https://doi.org/10.31351/vol34iss1pp10-25

A Design, Molecular Docking, ADMET Studies, Synthesis, Characterization, and Invitro Pharmacological Evaluation of Tetrazole Derivatives

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Received 1/8/2023, Accepted 16/11/2023, Published 29/3/2025

Abstract

A series of novel tetrazole derivatives were designed and synthesized through ring closure. The structures of compounds (T1-T9) were characterized by FT-IR, ^{1}H, and ^{13}C-NMR spectroscopy. All tetrazole derivatives were screened for their antimicrobial activities against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria. All compounds showed a high activity against *E. coli* at a concentration of 0.01 mg/mL, while the tested compound T2 did not exhibit remarkable activity against Gram-positive *Staphylococcus aureus*. The potential DNA gyrase inhibitory activity of these compounds (T1-T9) was investigated by Insilico using the molecular docking simulation method. Four compounds showed good results, especially compound (T8), which showed the lowest binding affinity (-6.685Kcal/mol).
Keywords: ADMET, Molecular docking, pharmacological, Tetrazole, Toxicity.

Introduction

Tetrazols is 5-member ring-heterocyclic compound. This compound is represented by the molecular formula CH_2N_4, which concern three different isomers. Tetrazole structure composes one C atom besides four N atoms. Tetrazoles conjugated system, which is rich with Nitrogen atoms, have particular features of donor-acceptor [1-3]. Tetrazoles act as stabilizer for negative charges through delocalization due to their cyclic planner structure. This is an important property for the interaction between acceptor and ligand. Compared to carboxylate, lipophilicity of tetrazolate anions is higher, which increases drug molecules flow through cell membranes. Nevertheless, metabolic degradation routes are resisted by tetrazoles, which lead to extending their action period. Because of their distinctive arrangement and promising pharmacokinetic profile, Tetrazoles and their correspondents are essential pharmacophores materials in pharmaceutical chemistry. Anti-hypertensive, anti-analgesic, anti-allergic, and anti-ulcer activities are involved in pharmacological profile of tetrazole [4-6].Many synthetic applications of tetrazoles and their analogous heterocyclic compounds, where they regarded as the forerunner for producing special heterocyclic materials such as propellants, exclusive materials and pharmaceuticals [7-9]. Also, the treatment of dopamine D2 receptors was firstly demonstrated using tetrazole hetrocycles correspondents [10]. Tetrazoles based heterocycles work as strong antimicrobial and anticancer agents Jackman et al. mentioned the robust cytotoxicity and growth inhibitory action of tetrazoles-involving-drugs. Tetrazoles based drugs have an incomplete interfering spectrum of antitumor action and toxicity profile in comparison with tomudex and possibly other Thymidylate synthase inhibitors presently being examined clinically [11-13]. Over the recent 10-15 years, various isomeric forms of tetrazole (NH-unsubstituted, 1H-1- substituted, and 2H-2-substituted tetrazoles) have been successfully used for the design of promising anticancer drugs)4,5(. Coordination compounds of transition metals, which contain tetrazoles as ligands, semisynthetic tetrazolyl derivatives of natural compounds (biogenic acids, peptides, steroids, combretastatin, etc.), 5-oxo and 5- thiotetrazoles, and some other related compounds have been recognized as promising antineoplastic agents) [14-16]. It was estimated that up to $40 billion is the worldwide cost for multi-drug-resistant bacteria. The development of new pharmaceuticals is the

priority in this cost. Catalyzing process of the ATP-dependent negative super-coiling of double-stranded closed-circular DNA requires a vital bacteria enzyme, which is well known as DNA gyrase. This enzyme is a member of enzymes class called topoisomerases, which actively contribute in controlling of DNA topological transitions. In view point of enzymology, the topological state of DNA being influenced by gyrase mechanism have an intrinsic attention. Moreover, DNA gyrase as an intracellular targeting for some antibacterial agents, which is a model for the rest of DNA topoisomerases have been drawn a lot of interest. In the recent decade, a lot of attention focused on DNA gyrase as a chosen target for the exploring of effective antibacterial agents[17-19]. On the other hand, quinolones and coumarins are the main inhibitors for DNA gyrase. A number of these Pharmaceuticals (i.e., ciprofloxacin) utilized for treatment of some diseases of bacterial infections [20-22]. As a result of side effects, however, no beneficial pharmaceutical derivative of coumarins has been confirmed. At the present time, one of the main serious medical problems that face health community is multidrug-resistant Gram-positive bacteria including methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant streptococcus pneumonia (PRSP), and vancomycin-resistant enterococci (VRE) [23-25]. Quinolone also resisted by these multidrug-resistant bacteria. To overcome this problem, it is essential to discover a novel sort of DNA gyrase inhibitors. Tetrazole antimicrobial derivatives medications including cefamandole, ceftezole, cephalosporin, and oxazolidinone-class tadalizolid were utilized by Clinicians. The antibacterial activity may be enhanced by the modification of tetrazole molecule structure [26-28]. In this work, we decided to design tetrazole hybrid structures for antimicrobial evaluation and carrying out in-silico studies including molecular docking (MD) using MOE software program. MD gives an idea about the activity of anti-bacterial through binding between targets and ligands (compounds). All the optimized compounds were subjected to ADMET studies to check toxicity risks and drug-relevant properties of molecules which are the key factors to determine the drug-likenes.

Materials and Methods

Stuart SMP3 apparatus was utilized for melting point measurements in an open capillary tube. Thin layer chromatography (TLC) was exploited to follow up the progress of reactions. The adsorbent was silica gel plates, and the mixtures of ethyl acetate: hexane (1:2) and Methanol: benzene (4:6) were the eluent. FT-IR spectroscopic measurements were carried out by "Perkin Elmer, tensor 27 (Bruker)" using potassium bromide (KBr) disc at a wavenumber range of (400-4000) cm^{-1} at College of Science Thi-Qar University. "The ^{1}H-$^{13}CNMR$ spectra were recorded using a Bruker spectrophotometer (400 MH_Z) at Basra University, Iraq".A mixture of aromatic diamine (10 mmol) or sulfamethoxazole (20 mmol) with sodium azide (20 mmol) and triethyl orthoformate (20 mmol) was dissolved in glacial acetic acid (30 mL) [29]. The reaction mixture was heated under reflux at 120^{O}C for 48 hrs. The progress of the reaction was monitored by TLC (ethyl acetate: hexane) (1:2) The solution was poured into crushed ice. The produced solid was then filtered and washed with water. The yielded product was recrystallized using a mixture of ethanol and water (1:1). *2,4-di(1H-tetrazole-1-yl)-5-(3,4,5-tri methoxy benzyl) pyrimidine T1*. Deep brown solid, Rf =0.35; Mp. = 225ºC; yield= 89%; MWt= 396.36. FT-IR (υcm^{-1}): 3152 (Ar C-H), 1723(N=N-N), 1611(C=C)[30]. ^{1}H-NMR (400 MHz, DMSO) δ: 9.6 (s, 1H, tetrazole), 6.8(s, 2H, aromatic), 4.11(s, 2H, CH_2), 3.54(s. 3H, methoxy) (Fig.1). ^{13}C-NMR (400MHz DMSO) δ: 29(CH_2), 59.4 (OCH_3), 110 (aromatic C), 129-157 (Tetrazole-C and pyrimidine C)[31].

2,6-di(1H-tetrazol-1-yl) pyridine T2.Green solid, Rf=0.82; Mp. = 191ºC; yield=62%. MWt= 215.17, FT-IR (υ cm^{-1}) : 3024(Ar C-H), 1675(N=N-N), 1559(C=C). ^{1}H-NMR (400 MHz, DMSO) δ: 8.91(s, 1H, tetrazole), 7.5-7.9 (m, 3H, aromatic). ^{13}C-NMR (400MHz, DMSO) δ: 117-136 (Pyridine C),145 (Tetrazole-C).

N-(5-methylisoxazol-3-yl)-4-(1H-tetrazol-1-yl) benzene sulfonamide T3

Pink solid, Mp. = 165, Rf=0.45, 156 ºC; yiled=83%, MWt= 306.30. FT-IR (υcm^{-1}): 3423 (N-H), 3242(CH, oxazole), 3139(Ar C-H), 1715(N=N-N), 1661(C=C). ^{1}H-NMR (400 MHz, DMSO) δ: 9.5(s, 1H, Tetrazole), 10.93(s,1H, NH-SO_2), 7.8-7.7(dd, 4H, aromatic), 6.8(s, 1H, oxazole), 2.33(s. 3H, methyl)fig.3)(. The tetrazole proton shifted to the solvent peak. ^{13}C-NMR (400MHz, DMSO) δ: 19.2(CH_3), 96.1(CH, Oxazole), 122-137 (aromatic C), 145 (Tetrazole-C) 174(CH, N-C, oxazole) [32].

1,1-(3,3-dimethyl-[1,1-biphenyl]-4,4-diyl)bis (1H-tetrazole) T4

Deep green solid, Rf=0.76; Mp. = 260 ºC; yield =77.5%. MWt=318.34. FT-IR (υ cm^{-1}): 3123, 3056(Ar C-H), 1695(N=N-N), 1602(C=C). ^{1}H-NMR (400 MHz, DMSO) δ: 9.1(s, 1H, Tetrazole), 7.2-7.68(m, 6H, aromatic), 1.85(s. 6H, methyl). ^{13}C-NMR (400MHz, DMSO) δ: 14.4(CH_3), 125-139 (aromatic C), 141 (Tetrazole-C)(Fig.2).

Synthesis of compounds (T5-T9).

Synthesis of 1-(4-(1H-tetrazole-1-yl) phenyl) ethanone T5.

4-amino acetophenone (10 mmol) was dissolved in AC (20 mL) with sodium azide (NaN_3) (10 mole) and triethylorthoformate (10 mmol) was added. The resultant mixture was heated under reflux. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was poured into crushed ice. The solid was

then filtered, washed with water, and the produced compound was recrystallized using ethanol.

Synthesis of monosubstituted tetrazole derivatives (T6-T9).

A mixture of compound T5 (2.6mmol), ethyl cyan acetate (2.6 mmol), ammonium acetate (2.08 mmol), and (2.6 mmol) of an appropriate aldehyde (3,4-dimethoxybenzaldehyde, vanillin, 4-bromobenzaldehyde, and 4- chloro benzaldehyde), respectively in ethanol (15 mL). The formed precipitate was filtered, dried, and recrystallized from a suitable solvent to get the desired compounds (T6- T9).

***6-(4-(1H-tetrazol-1-yl) phenyl)-4-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile* T6.**

Yellow solid, Rf=0.37; Mp.= 281ºC; yield=46%. MWt=400.39. FT-IR (υ cm^{-1}): 3342 (NH), 3170 (Aromatic C-H) 2215 (C≡N), 1703 (C=O), 1621(N=N-N), 1597(C=C) (Fig. 3). ^{1}H-NMR (400 MHz, DMSO) δ: 12.6(s, 1H, OH tautomeric), 10.6 (s,1H, CH=N, tetrazole) 7.7-7.9(d, 4H, aromatic C-H), 7.1-7.3 (s, 3H, aromatic C-H), 6.8 (s,1H, pyridone C-H), 3.8 (s,6H,OCH_3). ^{13}C-NMR (400MHz, DMSO) δ:169 (C=ONH), 162,150 (pyridone ring) 142 (Tetrazole ring) 111-140(aromatic C), 56(OCH_3), 39-40(DMSO)(Figure .4).

6-(4-(1H-tetrazol-1-yl) phenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile T7.

Deep yellow solid; Mp. = 261ºC; yield=46%; MWt=386.36. FT-IR (υ cm^{-1}): 3410 (OH), 3361 (NH), 3170(Aromatic C-H) 2205 (C≡N), 1712 (C=O), 1616(N=N-N), 1592(C=C). ^{1}H-NMR (400 MHz, DMSO) δ:.9.11 (s, 1H, NHCO), 9.41 (s, 1H, OH),10.2 (s,1H,CH=N, tetrazole) 7.6-7.9(d, 4H, aromatic C-H) ,7.2-7.4 (s, 3H, aromatic C-H), 6.5 (s,1H, pyridone C-H), 3.6 (s,6H,OCH_3). ^{13}C-NMR (400MHz, DMSO) δ:169 (C=ONH), 160,150 (pyridone ring) 144 (Tetrazole ring) 111-139(aromatic C). 56(OCH_3) [33].

***6-(4-(1H-tetrazol-1-yl) phenyl)-4-(4-bromophenyl) -2-oxo-1,2-dihydropyridine-3-carbonitrile* T8.**

Brown solid, Rf=0.51; Mp.= 201ºC; yield=40%; MWt= 419.2. FT-IR (υ cm^{-1}): 3351 (NH), 3170 (Aromatic C-H) 2207 (CN), 1717 (C=O), 1661(N=N-N), 1598(C=C). ^{1}H-NMR (400 MHz, DMSO) δ: 12.4 (s, 1H, NH), 10.2 (s,1H, CH=N, tetrazole) 7.5-7.7 (d, 4H, aromatic C-H) ,7.4-7.3(s, 3H, aromatic C-H), 6.4 (s,1H, pyridone C-H)[33]. ^{13}C-NMR (400MHz, DMSO) δ: 163 (C=ONH), 157, 146 (pyridone ring) 143 (Tetrazole ring) 114-139(aromatic C).

6-(4-(1H-tetrazol-1-yl) phenyl)-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile. T9.

Yellow solid, Rf=0.41; Mp.=186ºC; yield=63%; MWt=374.78. FT-IR (υ cm^{-1}): 3321 (NH), 3120 (Aromatic C-H) 2213 (CN), 1702 (C=O), 1643(N=N-N), 1600(C=C). ^{1}H-NMR (400 MHz, DMSO) δ: 11.8 (s, 1H, NH), 9.81 (s,1H, CH=N, tetrazole) 7.4-7.6 (d, 4H, aromatic C-H) ,7.2-7.3(s, 3H, aromatic C-H), 6.2 (s,1H, pyridone C-H). ^{13}C-NMR (400MHz, DMSO) δ: 160 (C=ONH), 154,143 (pyridone ring) 144 (Tetrazole ring) 103-136(aromatic C). [,33].

Insilco molecular docking study

The computerized method that is commonly employed for the binding orientation prediction of simple drug molecule, and subsequently prediction of the molecule activity and affinity towards a protein, is referred as in-silico molecular docking. Aiming to recognize the interactions between the created molecules (T1–T9) with the enzyme DNA-gyrase, (MOE-2014.0901) software was utilized to carry out a molecular docking study. for every compound, an upper limit of 30 conformers was considered in the docking method. The visualization of the ligand - receptor binding interactions was conducted. ChemDraw Professional 15.0 was utilized to draw all the created compounds (T1-T9). Energy minimization was run on Chem3D Ultra 15.0 with the MMFF94 force. Protein Data Bank (BDP) was the source of the crystal structure of the enzyme DNA gyrase (PDB ID: 1KZN). The resolution that greater than 2.30 Aº and comprising the gene code of the same bacterial was the principle for the protein selection. Eliminating the clorobiocin in the sequence editor technique was applied to prepare the enzyme. A molecule of H_2O was introduced in the active sites to ensure the formation of hydrogen bond between the ligands and the target. This attributed to significant role of H_2O molecule located in the active site of the targeted enzyme. Prior the addition of hydrogen atoms, the missing and broken bonds because X-ray diffraction were corrected by the protein structure [34]. Docking and scoring calculations were performed utilizing the Molecular Operating Environment (MOE-2014.0901). As it is stated, the RMSD values perfect score is closer to 2 Å and the energy of score should be = -7 Kcal/mol or less value [35]. In order to verify the docking results, these values were employed as standard values.

Study Absorption, Distribution, Metabolism, Excretion, and toxicity (ADMET)

In the field of drug designing because of unfortunate drug properties and various undesired effects, several drugs did not succeed in clinical trials and subsequent development processes. In this work, all optimized compounds were investigated by the online web tool Swiss ADME. While, in silico toxicity, evaluation was carried out utilizing an online server ProTox-II, which gave predicted oral toxicity, cytotoxicity, mutagenicity, carcinogenicity, hepatotoxicity, and immune toxicity values for compounds(T1-T9) [36].

Antimicrobial activity

Table 7 shows all sorts of bacteria utilized in this study. The bacteria strains (*Staphylococcus aureus and Escherichia coli*) were supplied by the biology department, College of Science, University of Waist. A solid-phase nutrient bath was utilized for growing up of the bacteria at a temperature of 37 ^{0}C for 24 hours. Different quantities from the synthesized compounds (T1-T9) were dissolved in DMF to prepare three solvents with concentrations of 0.1, 0.01, and 0.001 g/mL for each. The biological activities of these solvents were compared with those of Amoxicillin, Ampicillin, Ciprofloxacin and Streptomycin antibiotics. DMSO was spread on the blank disc which was exploited as a control. Also, this solvent is applied to the external layer of nutrient agar plates. Filter papers, Whatman no.3, were immersed in 20 mL of each solvent of the prepared compounds and then kept at room temperature. The measurements of the inhibition zone (in millimeters) were conducted upon incubation of the inculcated plates at the same conditions of the bacteria growth. The inhibition zone measurement was repeated three times, the mean was then calculated and given in Table 7.

Results and Discussion

Characterization methods have indicated the synthesis of Tetrazole derivatives (T1-T3) by the reaction of aromatic primary amine, triethyl orthoformate, and sodium azide. FT-IR spectra of tetrazole derivatives, in general, showed disappearance of (NH_2) absorption band and appearances of (C-N) absorption band of tetrazole at (1243- 1289) cm^{-1}, in addition to the appearances of (N=N) absorption band of tetrazole at (1675-1721) cm^{-1}. ^{1}H-NMR spectrum of compound T3 showed the following data (δ): (s, 8.5ppm) due to (CH) in tetrazole, (s, 10.9 ppm) corresponding to (NH-SO_2)[37], (s, 6.7ppm) attributed to (CH) in oxazole ring and (s, 2 .34 ppm) belongs to methyl group. Characterization of all compounds were mentioned in details in experimental part.

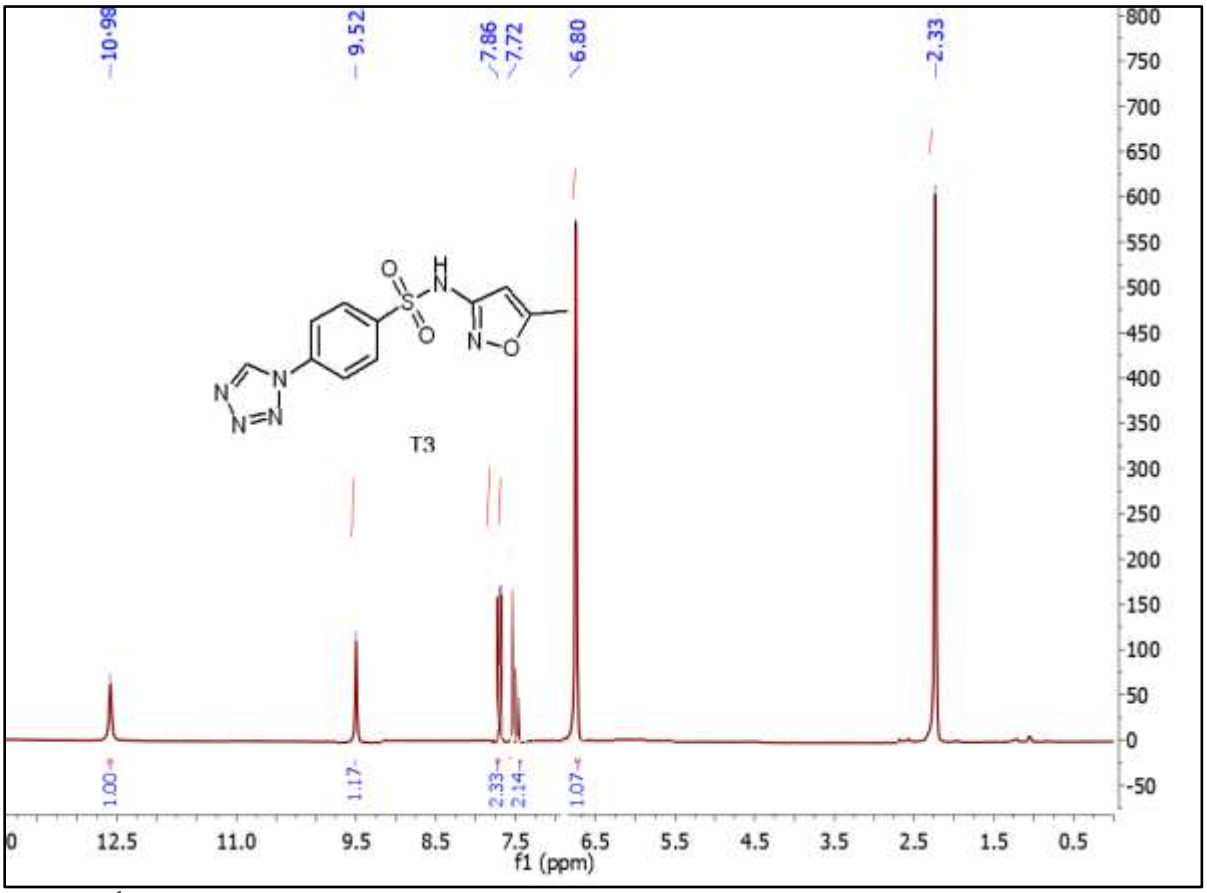
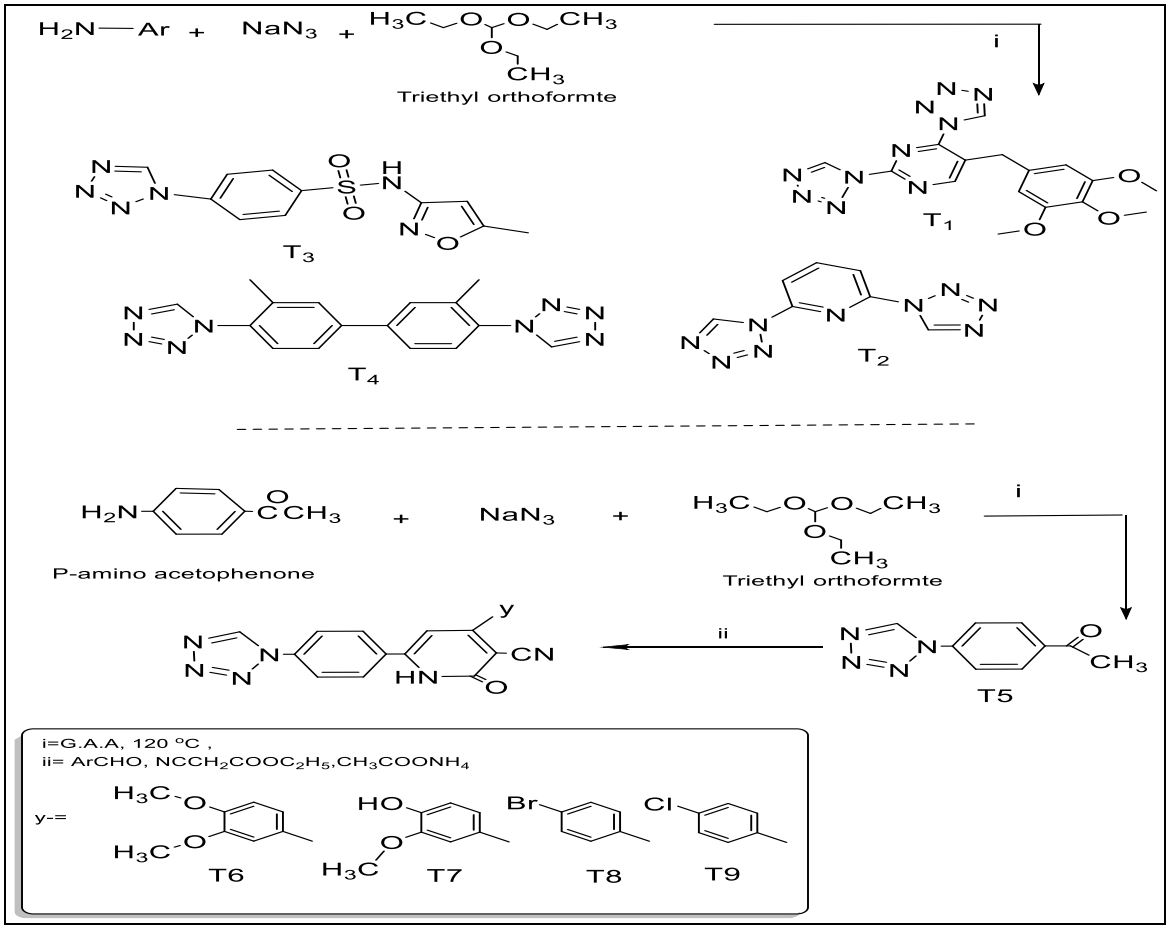


Figure 1.[1] HNMR of compound T3



Scheme 1. The synthesis of tetrazole derivatives (T1-T9).

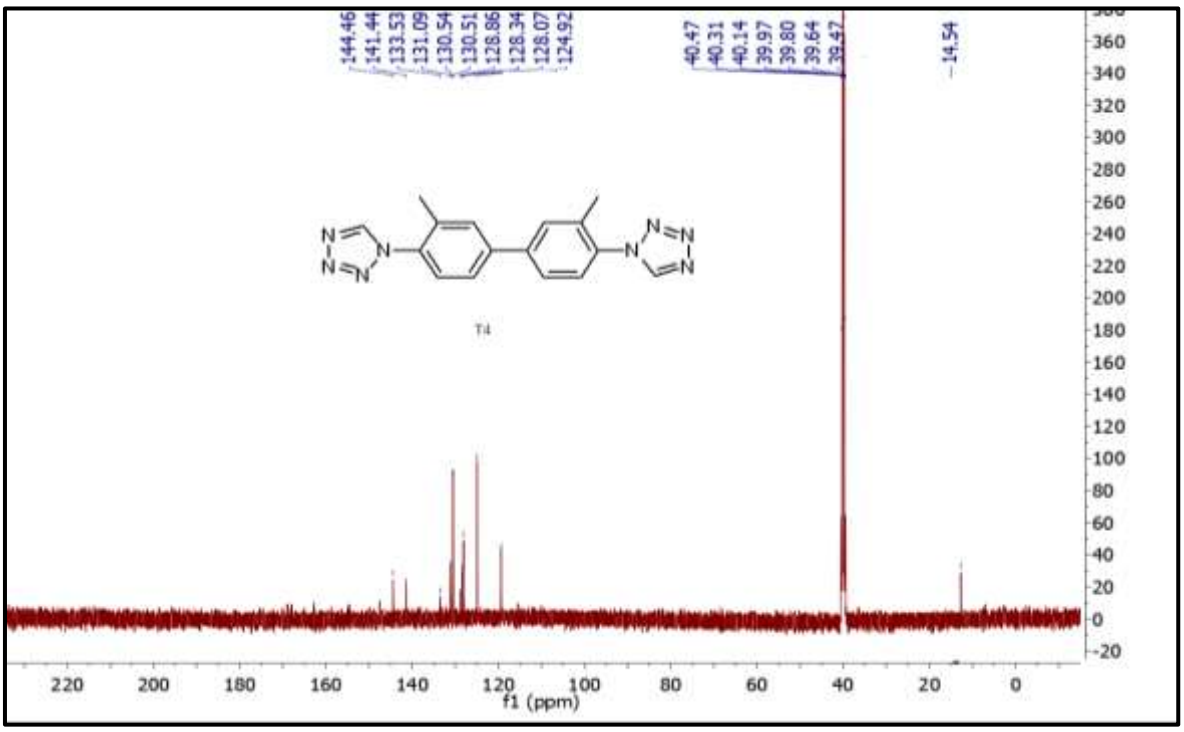


Figure 2.^{13}CNMR of compound T4

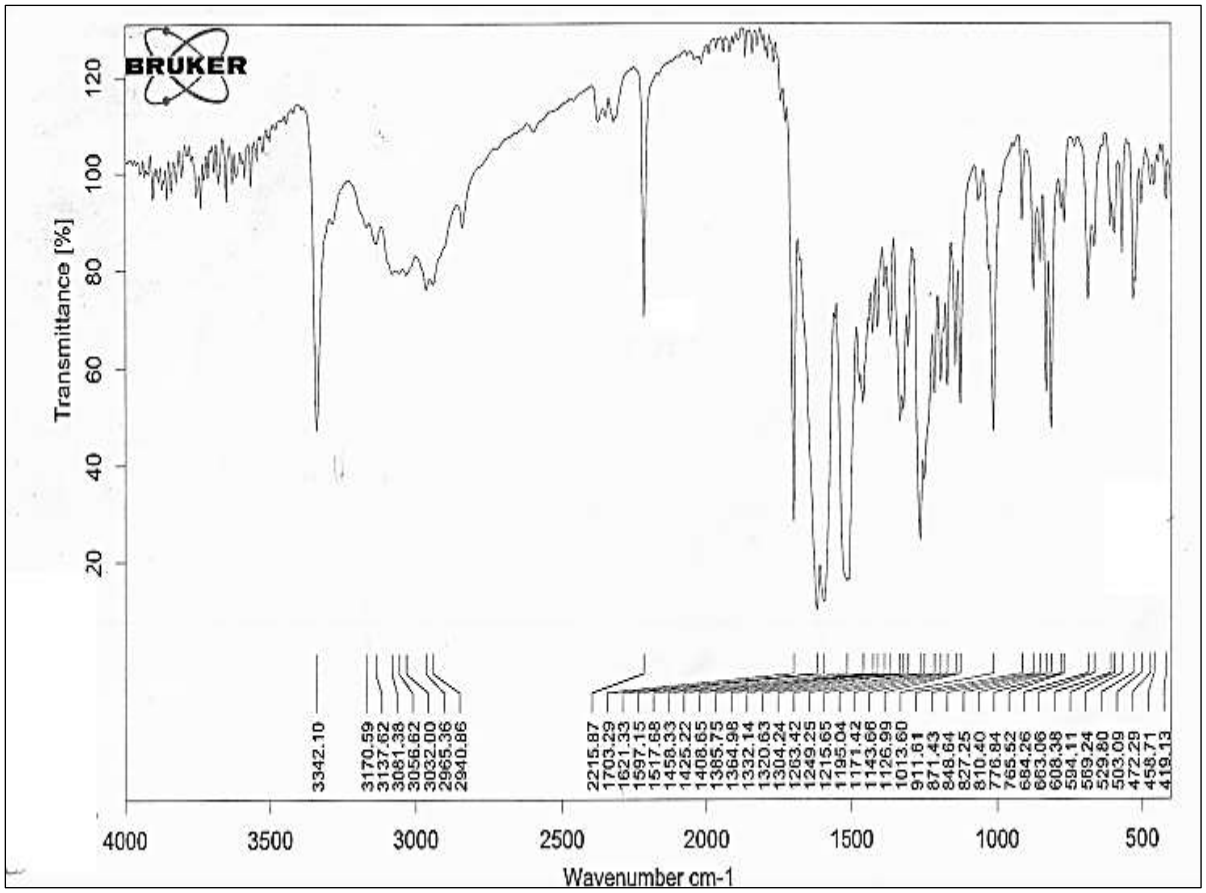


Figure 3. FT-IR of compound T6

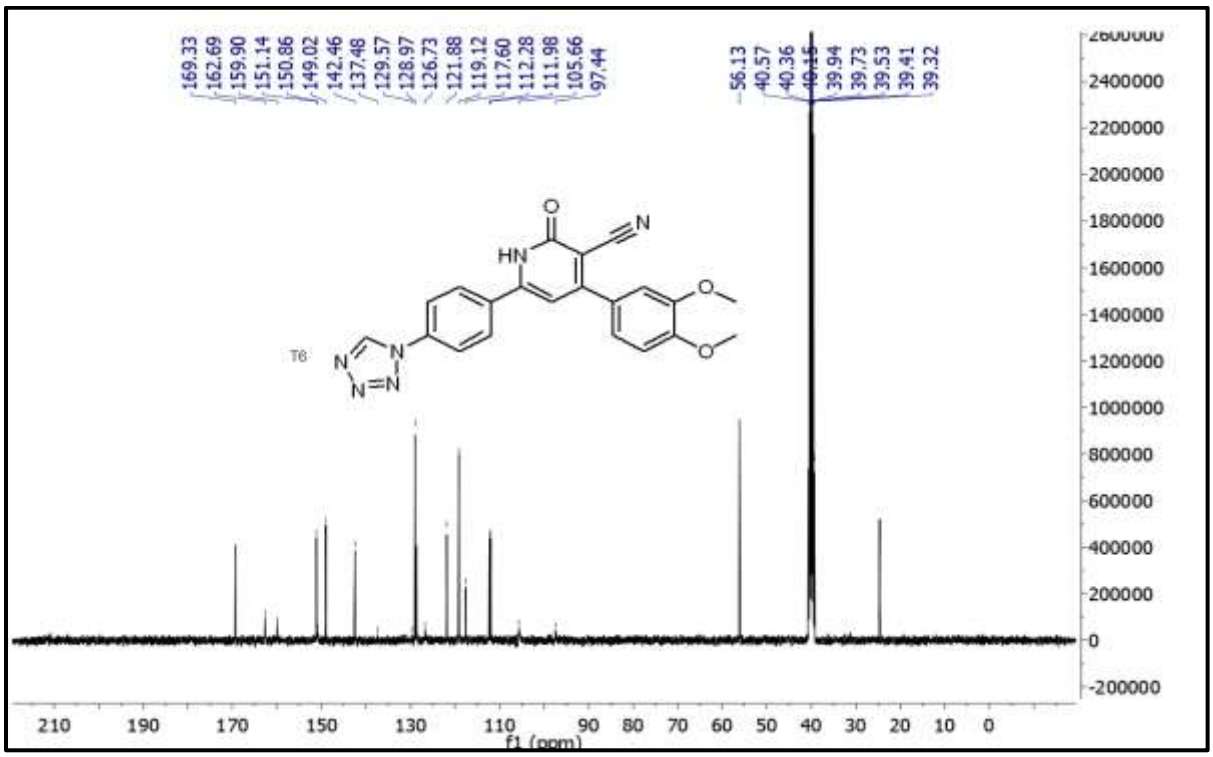


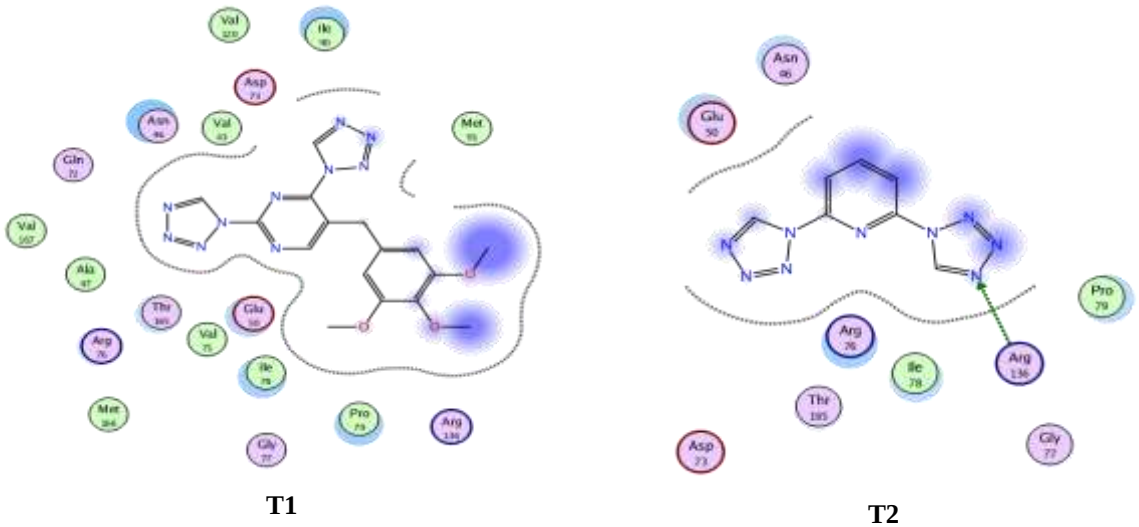
Figure 4. ^{13} C-NMR of compound T6.

Molecular Docking Study

MOE -2014 software program was utilized to evaluate the compounds (T1-T9) and clorobiocin for docking investigation towards DNA-gyrase. In the present work, the designated protein model was the crystal structure of E. coli 24kDa Domain in Complex with Clorobiocin (PDB code 1KZN) with 2.30 resolution [38] . The program default was defined the legends rotatable bonds. In a comparison with clorobiocin (as a reference), the highest score of the ligands (T1-T9) docking results were chosen and listed in Table 1. Utilizing MOE software, docking score results were from (-4.458) Kcal/mol to (-7.425) Kcal/mol against (1KZN) active side. The selected amino acids for the enzyme active site were (GLU42, VAL43, ASP45, ASN46, ALA47, ASP49, GLU50, VAL71, GLN72, ASP73, GLY75, ARG76, GLY77, ILE78, PRO79, ILE90, MET91, VAL93, LEU94, HIS95, ALA96, GLY117, VAL118, GLY119, VAL120, SER121, ARG136, THR165, MET166, VAL167). The clorobiocin - DNA-gyrase docking result score was (-6.462 Kcal/mol). As illustrated in Table 1, the results showed that the interactions took place between the receptor in the pocket with clorobiocin and just 4 ligands. Also, the results indicated that the top docking score was for T8 compound (-6.685 kcal/mol) and RMSDs value of1.961Å, then T6 compound with score of (- 6.727 kcal/mol) and RMSDs value of 2.076 Å. Nevertheless, RMSDs value were 2.361Å for the compound T2 and 1.935 for T9 compound. Whereas, no interactions occurred between (T1,T3,T4,and T7) compounds with the receptor. Additional tests for the interactions of bond lengths and hydrogen bonds in site were performed and the results displayed in Fig.5 and Table1. It can be seen from Table 1 that interactions occurred between T6 via H-pi with ASN46 and ILE78 amino acids residues. Table1 show the interactions of energy binding and distance of interactions. As exhibited in table1, clorobiocin interacted with His401 amino acid via H-pi interaction. On the other hand, H-acceptor interaction occurred between clorobiocin with both of ILE78 amino acid and with water molecule.

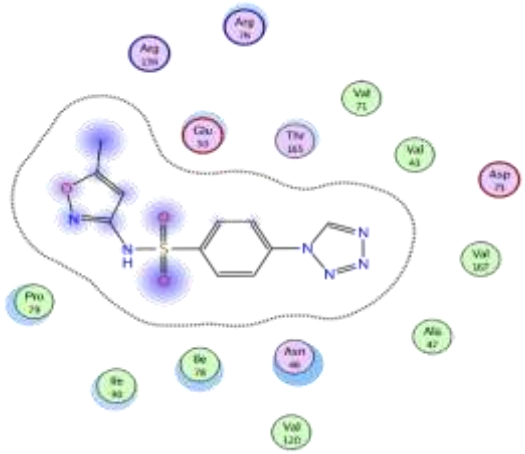
Table 1. The results obtained from docking of synthesis compound T1-T9 with 1KZN in active site.

Compd.	RMSD	Score (kcal/mol)	Bonds between Atoms of Compounds and Residues of Active Site of 1KZN					
			Compd Atoms	Receptor Atoms	Receptor Residues	Interaction	d (Å)	E (kcal/mol)
T1	1.73	-7.425	-	-	-	-	-	-
T2	2.361	-4.458		NH1	ARG136	H-A	2.97	-1.7
T3	2.111	-5.549	-	-	-	-	-	-
T4	2.098	-6.199	-		-	-	-	-
T_6	2.076	- 6.727	6-ring 6-ring	CB CGI	ASN 46 ILE78	pi-H pi-H	3.91 4.49	-1.0 -0.
T7	1.9921	-6.754	-	-	-	-	-	-
T8	1.961	-6.685	BR	O	VAL71	H-D	3.64	-0.5
T9	1.935	-6.314	6-ring	CB	ASN 46	pi-H	3.72	-0.6
Ligand	2.0046	-6.462	5-ring	CD	ILE78	Pi-H	3.97	-0.6

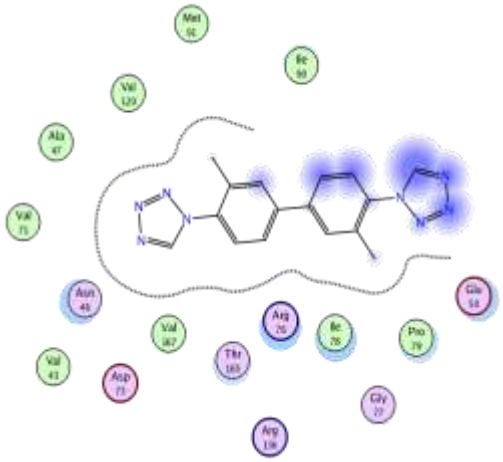


T1 **T2**

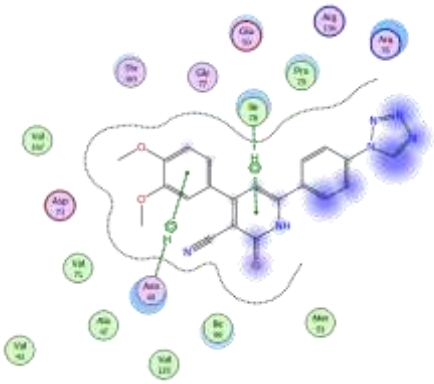
Figure 5. Binding affinity of compounds (T1 –T9 and clorobiocin) with 1KZN



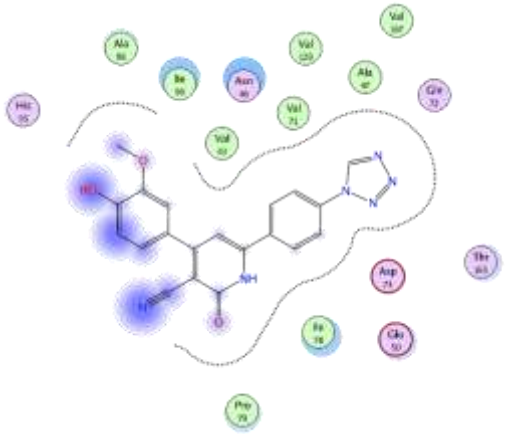
T3



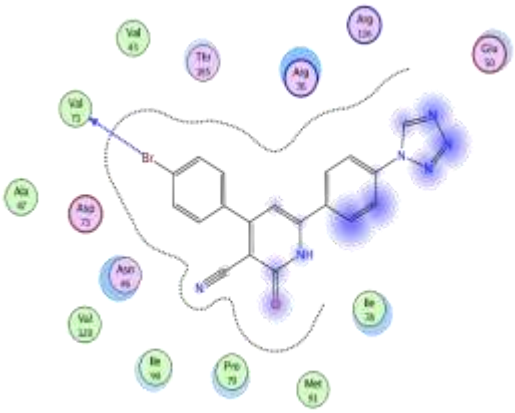
T4



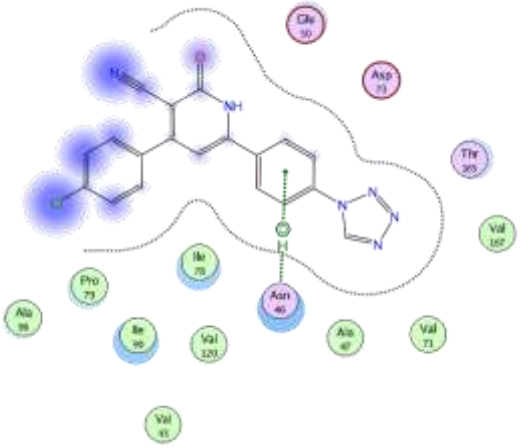
T6



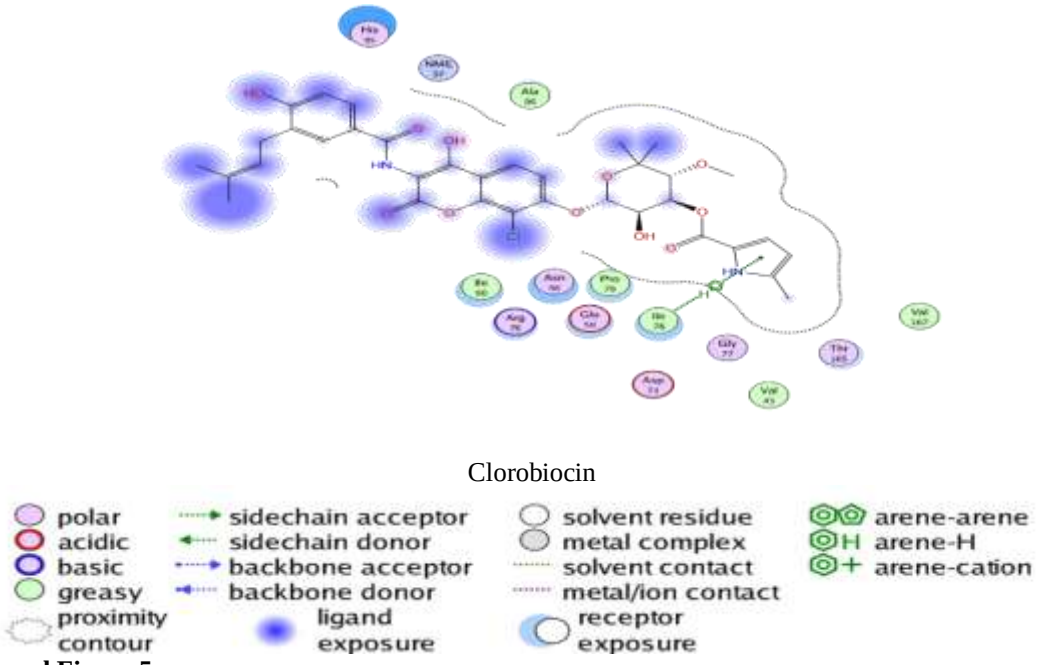
T7



T8



T9



Continued Figure 5.

Analysis of ADMET Properties

Study of physicochemical properties

The physicochemical properties are necessary for the design of new compounds that are intended to use as drugs. A drug-likeness profile can be evaluated via parameters of the molecule such as molecular weight (MWt), the number of heavy atoms (No heavy atoms), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), rotatable bonds, molar refractivity, and Topological polar surface areas (TPSA)[39]. These parameters were calculated for compounds T1-T9 and shown in Table2.

Table 2. Physicochemical properties of synthesized compounds T1-T9.

Compd	Formula	Mwt (g/mol)	Heavy atoms	HBA	HBD	Rotatable Bonds	Fraction Csp3	Molar Refractivity	TPSA (Å^2)
T1	$C_{16}H_{16}N_{10}O_3$	396.36	29	11	0	7	0.25	96.38	140.67
T2	$C_7H_5N_9$	215.17	16	7	0	2	0.00	49.66	100.09
T3	$C_{11}H_{10}N_6O_3S$	306.30	21	7	1	4	0.09	105.37	124.18
T4	$C_{16}H_{14}N_8$	318.34	24	6	0	3	0.12	87.23	87.20
T6	$C_{21}H_{16}N_6O_3$	400.39	30	7	1	5	0.1	108.35	118.71
T7	$C_{20}H_{14}N_6O_3$	386.36	29	7	2	4	0.05	103.88	129.71
T8	$C_{19}H_{11}BrN_6$	419.2	27	5	1	3	0.00	103.06	100.25
T9	$C_{19}H_{11}ClN_6$	374.78	27	5	1	3	0.00	100.37	100.25

The drug-likeness profiles were calculated based on Lipinski's (MW ≤ 500; HBA ≤ 10 and HBD ≤ 5), Ghose's (160 ≤ MWt ≤ 480; 40 ≤ MR ≤ 130 and 20 ≤ atoms ≤ 70), Veber's (rotatable bonds ≤ 10 and TPSA ≤ 140), Egan (TPSA ≤ 131.6) and Muegge (200 ≤ MW ≤ 600; the number of aromatic rings ≤ 7; several rotatable bonds ≤ 15; HBA ≤ 10 and HBD ≤ 5)"[39]. The rule-based score defines the compounds into four probability score classes i.e. 11%, 17%, 55%, and 85%. The acceptable probability score is 85% which indicates that it passed the rule of five. All compounds T1-T9 have appeared with a score of 85%, which indicates that compounds obeyed all the five rules without any violations with good bioavailability. Furthermore, the synthetic accessibility of the compounds was assessed to quantify the complexity of the molecular structure. The results showed that the score was in the range of 2.43 - 3.41. This revealed that the compounds do not have a complex synthetic route as shown in Table 3.

Table 3. Drug likeness, bioactivity and synthetic accessibility score.

Compd.	Lipinski	Ghose	Vebe r	Egan	Muegg	bioactivity Score	synthetic accessibility
T_1	Yes; 1 violation	Yes	No	No	No	0.55	3.41
T2	Yes; 0 violation	No	Yes	Yes	Yes	0.55	2.49
T3	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55	2.79
T4	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55	2.43
T6	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55	3.08
T7	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55	2.97
T8	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55	2.81
T9	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55	2.78

In order to determine the solubility medium (aqueous or non-aqueous) of the compounds, the anticipated mean of lipophilicity values was assessed and calculated taking into account of consent value of log Po/w. On this basis, when this value is more negative, the more compound solubility. The obtained results revealed that the compounds T1, T2, and T3 can be dissolved in non-aqueous media. On the other hand, the value of consensus log S is indicating the nature of solubility, where (log S) < -10: lack solubility; < - 6: moderate solubility; < -4: good solubility; < -2: very good solubility; and <0: high solubility [(40)]. Values of consensus log S demonstrated that most compounds (from T2 to T7) have moderate solubility in aqueous media, excluding the compounds T1, T8, and T9. The prediction of pharmacokinetic parameters including absorption, skin permeation, distribution, metabolism, and excretion were done. Based on the predictive model, there is an indication of passive gastrointestinal absorption when a molecule lies in the white area, while there is an indication of passive brain permeation when a molecule lies in the yellow area. According to the parameters the of predicted distribution of compounds from T2 to T9, all the created compounds were suggested to show a perfect GI absorption and lack of blood-brain permeate. Consequently, causing serious toxicants in the brain and bloodstream will be not possible. It is stated that poorer skin permeates as a higher negative log Kp value of a molecule. Accordingly, the molecules T1-T3 are the lower skin permeate since they have high values of negative log Kp (Table 4).

Table 4. Predicted absorption and distribution parameters of compounds T1-T9.

Compd.	Consensus Log Po/w	Consensus Log S (ESOL)	Solubility Class	GI	BBB	Log Kp (cm/s)
T1	0.97	-3.22	Moderately soluble	Low	No	-7.79
T2	0.08	-1.86	Soluble	High	No	-7.53
T3	0. 71	-2.59	soluble	High	No	-7.55
T4	2.42	-4-41	soluble	High	No	-6.20
T6	2.49	-3.94	soluble	High	No	-7.19
T7	2.14	-3.74	Soluble	High	No	-7.33
T8	3.13	-4.72	Moderately soluble	High	No	-6.77

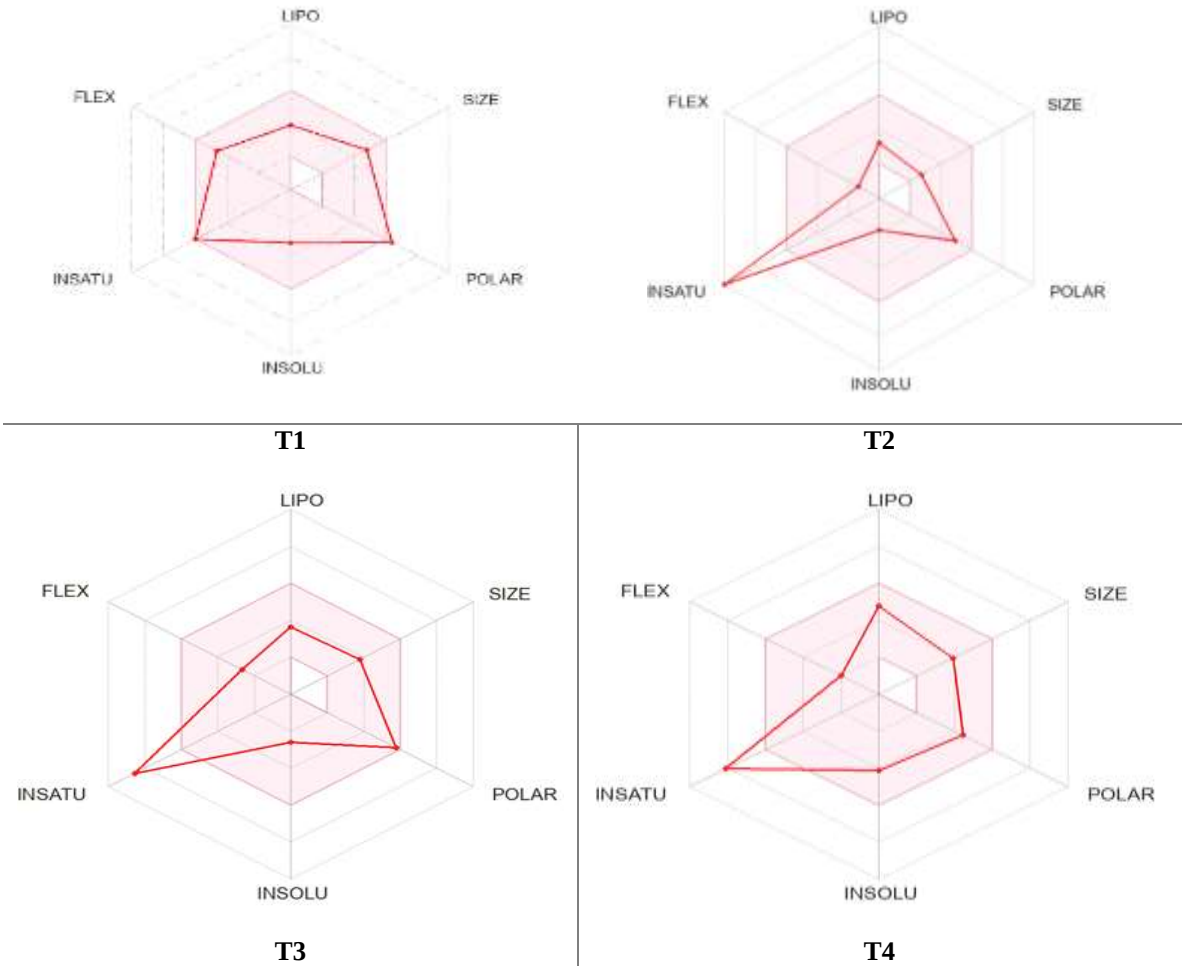
In addition to the bioavailability of drugs, metabolism has a significant role in drug-drug interactions. Metabolism parameters are necessary to recognize whether a molecule has an inhibition activity against certain proteins or not. The evaluation results of metabolism parameters of prepared compounds, T1-T9, exhibited that all these compounds, excluding T1, were non-substrates of permeability glycoprotein (P-gp). This protein (P-gp protein) is very important for evaluating active efflux via pharmacological membranes and cytochrome P450 (CYP) enzymes. Moreover, it is noticed that T1-T2 compounds were non-substrates of CYP2D6 inhibitor, while T2, T3, T6, and T7 compounds found to be non-substrates of CYP1A2. Nevertheless, T6, T, and T9 molecules were determined that substrates of CYP2C9 inhibitor, while the molecules (T3, T4, T8 and T9) were substrates of CYP2C19 inhibitor as shown in Table 6. The obtained data of ADMET revealed that perfect compound in metabolism is T2.

Table 5. Predicted metabolism parameters of the compounds T1-T9.

Compd.	p-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
T1	Yes	Yes	No	No	No	Yes
T2	No	No	No	No	No	Yes
T3	No	No	Yes	No	No	No
T4	No	Yes	Yes	No	No	No
T6	No	No	No	Yes	No	Yes
T7	No	No	No	No	No	No
T8	No	Yes	Yes	Yes	No	No
T9	No	Yes	Yes	Yes	No	No

Toxicity Prediction results

The toxicity of compounds (T1-T9) was calculated using ProTox-II (online software). Organ toxicity results suggested that all compounds were predicted to be hepatotoxicity, while toxicological endpoints results suggested that all compounds were predicted to be non-mutagenicity and non-cytotoxicity. All compounds were predicted to be carcinogenic except compounds T8 and T9. The compounds T1, T3, T8, and T9 were non-Mutagenic, and other compounds were carcinogenic. The toxicity class for all compounds was (4), but the toxicity



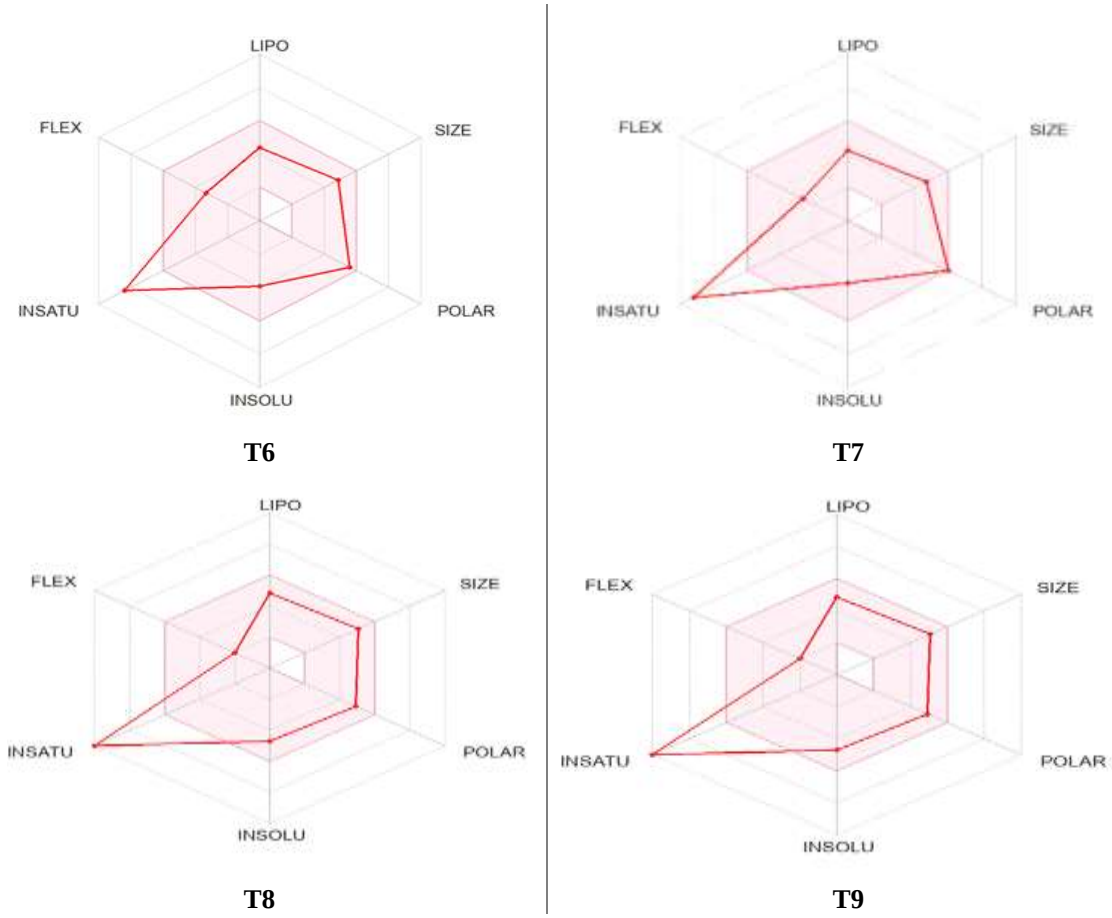


Figure 6. A spider shape of synthesized compound T1-T9.

class for (T1) and (T3) were (5). Notes [Class I: fatal if swallowed (LD50 ≤ 5) Class II: fatal swallowed (5 < LD50 ≤ 50) Class III: toxic if swallowed (50 < LD50 ≤ 300) Class IV: harmful if swallowed (300 < LD50 ≤ 2000) Class V: may be harmful if swallowed (2000 < LD50 ≤ 5000), Class VI: non-toxic (LD50 > 5000)" [41]. The predicted LD50 results that the compounds (T2, T4-T9) were harmful if swallowed and belong to class IV (Table 7). The compounds T1 and T3 were found to be harmful if swallowed and belong to class V (Table 6).

Table 6. Insilco toxicity evaluation of the compounds (T1-T9).

Compd.	Organ Toxicity	Toxicity - endpoints				Predicted LD50 (mg/kg)	Predicted Toxicity Class
	Hepatoto-xicity	Carcinog-enicity	Immunotoxicity	Mutagenicity	cytotoxicity		
T1	active	active	active	Inactive	Inactive	3470	5
T_2	active	active	Inactive	active	Inactive	1750	4
T3	Inactive	active	Inactive	Inactive	inactive	3471	5
T4	Inactive	active	Inactive	active	Inactive	1750	4
T6	active	active	Inactive	active	Inactive	400	4
T7	active	active	Inactive	active	Inactive	400	4
T8	active	Inactive	Inactive	Inactive	Inactive	890	4
T9	active	Inactive	Inactive	Inactive	Inactive	1000	4

Pharmacological activity

The antimicrobial activity of the compounds (T1-T9) was tested against gram-positive bacterial species (*Staphylococcus aureus) and Gram-negative (E. coil*). The results of pharmacological effects are shown in Table 8. Most of the synthesized compounds showed a good activity against both the Gram-positive and Gram-negative bacterial species. The obtained results of screened compounds against Gram-negative organisms showed that all compounds have the highest activities against *E. coli* at 0.01mg/mL concentration. In thecase of Gram-

positive bacteria, all compounds except compound T2, showed acceptable activity against Staphylococcus aureus at 0.01 and 0.001mg/mL concentration [42,43]. The antibacterial study revealed that compounds showed better bacteriostatic activity than bactericidal activity.

Table 7. Antibacterial activity of the synthesized compounds T1-T9.

Compd.	*Staphylococcus aurous*			*E. coil*		
	Conc. (mg/L)			Conc. (mg/L)		
	0.0001	0.001	0.01	0.0001	0.001	0.01
T1	-	++	++	-	-	+
T2	-	-	-	-	++	+++
T3	+	++	+++	+	++	+++
T4	-	-	-	-	-	+++
T6	+	++	+++	+	++	++
T7	+	++	+++	-	+	+
T8	+	++	+++	+	++	+++
T9	+	++	+++	-	+	+++
Amoxicillin	++			+++		
Ampicillin	+			+++		
Ciprofloxacin	++			+++		
Streptomycin	+++			+++		

Notes: No inhibition (-), Inhibition zone(10-15) mm(+), Inhibition zone(15-25) mm(++) and Inhibition zone (25-30) mm(+++)

Conclusion

Molecular docking study of tetrazole derivatives with crystal structure of (PDB code 1KZN) enzyme revealed that these compounds interact with this enzyme in a sufficient way. This result was reinforced by the lower bending energy and strong binding length with the active sites of proteins. Moreover, the toxic, absorption and physiochemical properties of the prepared compound aiming to recognize similarity of their features with those of drugs. It is can be concluded that tetrazole derivatives could be utilized for drug improvement through designing and modification of compounds to be more active. Tetrazole derivatives compounds (T1-T9) were synthesized via a ring-closing reaction of primary amine and azide in presence of acetic acid. Tetrazole derivatives (T6-T9) that contain pyridone moiety were also prepared by ring closure reaction. The prepared compounds were characterized utilizing FT-IR, ^{1}H-NMR and^{13}C-NMR spectroscopic methods, in addition to melting point measurements. The characterization methods supported the proposed structures of all prepared compounds. Regarding study antibacterial study, the compounds (T2, T3, T4, T5, T6, T7, T9) exhibited a high sensitivity against E. coli at 0.01mg/mL concentration. Also, all compounds except compound T2, showed an acceptable activity against Staphylococcus aureus at 0.01 and 0.001mg/mL concentration. To sum up, the heterocyclic compounds (T1-T9) are very important and could be considered as an essential material for future active medications, especially when they are used as inhibitors for (*Staphylococcus aureus*) and (*Escherichia coli*) bacteria.

Acknowledgment

The authors are thankful to the University of Wasit and the College of Sciences, for giving us the opportunity to carry out this research paper.

Conflicts of Interest

There is not conflict of interest.

Funding

The research didn't receive financial support from an Institution.

Ethics Statements

The study doesn't need ethical approval.

Author Contribution

The authors confirm their contribution to the paper as follows: study conception and design: Athra and Ammar; data collection: Athra; analysis and interpretation of results: Athra, and Jawad; draft manuscript preparation: Jawad, and Fatma. All authors reviewed the results and approved the final version of the manuscript..

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التصميم، الالتحام الجزيئي، ودراسات ADMET، تحضير، تشخيص، والتقييم الدوائي في المختبر لمشتقات التترازول.

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[١]قسم الكيمياء ، كلية العلوم ، جامعة واسط ،الكوت ، العراق

الخلاصة

تم تصميم وتصنيع سلسلة من مشتقات التترازول الجديدة من خلال تفاعل غلق الحلقة. شخصت المركبات (T9-T1) بواسطة التحاليل الطيفية FT-IR و ^{13}C-NMR - ^{1}H. تم فحص النشاط المضاد للبكتريا لجميع مشتقات التترازول ضد البكتيريا موجبة الجرام (المكورات العنقودية الذهبية) والبكتيريا سالبة الجرام (الإشريكية القولونية) ، أظهرت جميع المركبات فعالية عالية ضد الإشريكية القولونية بتركيز ٠,٠١ مغم/مل ، بينما لم يظهر المركب T2 نشاطًا ملحوظًا ضد المكورات العنقودية الذهبية موجبة الجرام. تم فحص النشاط التثبيطي المحتمل لانزيم DNA gyrase للمركبات (T9-T1) حاسوبيا باستخدام طريقة الارساء الجزيئي. أظهرت اربعة مركبات نتائج جيدة خاصة المركب (T8) الذي أظهر أقل نتائج في االارتباط بلغت (-٨,٨ كيلو كالوري / مول).

الكلمات المفتاحية: ADMET ، التقييم البيولوجي ، الالتحام الجزيئي ، تترازول ، السمية.