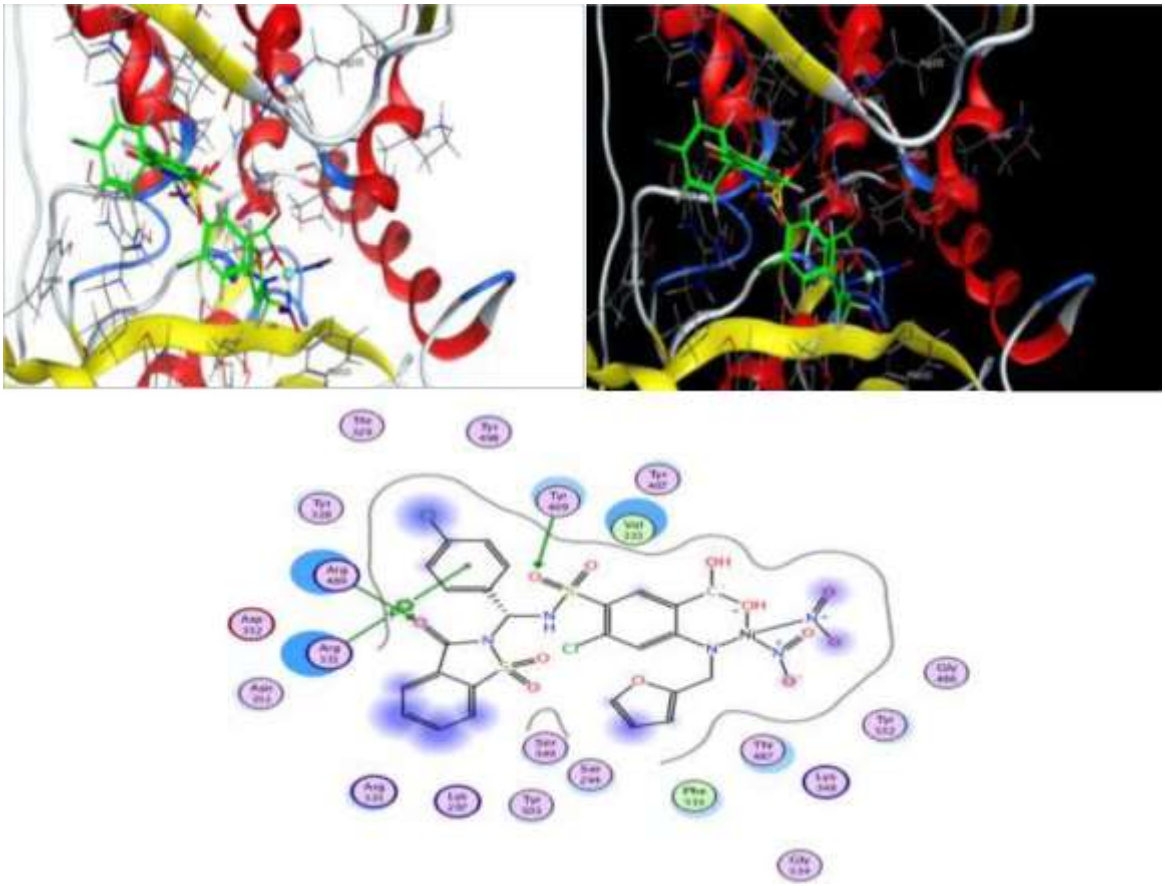


Fig. 7. Interactions A_3 with amino acids in 3D and 2D

Figures 6, 7, and 8 show two-dimensional and three-dimensional representations of molecular anchoring and association between prepared compounds and the 6R3X receptor (6R3X) single line of *Pseudomonas aeruginosa* bacteria.

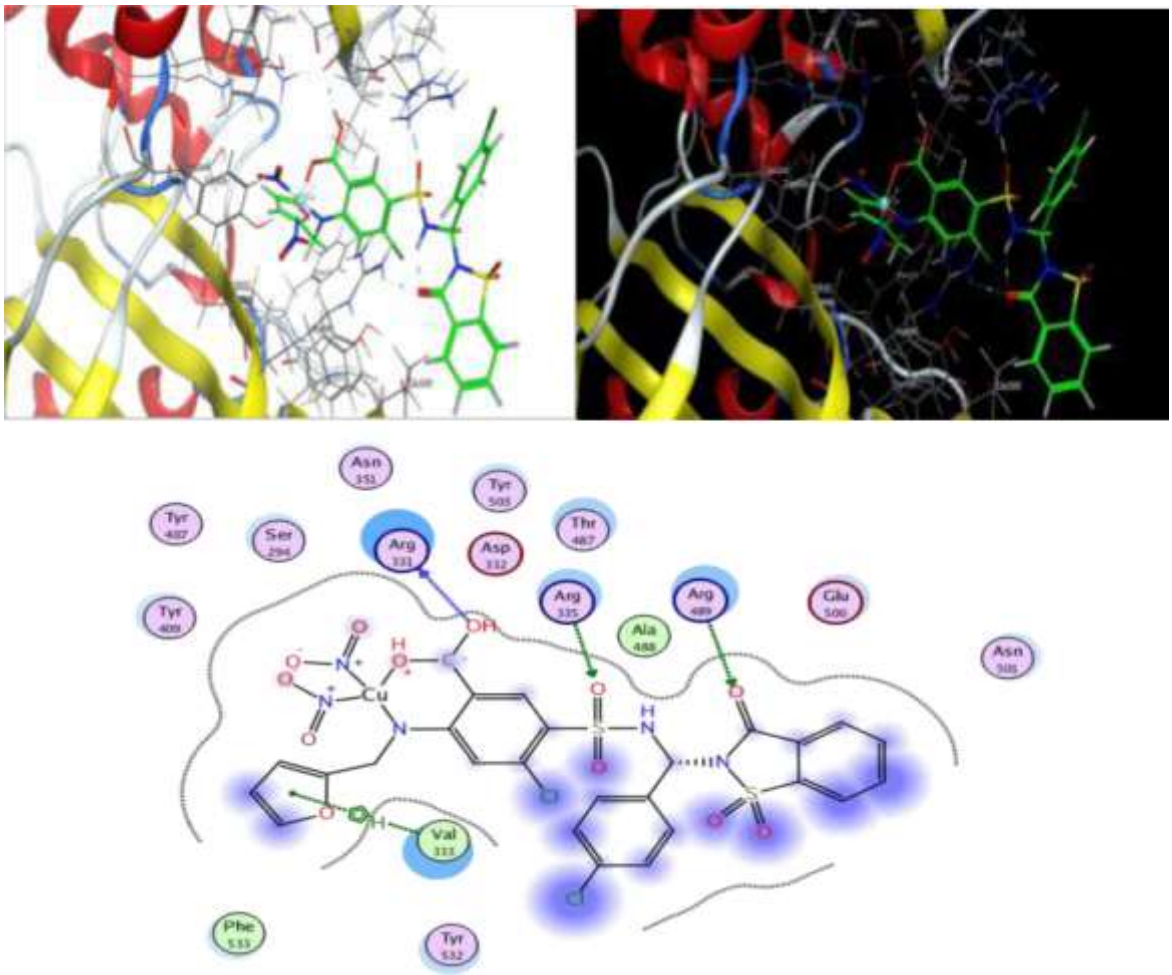


Fig. 8. Interactions A_4 with amino acids in 3D and 2D

4. Conclusions

Mannich base Ai was obtained from the reaction of furosemide, sodium saccharin, and bromobenzaldehyde. Then we obtained the complexes based on the Mannich base for the ions of the elements Co(II), Ni(II), Cu(II) and Zn(II). The symmetry of the Mannich base with the metals in the complexes A_2-A_5 was through the nitrogen atom of the amine group and the oxygen atom of the furosemide group and was used. These complexes are tetrahedral in shape.

The results of the biological study showed that Mannich base and its complexes have a higher inhibitory activity against ***Staphylococcus aureas*** bacteria than against ***Pseudomonas aeruginosa*** bacteria.

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FUROSEMID TÖRƏMƏSİNİN SİNTEZİ, DİAQNOSTİKASI, BİOLOJİ AKTİVLİYİNİN QİYMƏTLƏNDİRİLMƏSİ, MOLEKULYAR DOKİNQİ VƏ BƏZİ METALLAR İLƏ KOORDİNASİYASININ ÖYRƏNİLMƏSİ

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Xülasə: Bu tədqiqat yeni (4-bromo-5-(N-((4-xlorofenil) (1,1-dioksid-3-oksobenzo izotiyazol-2(3H)-il)metil)sulfamoil)2-((furan-2-ilmetil)amino)benzoy turşusu) birləşməsinin furosemid, saxarin və p-brom benzaldehidin 1:1:1 mol nisbətində etanolda reaksiyasından alınmasına və xassələrinin öyrənilməsinə həsr olunmuşdur. Bütün komplekslər Co, Ni, Cu və Zn keçid metallarının nitrat duzları ilə Mannix əsaslarının ekvimolyar nisbətdə (1:1) etanolda reaksiyasından sintez edilmişdir. Sintez edilmiş birləşmələr element analizi (CHNS), ^{1}H-NMR, İQ-spektroskopiya metodları ilə xarakterizə edilmiş, onların molyar keçiricilik və maqnit həssaslığı təyin edilmişdir. Nəticələr göstərir ki, furosemid törəmələri azot, oksigen atomları, metal ilə bi-dentant koordinasiya edir və nəticədə tetraedrik quruluş əmələ gətirir. Liqandların və onların komplekslərinin antibakterial aktivliyi aqar-diffuziya üsulu ilə öyrənilmişdir. Alınmış birləşmələr müxtəlif qatılıqlarda iki növ bakteriyaya qarşı tədqiq və tətbiq edilmişdir. Müəyyən edilmişdir ki, alınmış komplekslər *Pseudomonas aeruginosa* bakteriyalarına nisbətən *Staphylococcus aureas* bakteriyalarına qarşı daha yüksək inhibitor təsiri göstərirlər.
Açar sözlər: furosemid, Mannix əsasları, Mannix reaksiyası, parabromobenzaldehid, saxarin.

СИНТЕЗ, ДИАГНОСТИКА, ОЦЕНКА БИОЛОГИЧЕСКОЙ АКТИВНОСТИ И ИЗУЧЕНИЕ МОЛЕКУЛЯРНОГО ДОКИНГА ПРОИЗВОДНОГО ФУРОСЕМИДА И ЕГО КООРДИНАЦИИ С НЕКОТОРЫМИ МЕТАЛЛАМИ

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Абстракт: Настоящее исследование посвящено получению и изучению свойств нового соединения (4-бром-5-(№((4-хлорфенилX1,1-диоксид-3-оксобензоизотиазол-2(3H)-ил)метил)сульфамоил)- 2-((фуран-2-илметил)амино)бензойная кислота) реакцией фуросемида, сахарина и р-бромбензальдегида в мольном соотношении 1:1:1 в этаноле. Все комплексы получены реакцией оснований Манниха с нитратными солями переходных металлов, таких как Co, Ni, Cu и Zn, в эквимолярном соотношении (1:1) в растворителе этаноле. Полученные соединения были охарактеризованы элементным анализом (CHNS), *H- ЯМР, ИК-спектроскопией, а также определением молярной проводимости и магнитной чувствительности. Результаты показали, что производные фуросемида бидентатно координируются атомами азота и кислорода с металлом, придавая тетраэдрическую геометрию. Антибактериальную активность лигандов и их комплексов изучали методом агар-диффузии. Все полученные соединения были изучены и применены к двум видам бактерий в разных концентрациях. Показано, что полученные комплексы проявляют более высокий ингибирующий эффект по отношению к бактериям *Staphylococcus aureas,* чем к бактериям *Pseudomonas aeruginosa.*
Ключевые слова: фуросемид, основание Манниха, реакция Манниха, парабромбензальдегид, сахарин.