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Preparation, Characterisation and Study of the Molecular Docking of Some Derivatives of the Tetrazole Ring and Evaluation of their Biological Activity

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Abstract

This study included the preparation of a pentameric ring derived from tetrazole by reacting previously prepared Schiff bases with sodium azide in the presence of dioxane as a solvent. The structures were validated using physical measurements. From the melting point, colour change, and product ratio, spectroscopic analyses were used, including proton nuclear magnetic resonance and infrared spectroscopy. These compounds were also prepared against two types of bacteria, gram-positive and gram-negative. The molecular docking of some compounds M7 and M9 with proteins derived from E. Coli bacteria was also studied.

Keywords: Heterocyclic, Tetrazole, biological activity.

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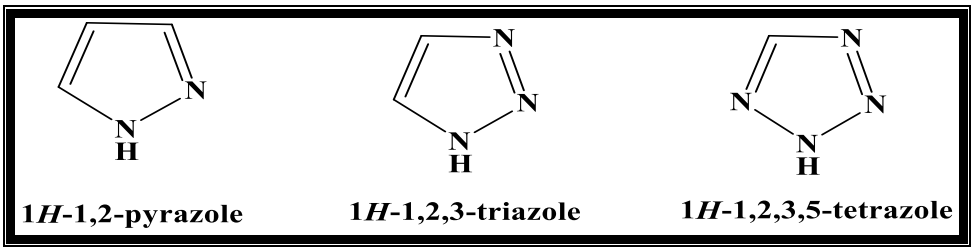
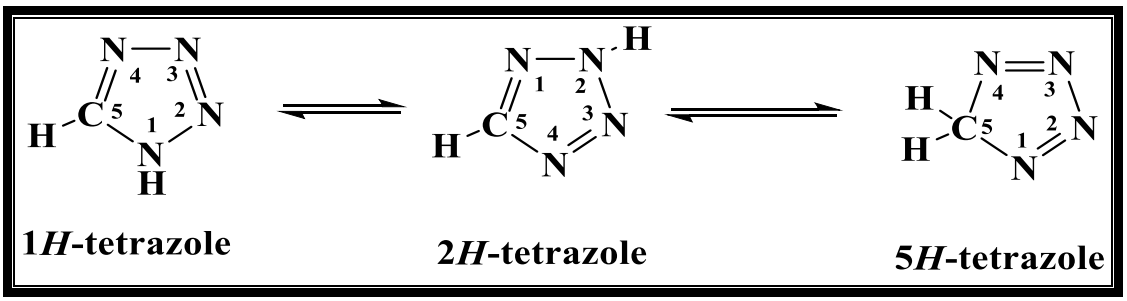
1. Introduction

Heterocyclic compounds contain ring structures containing different atoms, such as oxygen, sulfur, or nitrogen. These compounds are widely distributed in nature. It is essential and used in many fields, including industrial and medical. These compounds are involved in synthesising sugars and their derivatives, as well as enzymes, proteins, and nucleic acids[1]. Heterocyclic compounds can contain more than one heteroatom, and they are classified according to the type and number of atoms contained in the ring[2], as follows:



Tetrazole is a heterocyclic substance comprising four nitrogen atoms and one carbon atom. Three isomers of the chemical formula (CH2N4) [3]exist:



These compounds are considered among the most vital cyclic compounds. It is one of the electron-propelling compounds because it contains four pairs of free electrons corresponding to four nitrogen atoms[4]. Previous studies have shown its importance in medicine, especially biology. It shows antibacterial activity [5] and antifungal[6]. It is an antidote to viral immunodeficiency[7], and the following compounds show good anticancer activity[8]. In brief, this study aimed to prepare pentacyclic rings derived from tetrazole compounds by reacting the previously prepared Schiff base with sodium azide.

2. Materials and Methods:

2.1.Chemicals used: Chemicals prepared by Aldrich, BDH Thomas, Fluka, and Merck were used.

2.2. Instruments used: The melting point is measured using a thermometer 9300, KBr disk with a scale of 400-4000 cm-1, FT-IR 8400S Shimadzu spectrophotometer; 1H- and 13C-NMR spectra of Bruker equipment operating at 400 MHz. Thin-layer chromatography (TLC) was analysed using 0.2 mm thick Fluka silica gel plates.'

2.3. Preparation of Tetrazole derivatives (M6-M10).[9]

This compound is prepared as follows: (Dissolve 0.0001 mole of Schiff base prepared in advance in (10 ml of dioxane solvent in a round bottle)) and after dissolving it the next month except (0.05 g, 0.0002) (10 ml) mole mixture for it. Add sodium (NaN3) to this. Dioxane in the bath (10 hours), then cool and add to the crushed pulp, then the precipitate is filtered and dried, ready to be crystallised from ethanol to Table 1

2.4. Biological activity study

Staphylococcus aureus is gram-negative and gram-positive. The pathogen used in this study is Escherichia coli. The Department of Pure Science Education and Life Sciences use Molten Hinton Agar as a bacterial growth medium. Chemical solutions of M6, M8, M9, and M10 were prepared using dimethyl sulfoxide (DMSO) at concentrations of (0.01, 0.001, 0.0001) mg/mL[10][11]. The minimum inhibitory concentration (MIC) is determined and monitored. Mueller-Hinton agar was utilised as the nutritional medium, and the diffusion technique was performed to ascertain the susceptibility of the bacterial isolates used in the research. Once the medium is prepared, sterilise it, distribute it into Petri dishes, and allow it to solidify. Next, drill four small holes in each plate. They were then incubated at

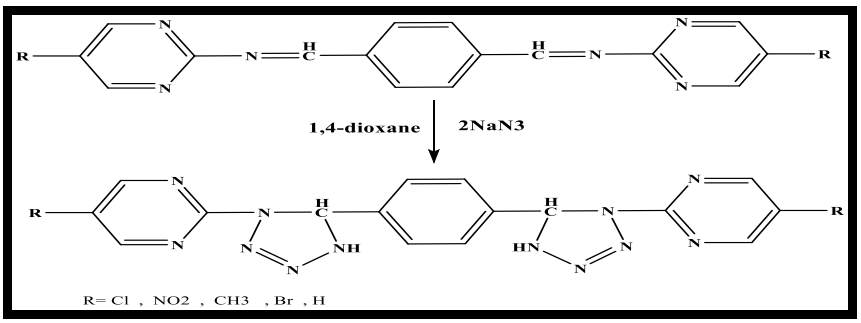
37°C for a full day. Derivatives used. These indicate the sensitivity of the derivatives used. As the diameter increases, these derivatives depend on the damping diameter of the plate surrounding the hole used. When the chemical produced shows an inhibitory effect, its biological activity increases, similar to antibiotics' inhibitory effect. [12][13]

2.4. Study of the molecular docking of some compounds (M7,M9)

The molecular docking of some prepared compounds (M7, M9) was studied on a single line of Escherichia coli using the MOE project (2009), where the examined chemicals' energy minimisation procedure was finished to produce the most stable stereoscopic form (lower energy barrier), after which the structure was downloaded. Escherichia coli from the World Protein Bank website, using a high-spec personal calculator, as these programs require advanced computers with fast, multi-core processors[14]. This allows the work to be completed quickly and circumvents limitations such as molecule size, number of atoms, etc.

3. Results and discussions

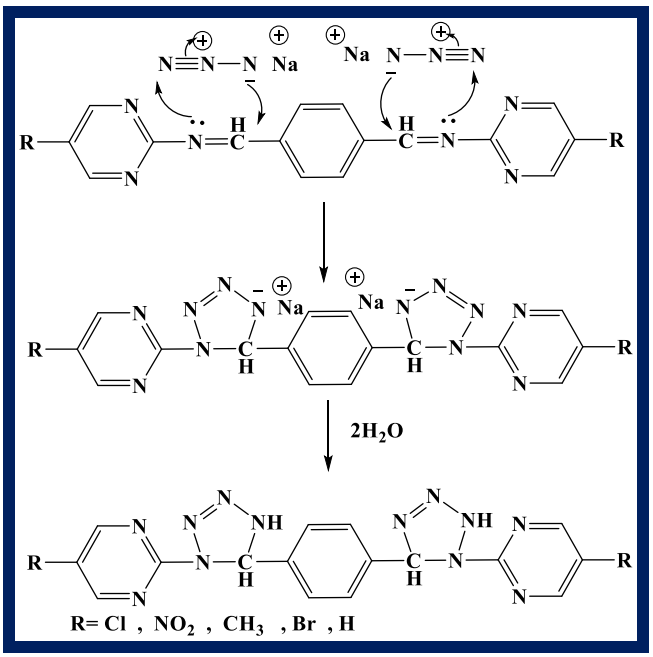
Scheme 1 shows the chemicals produced when sodium azide reacts with sherd bases to create the tetrazole ring.



Scheme (1): Path of the Ready Compounds (M6-M10)

3.1. Characterization of Tetrazole derivatives (M6-M10)

Tetrazole derivatives were prepared according to the following proposed mechanism:



Scheme 2: Mechanism of preparing tetrazole derivatives (M6-M10)

The FT-IR spectrum showed an absorption band identified as belonging to the (N=N) group in the range (1456-1438) cm-1, an absorption band attributed to the aromatic (CH) in the range (3010-3069) cm-1, and an absorption band attributed to (NH).) in the range (3231-3195) cm-1, and it also showed two aliphatic return (CH) absorption bands in the range (2978-2915) cm-1 and (2941-2870) cm-1. Moreover, two absorption bands in the range of (1517-1472)cm and (1570-1543)cm-1 are caused by the aromatic ring's stretching (C=C([15]. As in Table 2 and Figures 1 and 2

The H-NMR spectrum of compound M6 showed a signal at (3.40) ppm attributed to a proton (NH), a signal at (5.18) ppm attributed to a proton (CH) of the tetrazole ring, and two signals in the range (7.48-7.77) ppm. was ascribed to the aromatic ring's protons out of the million. The location (2.48) ppm usually refers to the DMSO solvent. As in Figure 3

The H-NMR spectrum of compound M8 showed a signal at (3.04) ppm attributed to a proton (NH), a signal at (5.32) ppm attributed to a proton (CH) of the tetrazole ring, a Signal at (3.91) ppm attributed to a proton (CH3(،and two signals in the range (7.18-7.75) ppm. Of the million were attributed to the protons of the aromatic ring. The location (2.47) ppm usually refers to the DMSO solvent. As in Figure 4

3.3. Evaluation of the Biological Activity of Prepared Compounds

These bacteria were chosen for their medical importance, as they cause many diseases and vary in antibiotic resistance. The bioavailability of many of the prepared compounds was evaluated using etching methods and antibiotic-level measurements[16][17]. The results showed that different ratios of Gram-positive and Gram-negative compounds could inhibit the growth of bacteria[18][19], as shown in Table 3.

3.4. Results of a molecular docking study of some prepared compounds

Some prepared compounds (M7, M9) were subjected to molecular docking studies on one line,

Escherichia coli. The binding energy values of the prepared compounds were calculated using MOE (2009) software, as shown in Table (4([20]. Research has demonstrated that the chemical (M7) forms two hydrogen bonds with amino acid residues in the active region. The first link forms an electrical pair bond with amino acid residue TYR 25 in the active site. In the second, the electron pair in the pyrimidine ring is connected to the amino acid residue HOH 718, which is situated at the active site.

According to the study, the molecule (M9) forms two interactions with the amino acid residues in the active site: a Pi-type bond and a hydrogen bond that connects the pyrimidine's electronic pair with amino acid residue LEU 206. Alkyl connects the aromatic ring's electronic pairs to the active site's amino acid residue VAL 376. Similar to Figure 5,6

Table (1): Some physical properties of for Prepared compounds (H1-H10).

Comp. No.	R	Molecular formula	m.p. °C	Yield%	Color
M6	4-Cl	$C_{16}H_{12}Cl_2N_{12}$	252-254	67	Yellow
M7	4-NO2	$C_{16}H_{12}N_{14}O_4$	241-239	64	White
M8	4-CH3	$C_{18}H_{18}N_{12}$	205-207	59	Yellow
M9	4-Br	$C_{16}H_{12}Br_2N_{12}$	247-248	72	Orange
M10	4-H	$C_{16}H_{14}N_{12}$	230-232	58	Brown

Table (2): FT-IR absorption results for Prepared compounds (H1-H10)

Comp. No.	R	ν(C-H) Arom.	ν(C-H) Aliph.	ν(N-H)	ν(N=N)	ν(C=C) Arom.	Others
M6	4-Cl	3058	2915,2876	3223	1441	1543,1472	ν (C-Cl) 735
M7	4-NO2	3013	2953,2881	3231	1438	1568,1483	ν (N-O) 1321
M8	4-CH3	3069	2946,2902	3195	1449	1549,1476	--
M9	4-Br	3031	2978,2941	3203	1438	1570,1510	ν (C-Br) 576
M10	4-H	3010	2927,2870	3207	1456	1558,1517	--

Table (3): Biological efficacy of produced substances and control methods (measured in millimeters of inhibition).

Comp. No.	E. Coil Conc. mg/ml			Staph. Aureus Conc. mg/ml		
	0.01	0.001	0.0001	0.01	0.001	0.0001
M6	17	15	10	20	15	10
M8	16	14	11	10	10	5
M9	21	15	10	15	10	5
M10	23	14	10	10	5	--
Amoxicillin	22	17	16	20	19	15

Table 4: Values of binding energies for the prepared compounds.

Comp. No.	S score (kcal/mol)	RMSD
M7	-6.97741	2.58113
M9	-7.18321	2.005022

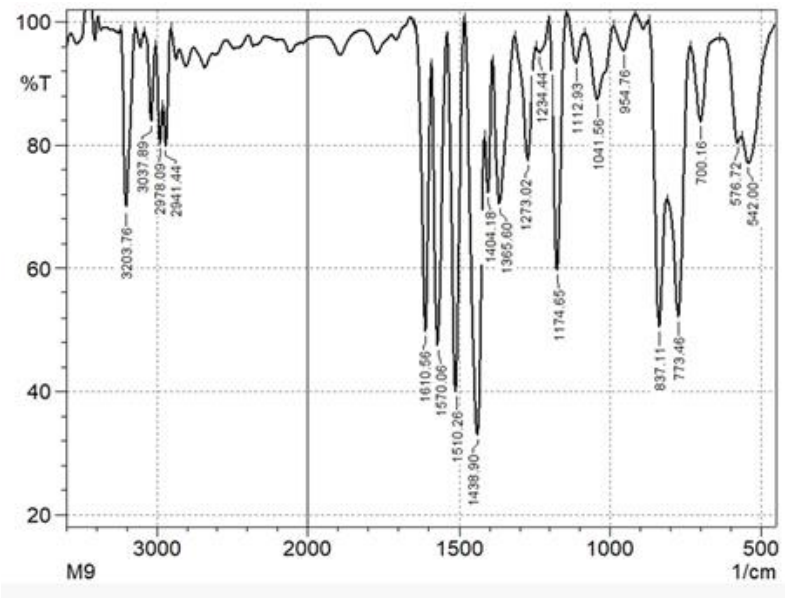


Figure (1): The compound's FT-IR spectra (M9).

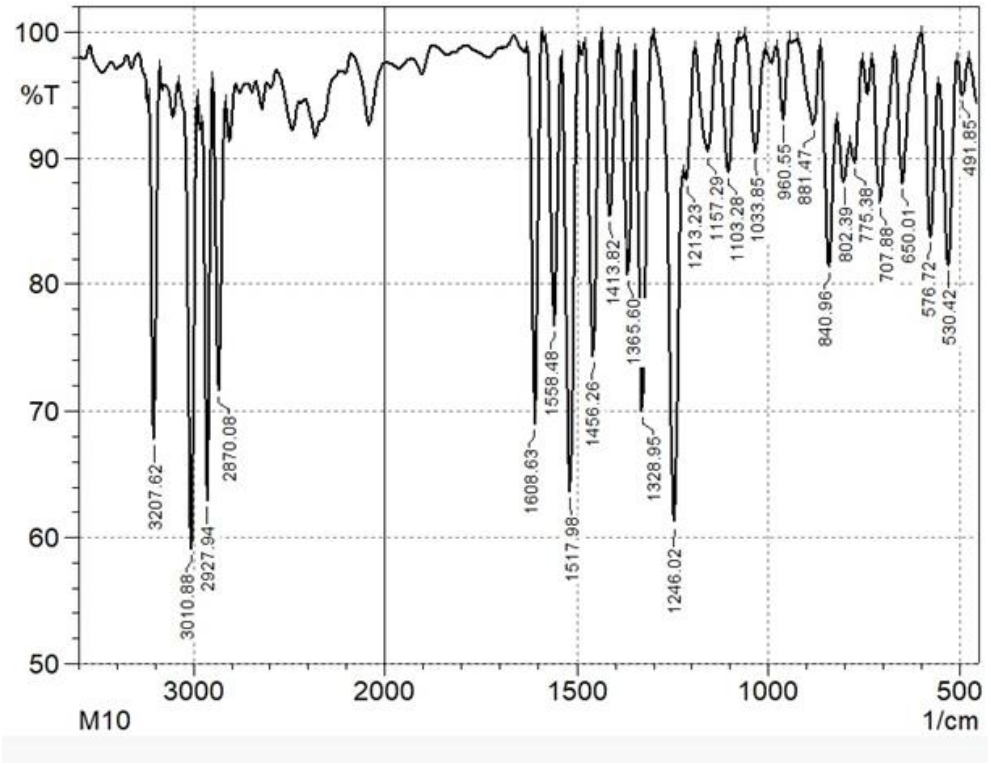


Figure (2): The compound's FT-IR spectra (M10).

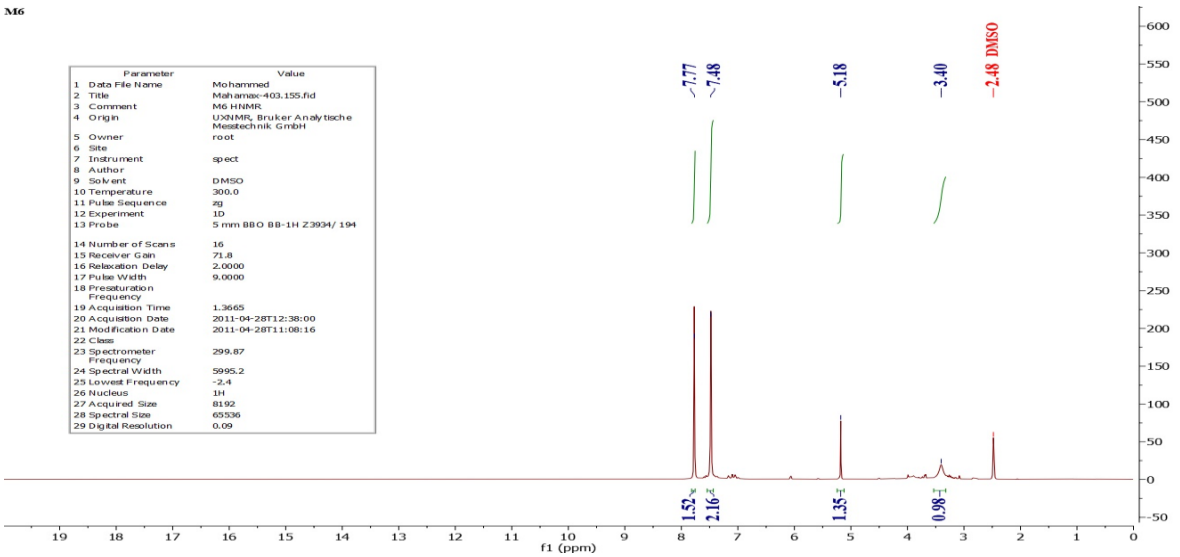


Figure (3): 1-H NMR spectra of the substance (M6).

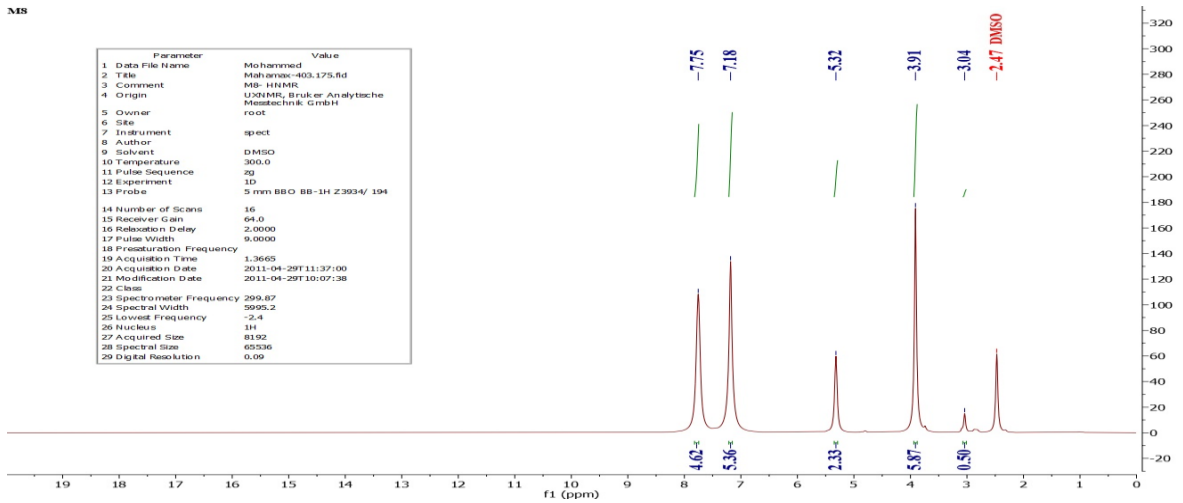


Figure (4): 1-H NMR spectra of the substance (M8).

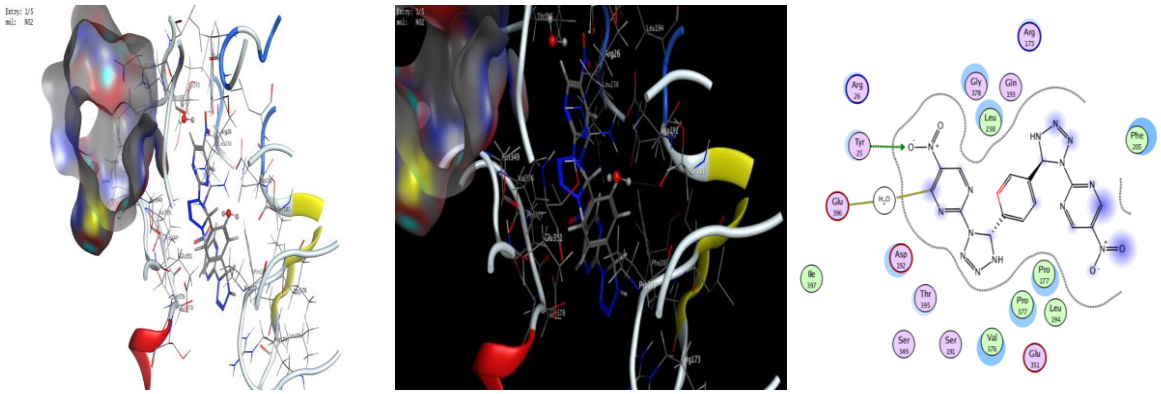


Figure 5: Interactions between compound M7 in 3D and 2D dimensions

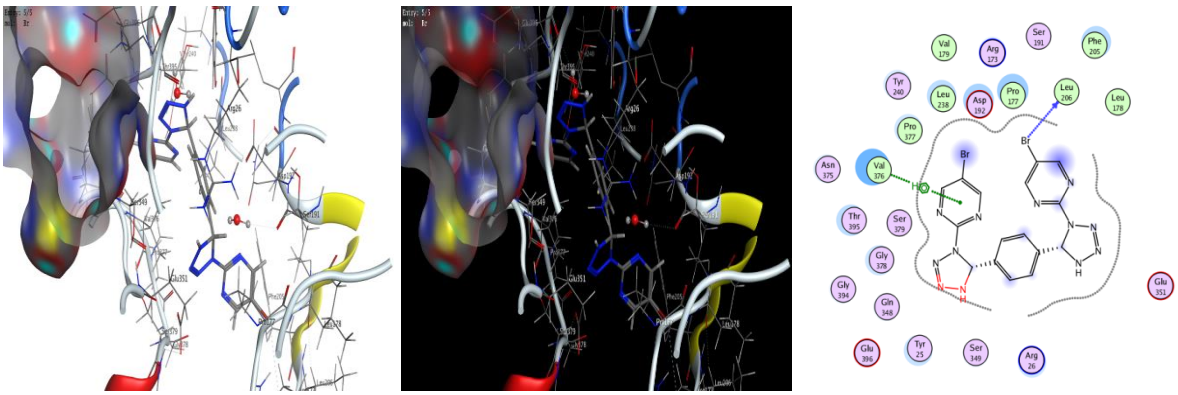


Figure 6: Interactions between compound M9 in 3D and 2D dimensions

4. Conclusions

Suppose that spectroscopic measurements of protein activity in the prepared compounds were achieved using infrared and magnetic resonance spectroscopy. In this case, the Schiff reaction with sodium azide invariably adds tetrazole rings, which are visible and potent against Klein-type bacteria. It is also quite effective in all gram-positive and gram-negative types. Some compounds also gave good values when their molecular docking with E.Coli bacteria was studied.

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