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Molecular Docking, I.R Characterization and Biological Investigation of New Schiff base Compounds Synthesized between Sulphanilic Acid with (Phenylalanine, Asparagine, and Arginine)

[1] Hana Faraj Saeid, [2] Hanan A Khalied, [3] Somia M Abdalla Elsheikhi, [4] Hamad MA Hasan, [5] Rana T Idres

[1, 2, 3] Faculty of Pharmacy, Omar Al-Mukthar University, Libya
[4, 5] Faculty of Science, Omar Al-Mukthar University, Libya

Corresponding Author: **Hana Faraj Saeid**

Abstract

New Schiff base compounds were prepared by reactions between Sulphanilic acid with different amino acids (Phenylalanine, Asparagine, and Arginine).The synthesized Schiff compounds were showed antibacterial and antifungal activities, Schiff base (Arginine, Asparagine and phenylalanine) of the tested products revealed significant antimicrobial effect against bacteria, In general, the antimicrobial activity for the Schiff base products was more effective against Gram-positive than Gram-negative bacteria strains. Some of physicochemical properties were calculated and revealed H-bond donors and acceptors to construct activity, also the properties of absorption, molecular weight, molecular formula, surface area and rotatable bonds. In addition, the interactions between the synthesized compounds were estimated by using docking protocol, also the types of interactions as H-Bond, Vander Waals and Carbon H –Bond were recorded different of the synthesized compounds.

Keywords: Sulphanilic Acid, Schiff Bases, Amino Acids (Arginine, Asparagine, Phenylalanine), Physiochemical Properties, Antibacterial and Antifungal Activity

Introduction

Schiff bases are formed by reacting aldehydes or ketones with amines to form imine or azomethine group. These Schiff bases are extensively utilized as drugs which are biological active compounds due this reason it is widely used for industries (Yılmaz *et al*., 2017) [45] and (Esmaielzadeh *et al*., 2016) [11]. Schiff bases are important due to carbon nitrogen double bond (C=N) which can coordinate with metal. These important compounds have been reported to possess different biological activities such as antifungal, analgesic, anti-inflammatory, antibacterial, antioxidant, antitumor, cardiovascular, antitubercular (Neelakantan *et al*., 2008) [28] and (Sharma *et al*., 2013) [37] and as local anesthetic (Singh *et al*., 2012) [38]. Apart from these synthetic imine groups are synthesized in labs various natural products compounds. The imine group present in such compounds has been shown to be critical in their biological activities. Schiff base ligands are able to coordinate in various oxidation states with many different metals (Sadeek *et al*., 2015) [32]. Amino acids have importance in Schiff base complexes formation in which these can act as ligands due to their physiological and pharmacological activities. Moreover, these metal chelates appear to be involved in many of biological processes, such as transamination, racemization and carboxylation (Abdel-Rahman *et al*., 2013) [3]. This study tries to create complexes by combining some amino acids (Phenylalanine, Asparagine and Arginine) with (Sulphanilic acid) by Schiff base reactions, the aims of the study some of biological application of the synthesized compounds on some species of bacteria.This manuscript was aimed to synthesis new Schiff base compounds by direct and rapid reactions and evaluate the anti –bacteria activity.

Materials and Methods

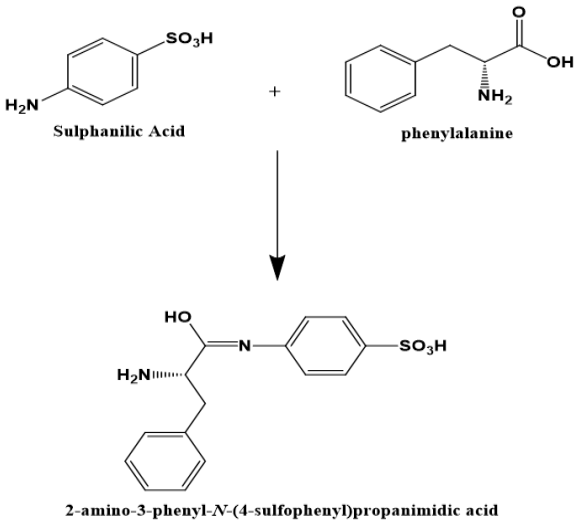
Chemical procedure:

All chemical used in this study were laboratory grade including: (Sulphanilic acid), different types of amino acids including (Phenylalanine, Asparagine and Arginine), metal ions of iron, Cadmium and Cobalt in addition to some solvents and solution: KOH, C_2H_5OH, CH_3OH and CH_3COOH, beside Nutrient agar, Subverted agar for antimicrobial activity.

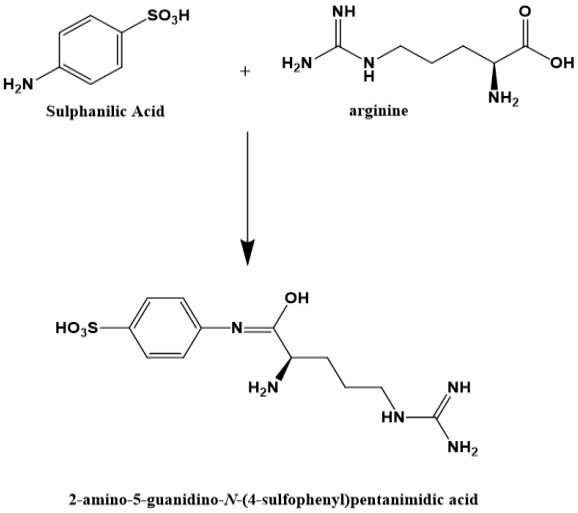
Synthesis of Schiff bases:

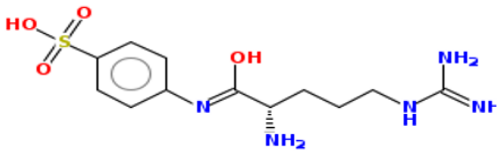
The amino acid Schiff bases were prepared as follows: KOH (20 mmol,) was dissolved in methanol (50 cm^3) and (10 mmol) of each the selected amino acids was added. The mixture was stirred magnetically at room temperature, when the mixture became homogeneous, a solution of Sulphanilic (10 mmol) in ethanol (50 cm^3) was added, after few 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 (Hasan *et al*., 2021). The schematic of each reaction between (Sulphanilic acid) with the selected amino acids (Phenylalanine, Asparagine and Arginine) in this study presented as following:

Scheme 1: Reaction between sulphanilic Acid and Phenylalanine, (comp.1)

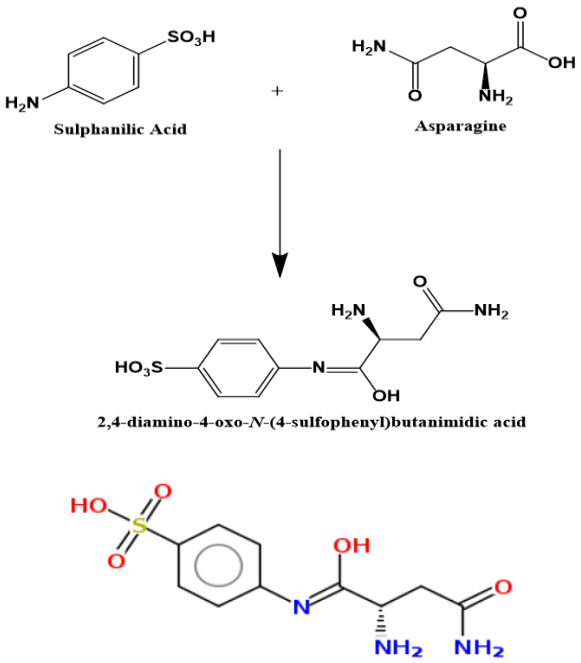


Scheme 2: Reaction between sulphanilic Acid and Arginine, (comp.2)

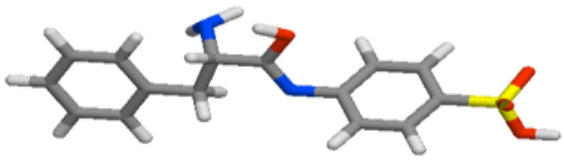




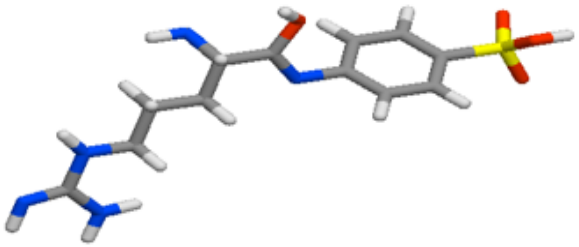
Scheme 3: Reaction between Sulphanilic Acid and Asparagine, (comp.3)



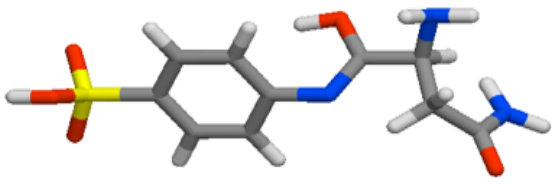
In addition, the 3D structure of the synthesized Schiff base given as following:



(Comp.1)



(Comp.2)



(Comp.3)

Infrared spectra:-

The infrared spectra of the Schiff base and their metal complexes 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}.

Computer programmers:

Software computer programmers was used to estimate some of chemical properties including:

a. Molecular docking was performed for the ten synthesis compounds using Autodock Vina (Trott and Olson, 2010). The compounds were built using Marvensketch and followed by energy minimization using Hyperchem 8 (Coleman and Arumainayagam, 1998), then saved to pdb format. Crystal structure of Staphylococcus aureus (PDB: 1JIJ) was obtained from Protein Data Bank with (PDB ID: 1JIJ) (Qiu *et al*., 2001). Proteins were edited using AutoDock Tools (ADT) by removing unwanted water molecules and Herero atoms and then added all hydrogen atoms, followed by computing Gasteiger and adding Kollman charge. A grid box of 60 × 60 × 60 points, with a spacing of 0.375A˚ and located at the centre of the active site. Discovery Studio visualizer 2016 (Systèmes, 2016) was used to visualize the docking results as well as Ligplot (Laskowski and Swindells, 2011).
b. The physicochemical properties of compounds were estimated by Molinspiration, ADME profiling by PreADMET.

Antibacterial test:

Bacterial cultures:

Plate cultures of nutrient agar (OXID) medium 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 (Salama *et al*., 2023) [33].

Antibacterial assay:

The antibacterial tests were assayed according to the diffusion method. The strains of bacteria used were Gram-positive bacteria (Klebcila and Pseudo) and Gram-negative (E.Coli & Staph). 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 of distilling water) were placed on the surface of the culture and incubated at 37 ^{0}C for 24h. After incubation, the average of inhibition zones recorded (µm). In this study, the compounds obtained were given numbers of (1-12) for the products of reactions between (Sulphanilic) with amino acids of (Phenylalanine, Asparagine, and Arginine). (Zawia *et al*., 2022) [46].

Results and Discusion

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 compound: 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:(Phenylalanine, Asparagine and Arginine,) with (Sulphanillic Acid). The obtained data are presented in Figures of (1-3). The fundamental I.R spectra of the compounds can be describing as following:

The IR spectra was used to describe the structure of the prepared complexes, the IR spectra assignment of the metal complexes was achieved by comparing their vibration frequencies with those of the Schiff: For comparative purposes and in order to facilitate the spectra assignment of the complexes, the IR spectrum of schiff base of the amino acids was recorded.

a. The band of Schiff base 3150, 3100 and 3050 $Cm^{-1}$are assigned to C-H Aromatic, respectively, this band of the Schiff base shifted to higher frequency in case of phenylalanine, but the band were shifted to lower frequency of arginine (Hasan and Awad, 2021).
b. The band of 2890, 2820 and 2720 Cm^{-1} of Schiff base compounds are assigned to C-H Aliphatic were shifted to higher frequency (Hasan *et al*., 2021).
c. The band of 1590, 1580 and 1540 Cm^{-1} of Schiff base compounds assigned to C = N, 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,
d. The band of 1710, 1640 and 1620 $Cm^{-1}$of Schiff base compounds assigned to C = O.
e. The band C = C of Schiff base compounds were appear in 1440, 1450 and 1410 Cm^{-1} and showed slight changes in frequency of most compounds.

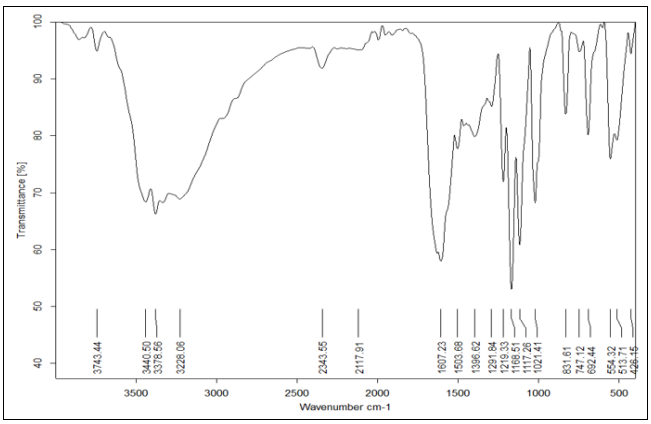


Fig 1: I.R Spectra for (phenylalanine- Sulphanilic) Schiff base

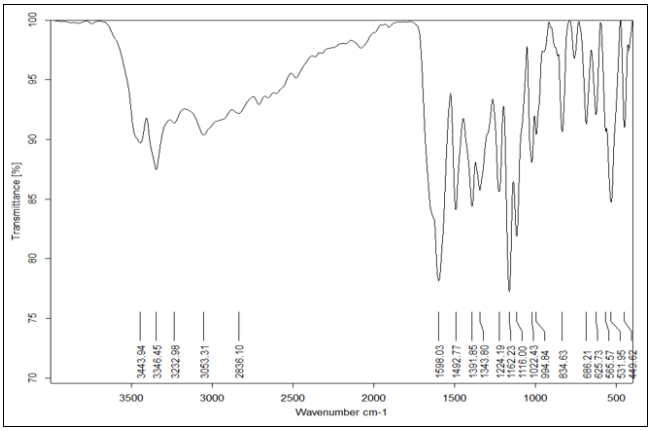


Fig 2: I.R Spectra for (Asparagine -Sulphanilic) Schiff base

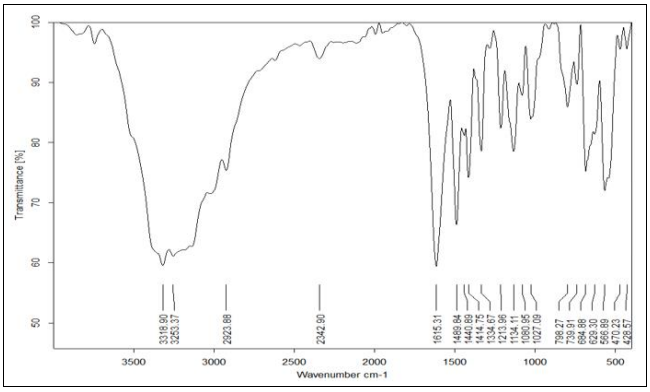


Fig 3: I.R Spectra for (Arginine- Sulphanilic)

Computational approaches:

a. The physicochemical properties of Schiff base Compounds were estimated by Moinspiration, ADME profiling by Preadmits

Compounds under analysis presented in Table 1. The all verified compounds possess log significant values from -3.44 to - 0.89 and were predicted to retain considerable ranges for H-bond donors (n-OHNH) except compound 2 and 3 (n-OHNH = 8 and 6 respectively**)** but hydrogen bond acceptors values (n-ON) indicated obeyed Lipinski's rule of five. Number of rotatable bonds is critical for conformational variations and the required to receptors or channels. It is shown that for transient oral bioavailability criteria, number of rotatable bond should be **≤10.**All tested compounds possessed (5-8) rotatable bonds. Topological polar surface area > 140 are consideration to have low oral bioavailability. The results revealed that the two compounds (1 and 3) shown TPSA within suitable values (TPSA = 122.98 and 128.78 respectively).

ADME properties of the compound including absorption, distribution, metabolism, excretion (**ADME**) was designed using Preadmits to estimate their general value as drug candidates. The verified compounds showed cell penetrability in the Caco-2 cell model with rate is between **0.41-0.89 nm/sec**, representing the molecules is having low permeability through cells derived from human colon adenocarcinoma. Besides, all compounds displayed low permeability through Madan-Darby canine Kidney cells with values from **1.32-5.49nm/sec.** The tested compounds (1 and 3) presented great HIA values (91.6 and 89.3**%** respectively) indicating very well- intestinal absorbed compounds.

In addition, all compounds exhibited low CNS penetration BBB values (0.008-0.036**%**). Furthermore, all compounds were valued to have weakly plasma protein binding (**PPB= 23.60-79.24 %**).

Table 1: Calculated physicochemical properties of Schiff base compounds

Cps. ID	Moinspiration						
	clog	M.W	MF	n-ON	n-OHNH	TPSA	NROTB
1	-1.04	320.08	$C_{15}H_{16}N_2O_4S$	6	4	122.98	5
2	-3.44	329.12	$C_{12}H_{19}N_5O_4S$	7	8	174.89	8
3	-2.62	287.06	$C_{10}H_{13}N_3O_5S$	7	6	156.08	5

Log: logarithm of compound partition coefficient between n-octanol and Water. **MW:** Molecular weight. **MF:** Molecular Formula **n-ON:** Number of hydrogen bond acceptors. **n-OHNH:** Number of hydrogen bond donors. **TPSA:** Topological polar surface area. **NROTB:** Number of rotatable bonds.

Table 2: ADME data of tested compounds

Cps. ID	Preadmits				
	Caco2[a]	MDCK[b]	HiA[c]	BBB[d]	PPB[e]
1	0.64	1.32	91.6	0.009	79.24
2	0.46	4.67	19.2	0.036	26.75
3	0.41	5.49	38.04	0.008	23.60

[a] **Caco2:** Permeability through cells derived from human colon adenocarcinoma; Caco2 values < 4 nm/*sec* (low permeability), values from 4 to 70 nm/ *sec* (medium permeability) and values > 70 nm/*sec* (high permeability).

[b] **MDCK**: Permeability through Madan–Darby canine kidney cells; MDCK Values < 25 nm/*sec* (low permeability), values from 25 to 500 nm/*sec* (medium permeability) and values > 500 nm/*sec* (high permeability).

[c] **HIA:** Percentage human intestinal absorption; HIA values from 0 to 20% (poorly absorbed), values from 20 to 70% (moderately absorbed) and values from 70 to 100% (well absorbed).

[d] **BBB:** Blood–brain barrier penetration; BBB values < 0.1 (low CNS penetration), Values from 0.1 to 2 (medium CNS absorption) and values > 2 (high CNS absorption).

[e] **PPB:** Plasma protein binding; PPB values < 90% (poorly bound) and > 90% (strongly bound).

b. Protein preparation and molecular docking

The protein preparation and docking calculations were performed using the Schrödinger Drug Discovery suite for molecular modeling (version 2022-1). The crystal structure of Staphylococcus aureus tyrosyl-tRNA synthetase (PDBID: 1JIJ, resolution 3.2 Å (Qiu *et al*., 2001) was obtained from Protein Data Bank (PDB, www.rcsb.org), and prepared using Protein preparation wizard (Madhavi Sastry *et al*., 2013) to fix the protonated states of amino acids residues, adding polar hydrogens and missing side-chain atoms and missing loops by using Prime (Jacobson *et al*., 2004).

All compounds as well as the co-crystallized ligand [2-amino-3-(4-Hydroxy-phenyl)-Propinyl amino]-(1,3,4,5 Tetra Hydroxyl -4-Hydrxyl methyl L-PIPERIDIN-2-YL)-acetic acid, herein referred as SB-239629) were drawn using Maestro and prepared using LigPrep (Shelley *et al.*, 2007) to generate the three-dimensional conformation, calculate the partial atomic charges, and adjust the protonation states at pH 7.4 using the force field OPLS3e (Roos *et al*., 2019).

Molecular docking studies were performed with the prepared ligands using Glide (v8.9) with extra precision (XP) (Friesner *et al*., 2004; Halgren *et al*., 2004). Ligands were docked in a grid box of 12 Å, and the center of the grid box was placed in the same co-crystallized ligand SB-239629. Docking poses were selected by visual inspection based on their common interactions with relevant residues and their docking score.

MM-GBSA analysis

The Molecular Mechanics, the Generalized Born model and Solvent Accessibility (MM-GBSA) analysis was performed to predict the free binding energy of selected ligand-protein complexes. For this, the Prime module of the Schrödinger Drug Discovery suite was used to calculate the binding energy of selected ligands in complex with the protein target. Prime MM-GBSA calculates the energy of optimized free receptors, free ligands, and protein-ligand complexes for the analysis. It also calculates the ligand strain energy by placing ligands in a solution generated by VSGB 2.0 suit and OPLS3e force field (Li *et al*., 2011).

Molecular docking

To explain the antibacterial activity of "compounds," molecular docking was carried out in the ligand-binding site

of *S. aureus* TyrRS. For this, the docking procedure was validated, and the results of SB-239629 (co-crystallized ligand) showed a similar pose to the crystallographic (RMSD = 0.7 Å, Docking score -10.251). In this sense, our docking results show that SB-239629 is located in a pocket made up of residues Tyr 36 – Thr 42, Gln 174 – Asp 177, and Gln 190 – Asn 199, making a hydrogen bond with residues Asp 40, His 50, Asp 80, Tyr 170, Asp 177, Asp 195, and Gln 196 (Fig 4).

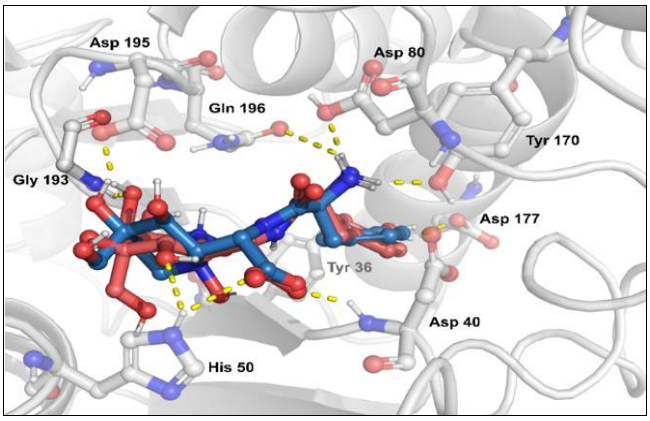


Fig 4: Superimposition of docked and crystallographic poses of SB-239629, co-crystallized ligand (deep salmon), and docked compound (sky-blue) RMSD= 0.7 Å. *S. aureus* TyrRS' residues are colored according to the atom type of the interacting amino acid residues (protein's carbon, light grey; oxygen, red; nitrogen, blue). Dash lines represent the protein-ligand interactions as follows: Hydrogen bond interactions are colored in yellow

As shown in Fig 5, our docking results showed that selected compounds are located in the same pocket as co-crystallized ligand making similar interactions with key amino acid residues. Compound 1 (docking score -5.965; -50.08 Kcal/mol, Table 6) is in a pocket made of residues Tyr 36 – Thr 42, Gln 190 – Ile 200, and Asp 80 – Lys 84. Its sulfonic group makes hydrogen bond interactions with residues His 50, Arg 88, and Lys 84, and additional H-bond with amine and carbonyl group with amino acids Asp 80 and Asp 40, respectively. Finally, π-π stacking between the phenyl group and Tyr 36 (Fig 4). In a similar binding pocket, compound 2 (docking score -6.523; -50.31 Kcal/mol, Table 2) makes hydrophobic interactions with residues Tyr 36 – Thr 42, Gln 174 – Asp 177, and Leu 70 – Thr 75. The sulfonic and phenyl groups make H-bond interactions with residues His 47, His 50, and π-cation interaction with Lys 84. Additionally, compound 2 is stabilized by making H-bond interactions with residues Asp, 80, Gln 196, Tyr 170, Asp 177, and Tyr 36. In the same way, compound 3 (docking score -6.936; -34.31 Kcal/mol, Table 2) and compound 4 (docking score -6.707; -52.68 Kcal/mol, Table 2) are located in the same pocket as compounds 1 and 2. Compounds 3 and 4 are making H-bond interactions between their sulfonic group and amino acid residues Lys 84, His 50, and Arg 88. Whereas compound 3 has H-bond interaction with residues Gln 196, Gln 174, Gln 190, Asp 177, and Tyr 36 (Fig 5); compound 4 makes H-bond interaction with amino acid residues Asp 80, Tyr 170 and stabilized by making π-π interaction with residues Tyr 36 (Fig 5).

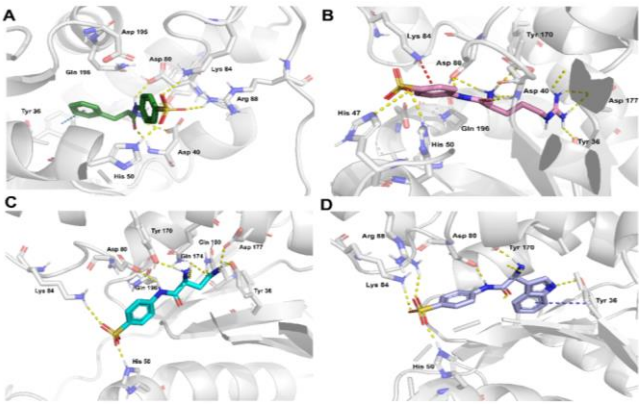


Fig 5: A representative snapshot of the docking pose of our selected compounds. *S. aureus* TyrRS' residues are colored according to the atom type of the interacting amino acid residues (protein's carbon, light grey; oxygen, red; nitrogen, blue). A: compoun1, B: Compound 2, C: Compound 3. Dash lines represent the protein-ligand interactions as follows: Hydrogen bond interactions are colored in yellow, π-π interactions are colored in blue, and π-cation interactions are colored in red

Table 2: Docking score and binding-free energy calculations of selected compounds against *S. aureus* TyrRS

Compound	Docking score	Binding affinity (Kcal/mol)
Compound 1	-5.965	-50.08
Compound 2	-6.523	-50.31
Compound 3	-6.936	-34.31

Multidrug resistance is a public health problem that promotes the development of new antimicrobial drugs against effective and selective targets (Xiao *et al*., 2011). Within these targets, tyrosyl-tRNA synthetase has raised interest in antibacterial drug discovery. This target and all aminoacyl-tRNA synthetases are responsible for the transcription processes of nucleic acid information into new proteins (Qiu *et al*., 2001; Xiao *et al*., 2011). In the case of tyrosyl-tRNA synthetase, its structure has three domains, the N-terminal domain (residues 0-22) and the α-helical domain (residues 248-323) are linked through a loop (221-247) to the C-terminal domain (324-420) (Perona & Gruic-Sovulj, 2013). Additionally, the active site of YRS is highly conserved in several bacteria; this active site in *S. aureus* is made of residues Tyr 36, Asp 177, Gln 174, Gln 196, Tyr 170, and Asp 80. On the other hand, these same residues in *Bacillus stearothermophilus* correspond to the amino acid residues Tyr 34, Asp 176, Gln 173, Gln 195, Tyr 169, and Asp 78 (Li *et al*., 2008).

In this sense, our proposed compounds' binding mode suggests that interactions with relevant residues such as Tyr 36, Gln 174, Gln 196, and Asp 80 may be involved in observed antibacterial activity since all of them are included within the enzyme active site. Furthermore, Farshadfar *et al*., 2020 concluded that the side chain of Lys 84 is involved in tyrosine substrate binding and their findings suggest that interactions with this residues during the 100 ns MD is the mechanism of inhibition of compound ZINC59675144 (Farshadfar *et al*., 2020).

In this sense, since the sulfonic group of our selected compounds is making a H-bond interaction with Lys 84, our results suggest that tyrosine interaction with the enzyme

may decrease due to the interaction with our inhibitors. Finally, amino acid residues Asp 40, and His 50 are reported as an important residues with a role in binding potency in arylaminofuranones derivatives, raising an interest as a relevant residues in antibacterial activity since our compounds have a H-bond interactions with these key residues as well (Xiao *et al*., 2011).

Biological studies:

The antimicrobial and antifungal activities were carried into two types of each organism.

The antimicrobial activity of prepared complexes was tested against representatives of acid-fast bacilli (Mycobacterium phalli), Gram-positive bacteria (***pseudo& staph***), Gram-negative bacteria (***E-coil*** & ***Klebsiella***) Applying the agar diffusion method by cup plate technique (1tap) using trypticase soy agar for bacteria. The products were dissolved in sterile dist water at concentration of 10 mg/ml then 100 µl were aseptically transferred to preformed cups (100 µg/cup) in the dried inoculated Triticale soy agar plates. All culture plates put on its surface from all concentrations of the solution complexes which prepared from 10-1 to 10 -5 mg/ml, thereafter the plates were incubated inverted at 37 ^{0}C for 24 hr.

In case of bacteria. The Minimum inhibitory concentration (MIC) was determined for bacterial species tested against serial dilution of the active compounds. Then 100µl of each dilution was transferred in cups preformed in nutrient agar inoculated with suspension of 105/ml microbial cells on the surface of agar plates and incubated at 37 ^{0}C for 24 - 48 hours. After incubation, the lowest concentration producing inhibition was recorded as the minimum effective concentration (Hasan *et al*., 2019).

Only Schiff base (Arginine, Asparagine and phenylalanine) of the tested products revealed significant antimicrobial effect against on bacteria activity with respect to The Minimum inhibitory concentration (MIC), the tested compounds showed comparable antimicrobial activity. With respect to MIC, the tested compounds showed comparable antimicrobial activity. In general, the antimicrobial activity for the tested products was higher on Gram-positive than Gram-negative bacteria.

The antimicrobial and antifungal activities were carried into two types of each organism. The antimicrobial activity of prepared complexes was tested against representatives of acid-fast bacilli (Mycobacterium phalli), Gram-positive bacteria (***pseudo& staph***), Gram-negative bacteria (***E-coil*** & ***Klebsiella***) Applying the agar diffusion method by cup plate technique (1tap) using trypticase soy agar for bacteria.

The products were dissolved in sterile dist. water at concentration of 10 mg/ml then 100 µl were aseptically transferred to preformed cups (100 µg/cup) in the dried inoculated Triticale soy agar plates. All culture plates put on its surface from all concentrations of the solution complexes which prepared from 10-1 to 10 -5 mg/ml, thereafter the plates were incubated inverted at 37 ^{0}C for 24 hr. in case of bacteria (Salama *et al*., 2023) [33] The Minimum inhibitory concentration (MIC) was determined for bacterial species tested against serial dilution of the active compounds. Then 100µl of each dilution was transferred in cups preformed in nutrient agar inoculated with suspension of 105/ml microbial cells on the surface of agar plates and incubated at 37 ºC for 24 - 48 hours. After incubation, the lowest concentration producing inhibition was recorded as the minimum effective concentration.

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Fig 6: Effect of Asparagine - (Schiff base) on *E-Coli*

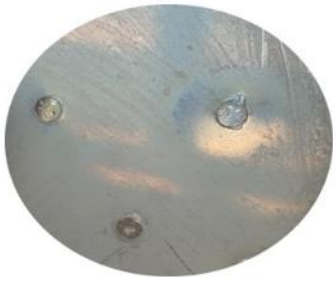

Fig 7: Effect phenylalanine (Schiff base) (A), asparagine base (Schiff base) (B) and Arginine (Schiff base) base (c) concentrations on *pseudo*

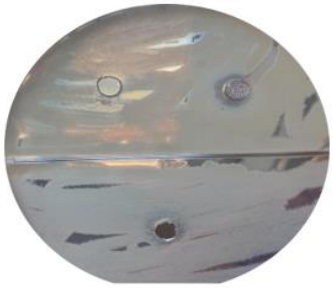

Fig 8: Effect, phenylalanine – (Schiff base) concentrations on *E-coil*

Fig 9: Effect asparagines- (Schiff base) (A), phenylalnine - (Schiff base) (B) and arginine -(Schiff base) (c),phenylin (Schiff base} on *staph*

Fig 10: Effect arginine - (Schiff base) on *klebcila*

Fig 11: Effect asparagine (Schiff base)), arginine (Schiff base arginine (Schiff base) and phenylalanine (Schiff base) Concentrations on *pseudo*

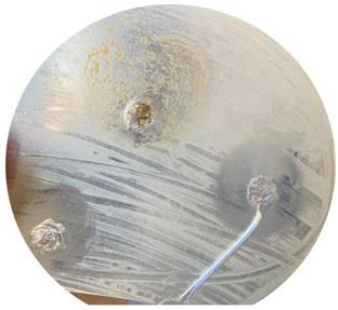

Fig 12: Effect arginine (Schiff base), phenylalanine - (Schiff base) & arginine (Schiff base) on *kabebcila*

Fig 13: Effect of asparagine - (Schiff base), arginine - (Schiff base) and arginine - (Schiff base) concentrations on *E-Coli*

Fig 14: Effect of arginine - (Schiff base) concentrations on *staph*

Fig 15: Effect phenylalanine - (Schiff base) concentrations on *E-coli*

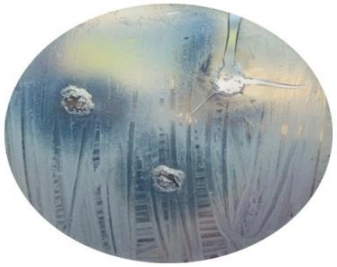

Fig 16: Effect phenylalanine - (Schiff base) concentrations on *klebcila*

Fig 17: Effect phenylalanine - (Schiff base) concentrations on *staph*

Conclusion

The applied method gave rapid and sensitive reactions for synthesis Schiff base compounds, also most of compounds showed anti-bacterial activity.

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