Original Article

# Molecular Docking, ADME Study, Synthesis And Characterization Of Some 1,2,3-Triazole Derivatives Of 4-(1H-Benzimidazol-2-Yl) Aniline

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## Abstract

A number of novel 1,2,3-triazole-based benzimidazole derivatives (4a-c) have been created using the Cu-catalyzed cycloaddition of alkyne and azide reaction (CuAAC). Compound **1** was synthesized from treatment of p-amino benzoic acid with o-phenylenediamine, it was converted into azide (compound **3**) by treatment compound **2** (amide that prepare from reaction of compound **1** with chloroacetyl chloride) with sodium azide. Compound **3** was converted into 1,2,3-triazole derivatives (**4a-c)** by treatment with acetylene derivatives. The intermediates and final compounds molecular structures are characterized and confirmed by FTIR, $^1$H-NMR and Mass spectra. In this present research, some benzimidazole derivatives bearing 1,2,3-triazole moiety were subjected to molecular docking to create safe and efficient molecules. To test each derivative's ability to bind to the enzyme's active site, it was docked into the active sites of Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, and Streptococcus pyogenes bacteria that originate from the crystal structure form of the enzymes in complex with anti-bacterial drug, Trimethoprim ( reference drug), whose PDB ID were 1NNI, 3G7E, 4HL2, 2W9S, and 4RKX. Swiss ADME was used to undertake ADME study to determine the topological polar surface area, bioavailability, and drug-likeness of the synthesized molecule. The outcome demonstrated that the investigated chemicals were orally absorbed and adhered to the Lipinski rule.

**Keywords:** 1,2,3-triazole, acetylene derivatives , Molecular docking, ADME study.

## Introduction

The existence of microbial pathogens has long been recognized.(1)(2) The spread of infection around the world has increased mortality, with more than 13 million deaths per year during the 20th century, as a result of the most sophisticated infectious agents, the emergence of antimicrobial resistance, as well as the very severe use of antibiotics that lead to resist antibacterial agents.(3) The development of numerous antibiotics was spurred by Alexander Fleming's discovery of penicillin in 1929, which has improved human health by helping to contain and stop the spread of infection.(4) Nevertheless, frequent use of antibiotics can result in major health issues brought on by bacterial resistance to the drugs.(5) As a result, the creation of new and numerous antibiotics provides a means of treating resistant strains of organisms that were previously responsive to another antibiotic.(6) Over the course of a few decades, heterocyclic compounds particularly 1,2,3-triazole became promising candidates in the drug development process due to their wide range of pharmacological properties. Due to their rarity in nature, the synthetic moieties containing these chemical structures have been extensively used in the development of medications.(7) According to literature reviews, 1,2,3-triazoles and their derivatives have attracted a lot of attention because of their use in pharmaceutical and therapeutic products for conditions like cancer(8), viruses(9), bacteria(10)(11) ,inflammation(12), antioxidants (13),diabetes(14) and human (GABA) receptors antagonists(15). Additionally, some medications with 1,2,3-triazole scaffolds are in use today, including TSAO (16)(an anti-HIV agent), Cefatrizine (17)(an antibiotic agent), CAI (18)(an anti-cancer agent), and Tazobactum(19) (an anti-bacterial agent) (Figure 1). Numerous studies have been done on 1,2,3-triazole synthesis.(20)(21)(22) Cu-catalyzed azidealkyne cycloaddition process (CuAAC), also known as the "Click-reaction," was separately created by Sharpless group and results in 100% regioselectivity (only the 1,4-disubstituted regioisomer is produced) and excellent yields.(23)(24)

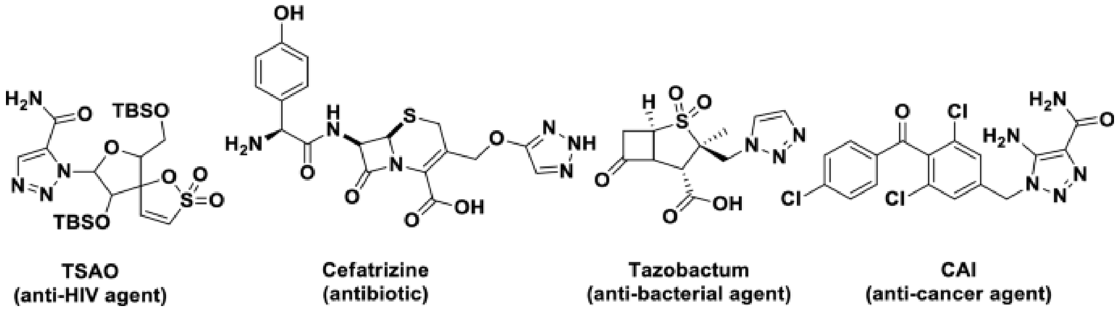
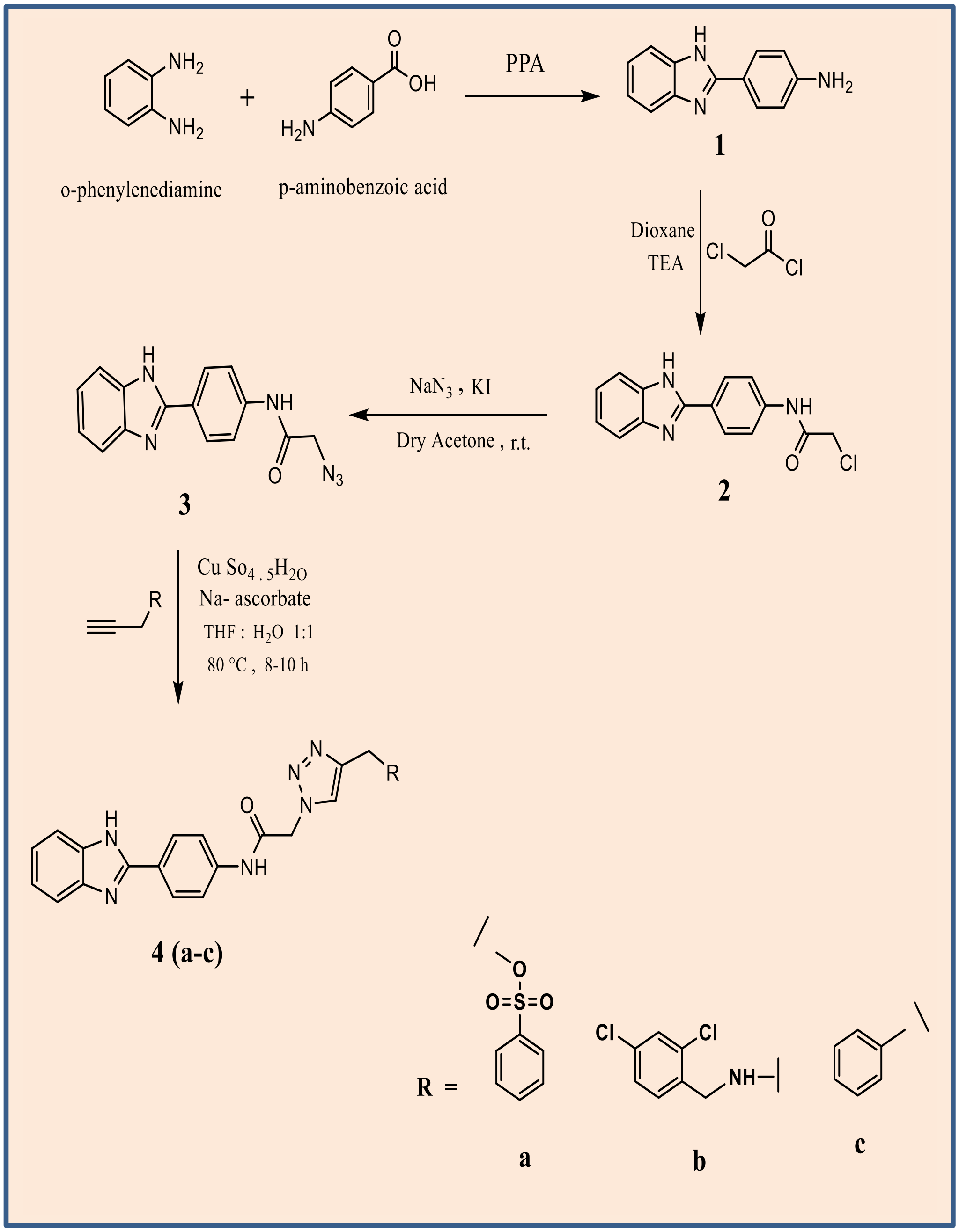

TSAO (anti-HIV agent)
Cefatrizine (antibiotic)
Tazobactum (anti-bacterial agent)
CAI (anti-cancer agent)

**Figure (1) Some medications on the market today include the 1,2,3-triazole ring.**

## Materials and general Methods

Commercial sources provided the synthetic chemicals employed in the synthesis as well as the solvents needed in the purification, recrystallization, and analysis of generated products (BDH-England, Himedia-India, CDH-India, HyperChem-China and Sigma Aldrich-Germany). At Mustansiriyah University/College of Science/Department of Chemistry/Iraq, the melting points of the produced compounds were measured using a (digital Stuart scientific SMP30) and were uncorrected. At Mustansiriyah University, College of Science, Department of Chemistry in Iraq, the infrared spectrum (IR) was measured using a (SHIMADZU FT-IR 8400S spectrophotometer) in the range (4000 – 600 $cm^{-1}$). At Sharif University of Technology in Iran, the $^{1}H$ -NMR spectra were recorded using a 500MHz Bruker DMX-500 NMR spectrophotometer and DMSO- $d_6$ solution with TMS (tetramethylsilane) as an internal standard reference. At Tehran University, Varrian 3900 and 5793 Network, Mass Selective Detector was used to record mass spectra.

## Chemical synthesis:



**Scheme (1): synthesis of the intermediates and target products.**

## Synthesis of 4-(1H-benzo[d]imidazol-2-yl) aniline (1):

Equimolar amounts of o-phenylenediamine (1.08 g, 10 mmol) and 4-aminobenzoic acid (1.37 g, 10 mmol) were mixed with the appropriate amount of polyphosphoric acid to create a stirrable paste. The mixture was gradually heated to 160°C, agitated at that temperature for four hours, then allowed to cool to room temperature before being poured into in a thin stream into a sizable volume of rapidly stirring water. Then neutralized with a 40% NaOH solution. After being filtered, collected, and dried, the precipitated substance was recrystallized from ethanol.(25)(26)(Light brown powder), 82.9 %, mp.235–236°C, FTIR v ($cm^{-1}$ ), 3330 (of N-H secondary amine), 3280, 3205 N-H asymmetric and symmetric primary amine, 3043 C-H aromatic ring, 1616 C=N of imidazole ring , $^{1}H$ -NMR(DMSO-$d_6$,500MHz)(ppm), 3.56( 2H, Singlet, $NH_2$) , 7.20 -7.24 (2H,Doublet,CH of the benzene ring, 7.26 – 7.70 (4H, Multiplet, benzimidazole ring ), 7.72 – 7.76 (2H,Doublet, CH of the benzene ring, 12.47 (1H, Singlet, NH proton). Mass, molecular ion (m/z , 209.00 ) calculated Mwt (209.25 g/mol ).

## Synthesis of N-(4-(1H-benzo[d]imidazol-2-yl) phenyl)-2-chloroacetamide (2):

Triethylamine (0.5 mL) and compound (**1**) (2.09 g, 10 mmol) were dissolved in dioxane (30 mL) and agitated for 15 minutes. Chloroacetyl chloride (0.79 mL,10 mmol ) was then gradually added, and the mixture stirred for two hours. After the reaction was finished, the mixture was poured onto crushed ice. The resulting solid was filtered out, wash with water, and recrystallized from ethanol to produce the pure compound.(26) (Light green powder), 79 %, mp. 284-286 °C, FTIR v ($cm^{-1}$ ), 3267 ( N-H secondary amide), 3174 ( N-H secondary amine), 3078 (C-H aromatic ring), 2929, 2854 (of C-H alkane (Asymmetric and Symmetric), 1668 (C=O,amide), $^1$H -NMR(DMSO- $d_6$,500MHz)(ppm), 4.19 (2H,singlet , CH2 of amide ) , 7.46 – 7.78( 8H, Multiplet, for aromatic ring protons), 9.66 (1H , Singlet, for NH amide) , 12.66 (1H , Singlet, for NH benzimidazole), molecular ion (m/z , 285.00 ) calculated Mwt (285.73 g/mol ).

## Synthesis of N-(4-(1H-benzo[d] imidazole -2-yl) phenyl)-2-azidoacetamide (3):

Compound (**2**) 2.8 g in 15 ml of dry acetone, and potassium iodide (1.6 g, 10 mmol) were agitated for two hours. Then sodium azide solution (0.6 g, 10 mmol in 10 ml of water) added and the mixture was agitated for an additional one hour. The mixture was continuously agitated while it was poured onto crushed ice when the reaction was complete. The produced solid was collected by filtration and then recrystallized from ethanol to produce the pure component.(27) Light pink powder, 83.4 %, mp. 305 -307 °C , FTIR v ($cm^{-1}$ ), 3240 ( N-H secondary amide) , 3207(N-H secondary amine), 3064 (of C-H aromatic ring), 2953, 2879 (C-H alkane (Asymmetric and Symmetric), 2207 ( N=N=N-, azide group), 1661( C=O, carbonyl amide) ,1637(C=N), $^1$H -NMR(DMSO- $d_6$,500MHz)(ppm), 4.22 (2H, Singlet, for CH2 of amide) , 6.72 – 6.75( 2H, Doublet, aromatic ring protons near NH group) , 7.22 – 7.25 ( 2H, Doublet, aromatic ring protons far NH group), 7.52 – 7.75 (4H, Multiplet, benzimidazole ring, 9.82 (1H, Singlet, for NH amide) , 12.52 ( 1H , singlet, benzimidazole ring ) , molecular ion (m/z , 292.00 ) calculated Mwt ( 292.30 g/mol).

## General procedure for the synthesis 1,2,3-triazole derivatives (4a - c):

Copper sulfate pentahydrate (0.10 g), sodium ascorbate (0.15 g), and azide compound (1 mmol) were added with stirring to a solution of terminal alkyne (1 mmol) in a 1:1 mixture of tetrahydrofuran (THF) and water (20 mL). For eight to ten hours, the resultant mixture was stirred at 80 °C. With water, the reaction mixture had been quenched. The solid that had been produced as a result of this process was then filtered, cleaned with a saturated sodium chloride solution, and dried. Recrystallizing target compound from ethanol to give pure 1,2,3-triazoles derivatives. (28)

## Compound 4a: (1-(2-((4-(1H-benzo[d]imidazol-2-yl) phenyl) amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl benzenesulfonate.

Greenish white, 85.7 %, mp. 255-256°C, FTIR v ($cm^{-1}$ ), 3300 ( N-H secondary amide), 3113( N-H secondary amine), 3041( C-H aromatic ring ), 2962, 2812 (C-H alkane (Asymmetric and Symmetric),1665 ( C=O , of carbonyl amide ), 1602, 1585, 1525 ( C=C aromatic ring ), 1365, 1170 ( $SO_2$ sulfonyl group ), $^1$H-NMR(DMSO- $d_6$,500MHz)(ppm), 4.21 (2H, Singlet, $CH_2$ of amide ) , 4.66 ( 2H, Singlet, for CH2 between the carbonyl and the triazole ring) , 7.20 – 7.42 (4H , of benzimidazole ring ), 7.44 (Singlet, for CH proton of triazole ring) , 7.65 – 8.15 ( 5H, of phenyl ring) , 8.15 - 8.18 (2H, Doublet, for aromatic ring protons near NH) , 8.19 – 8.22 (2H, Doublet, for aromatic ring protons far NH) , 9.89 (1H, singlet for NH amide ), 12.41 (1H, singlet for NH of benzimidazole ), molecular ion (m/z , 488.00 ) calculated Mwt ( 488.52 g/mol).

## Compound 4b: N-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-2-(4-(((2,4-dichlorobenzyl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamide.

Off white powder, 82 %, mp. 233-235°C, FTIR v ($cm^{-1}$ ), 3186 ( N-H secondary amide), 3156 ( N-H secondary amine cyclic), 3106 (N-H secondary amine Acyclic, 3061 ( C-H aromatic ring ), 2931, 2831 ( C-H alkane (Asymmetric and Symmetric) , 1665 ( C=O , of carbonyl amide ), 1610, 1595, 1510 ( C=C aromatic ring ) , 1575 (N=N triazole ring), $^1$H -NMR(DMSO- $d_6$,500MHz)(ppm), 3.56 (2H, Singlet, $CH_2$ near phenyl ) , 3.78 ( 2H, Singlet, for CH2 between the amine and the triazole ring) , 4.20 (1H, singlet for NH of amine), 4.81( 2H, Singlet, for CH2 between carbonyl and the triazole ring) (7.40 – 7.52 (4H , of benzimidazole ring ), 7.56 (Singlet, for CH proton of triazole ring) , 7.65 – 8.15 ( 5H, of phenyl ring) , 7.58 – 7.97 (2H, Doublet, for aromatic ring protons near NH) , 7.98 – 8.16 (2H, Doublet, for aromatic ring protons far NH), 8.17- 8.20 (3H, Multiplet, for dichlorophenyl) , 9.87 (1H, singlet for NH amide ), 12.47 (1H, singlet for NH of benzimidazole ), molecular ion (m/z , 506.00 ) calculated Mwt (506.39 g/mol).

## Compound 4c: 1-[4-(1H-benzimidazol-2-yl) phenyl]-3-(4-benzyl-1H-1,2,3-triazol-1-yl)propan-2-one

Brown powder, 81 %, mp. 228-230°C, FTIR v ($cm^{-1}$ ), 3290 ( N-H secondary amide), 3137 ( N-H secondary amine), 3070 ( C-H aromatic ring ), 2958, 2854 (C-H alkane (Asymmetric and Symmetric) , 1665 ( C=O , of carbonyl amide ), 1590, 1510 ( C=C aromatic ring ) 1570 of N=N triazole ring), $^1$H-NMR(DMSO- $d_6$,500MHz)(ppm), 2.02 (2H, Singlet, for $CH_2$ between phenyl and triazole ) , 4.22 (2H, Singlet, $CH_2$ of amide ) ,7.20 – 7.42 ( 5H, of phenyl group), 7.60 – 7.69 (4H , of benzimidazole ring ), 7.44 (Singlet, for CH proton of triazole ring) , =7.71 – 8.15 (2H, Doublet, for aromatic ring protons near NH) , 8.17 – 8.18 (2H, Doublet, for aromatic ring protons far NH) , 9.85 (1H, singlet for NH amide ), 12.44 (1H, singlet for NH of benzimidazole),molecular ion (m/z , 408.00 ) calculated Mwt ( 408.47 g/mol).

## Molecular docking studies:

Due to the expense and effort needed to create novel compounds with appropriate pharmacological characteristics, drug discovery and development has become a significant problem in recent years. Due to the toxicity and lack of action of many medications during phase II and phase III of clinical trials, this expense has partially increased.(29)(30) The use of computational tools is fast gaining popularity and playing an increasingly important role in the discovery and development of medications since they save researchers' time, money, and effort. One of these methods for predicting the conformation and orientation of the ligand within the binding site of the target is the docking procedure. Generalized accurate structural modeling and precise knowledge of chemical action are the primary objectives of docking investigations.(31) The molecular docking was examined by utilizing GlideTM, (version 5.7, Schrödinger, LLC, New York, NY, 2011). The most active compounds were docked on the active sites of Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, and Streptococcus pyogenes bacteria that originate from the crystal structure form of the enzymes in complex with anti-bacterial drug, Trimethoprim, whose PDB ID were 1NNI, 3G7E, 4HL2, 2W9S, and 4RKX. The molecules of hetero atoms and water were eliminated from enzymes behind 5Å radius of reference ligand (Trimethoprim).The Protein Preparation Wizard™ application employed the OPLS-2005 force field to minimize protein structure, and the Receptor Grid Generation program was used to create the grid of Bacillus subtilis, Staphylococcus aureus, Streptococcus pyogenes, Klebsiella pneumoniae and Escherichia coli. Then, using the OPLS-2005 force field, the Ligand Preparation™ program optimized each ligand to produce the lowest energy state. The best pose (with the highest score) for each molecule was displayed after docking simulations produced 5 poses for each ligand.

## Procedures of ADME

The full set of compounds (**4a-c**) was drawn using Chem Create Sketch (v. 19), and then the Swiss ADME tool software transformed these ligands into the name SMILE in order to predict their physical, chemical, and pharmacokinetic properties. Using BOILED EGG, we could determine the polarity and lipophilicity of the small molecules.(32)

## Results and Discussion

## Interpretation of ADME results:

Swiss ADME examined the desired compounds' ADME properties (4a-c).The ADME (adsorption, distribution, metabolism, and excretion) method of drug analysis was assessed. Also the topological polar surface area (TPSA), another critical factor that has been linked to the bioavailability of medication was calculated. It is thought that drugs with a TPSA > 140 are passively absorbed and have a low oral bioavailability.(33) According to the ADME prediction data, all of the ligands were within the acceptable value range, had TPSAs < 140 Å except compound **4a** that had TPSA equal to 140.24 Å and had a bioavailability of 0.55 for all compounds that were tested, indicating that they enter systemic circulation. The ligands also adhere to Lipinski's Rule of Five (RO5) and the topological descriptors and fingerprints of the LogP and LogS molecular drug-likeness structure keys (table 1). As expected given their high intestine absorption, all drugs also demonstrated great absorption rates.

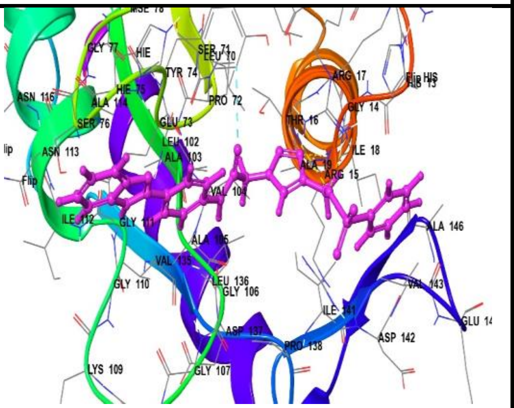
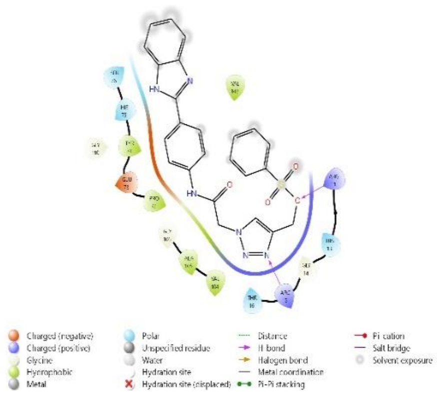
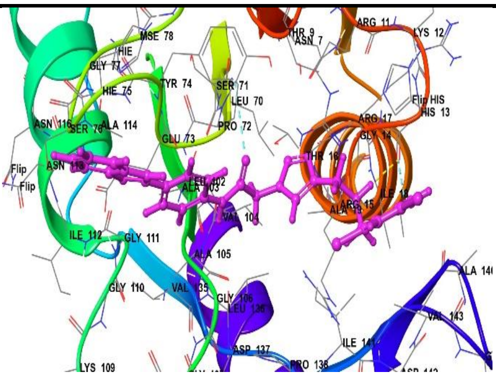
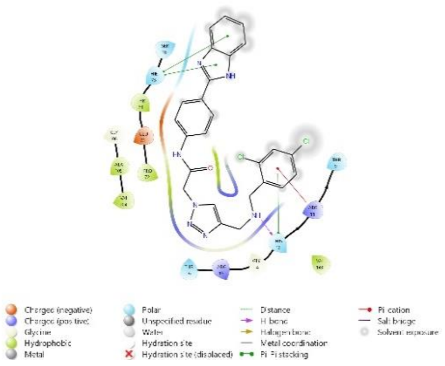
**Table (1) ADME result of the final derivatives.**

| Comp | Formula | MWT | H-bond acceptor | H-bond donor | MR | TPSA | GI Abs | BBB permeant | Bioavailability | Lipiniski violation |
|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | $SC_{24}H_{20}N_6O_4$ | 488.52 g/mol | 7 | 2 | 128.87 | 140.24 | low | No | 0.55 | 0 violation |
| **4b** | $C_{25}H_{21}CL_2N_7O$ | 506.39 g/mol | 5 | 3 | 137.29 | 100.52 | High | No | 0.55 | 0 violation |
| **4c** | $C_{24}H_{20}N_6O$ | 408.46 g/mol | 4 | 2 | 119.66 | 88.49 | High | No | 0.55 | 0 violation |

## Docking results interpretation:

Computer programs select compounds in virtual screening (VS) according to their ability to bind to the target receptor.(34)The resulting compounds were docked on the active site of each receptor of gram positive bacteria (Bacillus subtilis, Staphylococcus aureus and Streptococcus pyougenes) and gram negative bacteria (Klebsiella pneumoniae and Escherichia coli). In virtual screening (VS), their affinity for binding and orientation with amino acid residues were investigated. Virtual screening findings showed that all compounds had binding affinity scores between (-3.172 and -1.728) kcal/mol on Bacillus subtilis, (-5.14 and -3.493) kcal/mol on Escherichia coli, (-6.558 and -4.987) kcal/mol on Klebsiella pneumoniae, (-7.41 and -5.795) kcal/mol on Staphylococcus aureus, (-6.082 and -3.49) kcal/mol on Streptococcus pyougenes. The docking scores, orientations, and interactions between synthetic chemicals and the amino acid residues of the fife species of bacteria are shown in tables (2-1) to (2-5). H-bonds, Pi-Pi stacking, pi-cation interactions, and hydrophobic interactions are the key interactions visible in these tables; these interactions promote and give the compounds high effectiveness against bacteria. The highest binding affinity was (-3.172) kcal/mol for compound (**4c**) on Bacillus subtilis and the type of interaction between them include (H-bond interaction between GLY 106 and carbonyl group, H-bond interaction between GLU 73 and NH amide group, pi-cation interaction between both ARG 11 and ARG 15 with indole ring in addition to hydrophobic interaction), while the highest binding affinity was (-5.14) kcal/mol for compound (**4c**) on Escherichia coli and the type of interaction between them include (H-bond interaction between GLU 50 and NH amide group, H-bond interaction between both ASP 73 and ARG 76 with nitrogen of triazole ring via water molecule ($H_2O$) in addition to hydrophobic interaction). Also it is observed that (-6.558) kcal/mol is the highest binding affinity for compound (**4a**) on Klebsiella pneumonia and the type of interaction between them include Pi-Pi stacking interaction between HIS 250 and HIE 122 with benzene ring and triazole ring respectively, H-bond interaction between GLN 123 and oxygen molecule beside $SO_2$ in addition to hydrophobic interaction).On the other hand the score (-7.41) kcal/mol represents the highest binding affinity for compound (**4b**) on Staphylococcus aureus and the type of interaction between them include (H-bond interaction between SER 49 and NH amide group in addition to hydrophobic interaction), and (-6.082) kcal/mol was the highest binding affinity for compound (**4a**) on Streptococcus pyougenes in which the type of interaction include (H-bond interaction between GLN 304 and carbonyl of amide group , H-bond interaction between GLN 390 and NH of indole ring in addition to hydrophobic interaction).

**Table (2-1): Compounds with docking score that are surrounded by amino acids inside the active site of Bacillus subtilis (PDB ID: 1NNI).**

| **Comp.** | **A compound as ball and stick, receptor as ribbon.** | **Ligand interaction view of the compound.** | **Docking Score in kcal/Mol** |
|---|---|---|---|
| **4a** |  |  | **-1.728** |
| **4b** |  |  | **-2.919** |

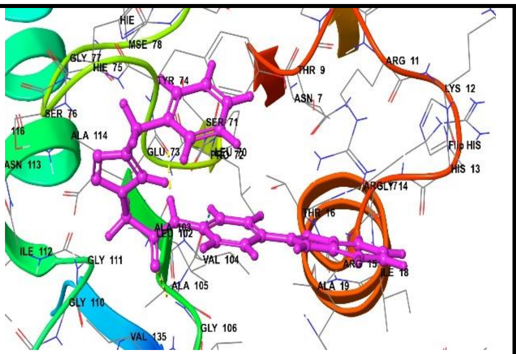
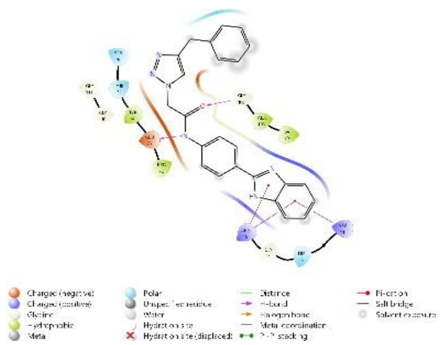
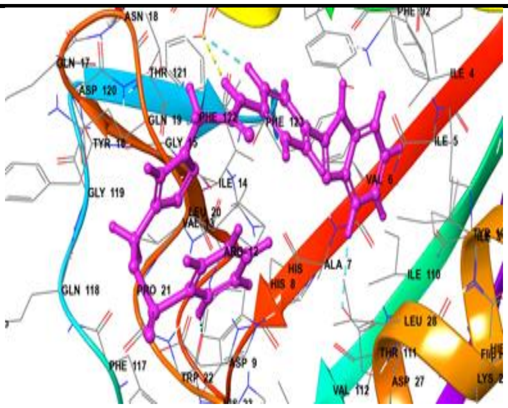
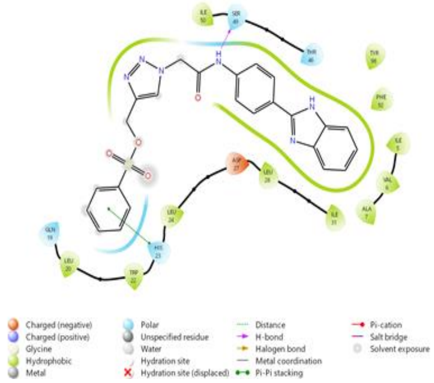
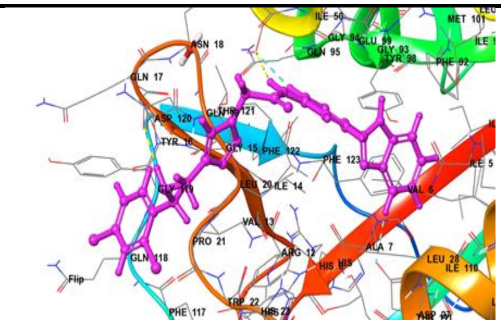
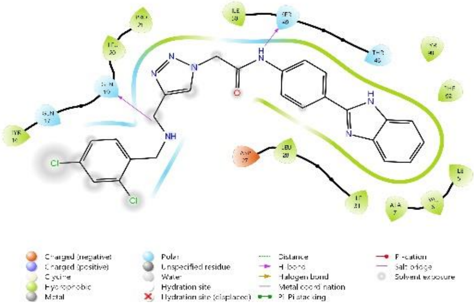
| | | | |
|---|---|---|---|
| **4c** |  |  | **-3.172** |

**Table (2-2): Compounds with docking score that are surrounded by amino acids inside the active site of Staphylococcus aureus (PDB ID: 2W9S).**

| **Comp.** | **A compound as ball and stick, receptor as ribbon.** | **Ligand interaction view of the compound.** | **Docking Score in kcal/Mol** |
|---|---|---|---|
| **4a** |  |  | **-6.046** |
| **4b** |  |  | **-7.41** |

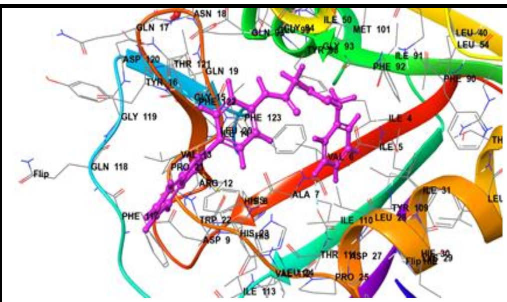
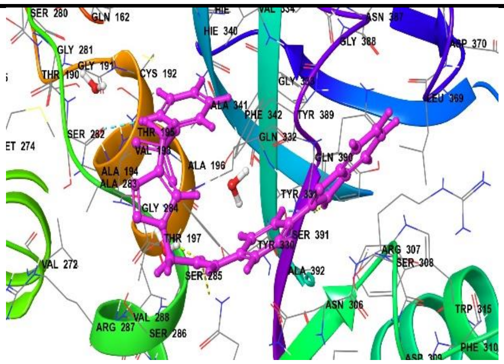
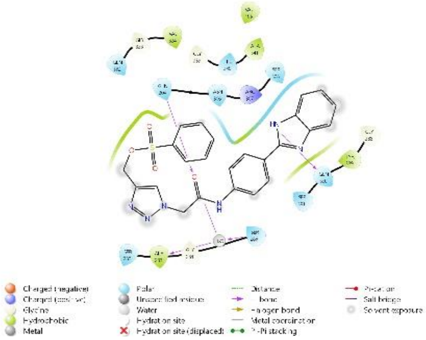
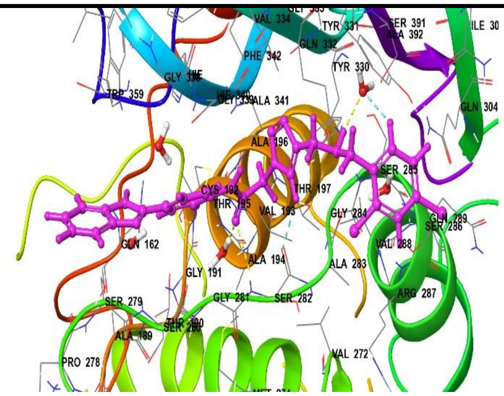
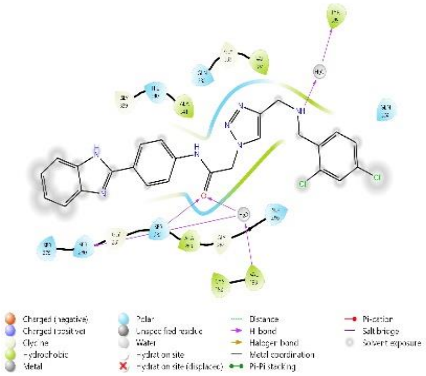
| | | | |
|---|---|---|---|
| **4c** |  |  | **-5.795** |

**Table (2-3): Compounds with docking score that are surrounded by amino acids inside the active site of Streptococcus pyougenes (PDB ID: 4RKX).**

| **Comp.** | **A compound as ball and stick, receptor as ribbon.** | **Ligand interaction view of the compound.** | **Docking Score in kcal/Mol** |
|---|---|---|---|
| **4a** |  |  | **-6.082** |
| **4b** |  |  | **-4.84** |

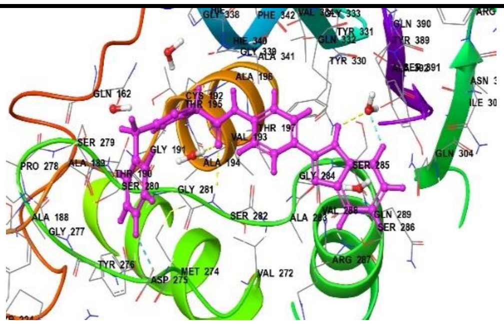
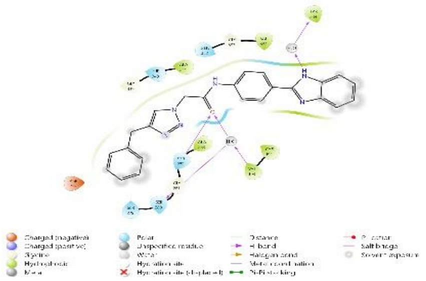
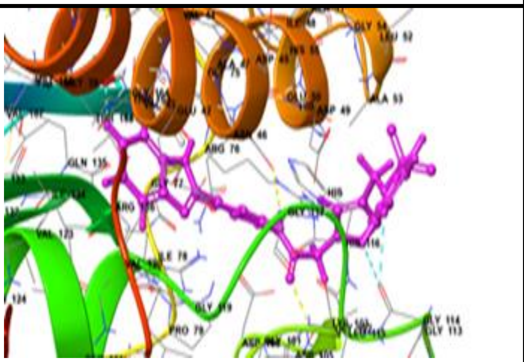
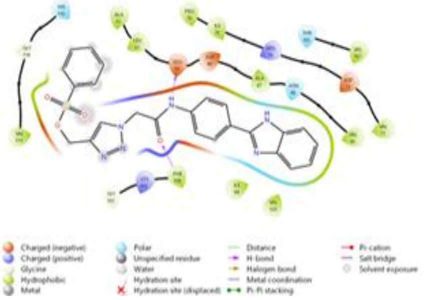
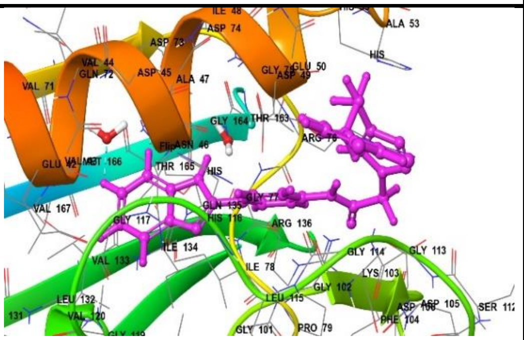
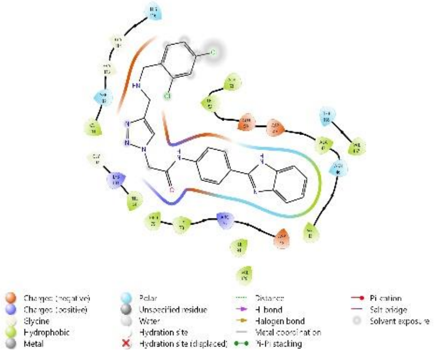
|  |  |  |  |
|---|---|---|---|
| **4c** |  |  | **-3.49** |

**Table (2-4): Compounds with docking score that are surrounded by amino acids inside the active site of Escherichia coli (PDB ID: 3G7E).**

| **Comp.** | **A compound as ball and stick, receptor as ribbon.** | **Ligand interaction view of the compound.** | **Docking Score in kcal/Mol** |
|---|---|---|---|
| **4a** |  |  | **-5.119** |
| **4b** |  |  | **-3.493** |

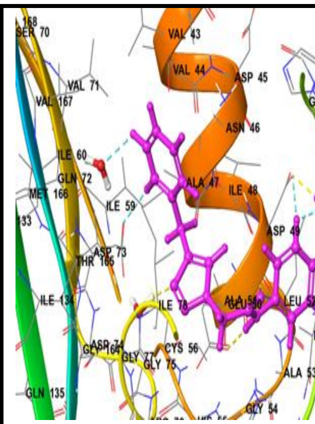
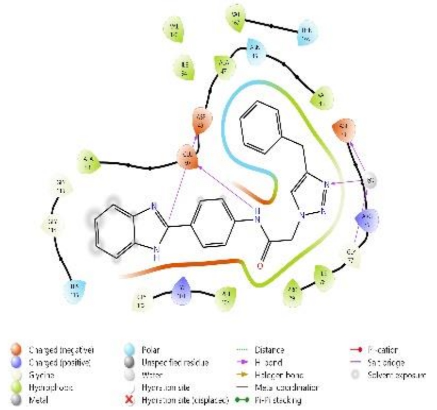
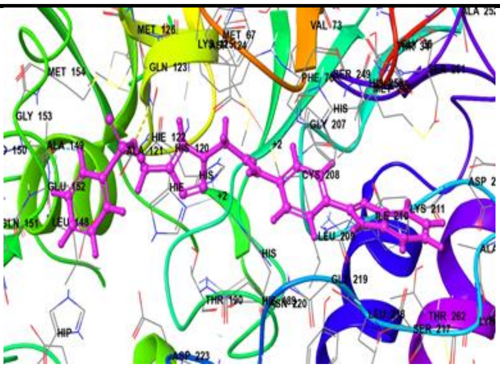
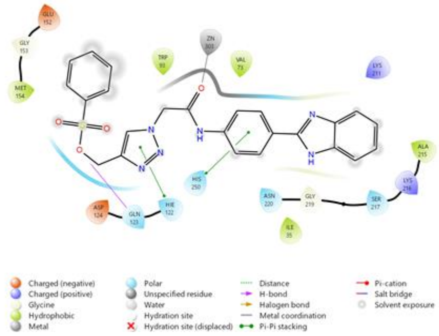
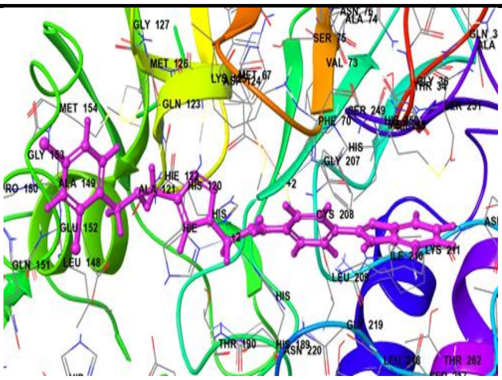
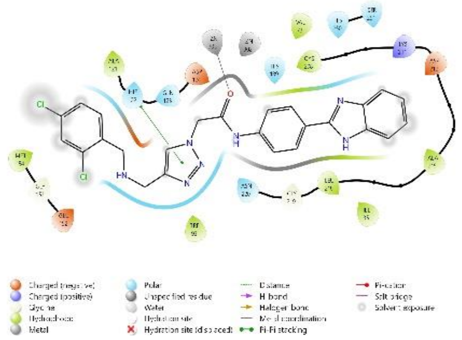
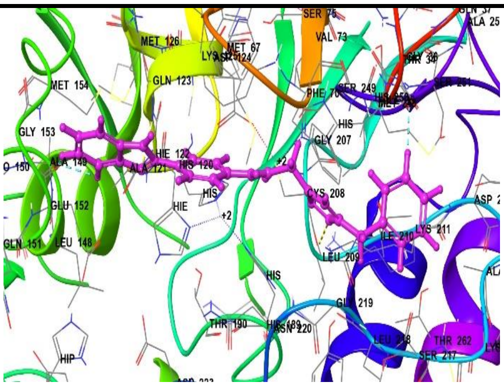
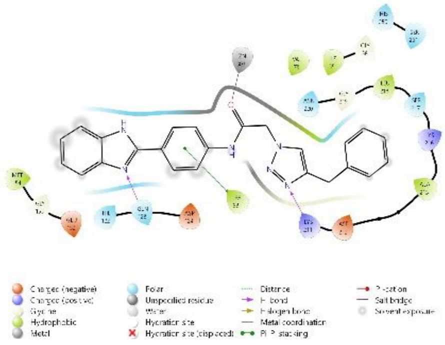
| | | | |
|---|---|---|---|
| **4c** |  |  | **-5.14** |

**Table (2-5): Compounds with docking score that are surrounded by amino acids inside the active site of Klebsiella pneumoniae (PDB ID: 2HL2).**

| **Comp.** | **A compound as ball and stick, receptor as ribbon.** | **Ligand interaction view of the compound.** | **Docking Score in kcal/Mol** |
|---|---|---|---|
| **4a** |  |  | **-6.558** |
| **4b** |  |  | **-4.987** |

|  |  |  |  |
|---|---|---|---|
| **4c** |  |  | **-5.864** |

## Conclusion:

A common technique for doing experiments on a computer before using the study in a lab is molecular modeling. This method enables computation of molecular characteristics as well as computer-aided generation of molecular structures. By using this method, we were able to identify the 1,2,3-triazole active compounds that exhibited greater potency and increased bacterial enzyme binding affinity. Furthermore the ADME tests showed that the newly created chemical (**4b** and **4c**), which was absorbed from the GIT, complied with the Lipinski criterion.The proposed triazole derivatives were successfully synthesized, and its structural formula was examined using melting point, IR spectroscopy, $^{1}$H –NMR and Mass spectroscopy. To understand the negative effects and toxicity of every newly created chemicals, biological and pharmacological screening is crucial.

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## References:

1. Morse SS. Factors in the emergence of infectious diseases. Plagues Polit. 2001;8–26.
2. Jwaid MM, Ali KF, Abd-alwahab MH. Synthesis, Antibacterial study and ADME Evaluation of Novel Isonicotinoyl Hydrazide Derivative Containing 1, 3, 4-Oxadiazole Moiety. Al Mustansiriyah J Pharm Sci. 2020;20(4):113–21.
3. Mölstad S, Löfmark S, Carlin K, Erntell M, Aspevall O, Blad L, et al. Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. Bull World Health Organ. 2017;95(11):764.
4. Carvalho IT, Santos L. Antibiotics in the aquatic environments: a review of the European scenario. Environ Int. 2016;94:736–57.
5. Ismaeel SS, Mahdi MF, Abd Razik BM. Design, synthesis and antibacterial study of new agents having 4-thiazolidinone pharmacophore. Egypt J Chem. 2020;63(7):2591–603.
6. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev. 2010;74(3):417–33.
7. Ashok D, Reddy MR, Dharavath R, Ramakrishna K, Nagaraju N, Sarasija M. Microwave-assisted synthesis of some new 1, 2, 3-triazole derivatives and their antimicrobial activity. J Chem Sci. 2020;132(1):1–9.
8. Rajender O, Narsimha S, Reddy VN. Design, synthesis and in vitro anticancer evaluation of new 2H-benzo [b][1, 4] thiazin-3 (4H)-one based 1, 2, 3-triazoles. Asian J Chem. 2019;31(11):2647–52.
9. He Y-W, Dong C-Z, Zhao J-Y, Ma L-L, Li Y-H, Aisa HA. 1, 2, 3-Triazole-containing derivatives of

rupestonic acid: click-chemical synthesis and antiviral activities against influenza viruses. Eur J Med Chem. 2014;76:245–55.

10. Kaushik CP, Luxmi R, Kumar A, Kumar K, Pahwa A. Antibacterial evaluation and QSAR studies of 1, 2, 3-triazole bridged with amide functionalities. 2019;
11. Satheeshkumar C, Ravivarma M, Arjun P, Silambarasan V, Raaman N, Velmurugan D, et al. Synthesis, anti-microbial activity and molecular docking studies on triazolylcoumarin derivatives. J Chem Sci. 2015;127(3):565–74.
12. Angajala KK, Vianala S, Macha R, Raghavender M, Thupurani MK, Pathi PJ. Synthesis, anti-inflammatory, bactericidal activities and docking studies of novel 1, 2, 3-triazoles derived from ibuprofen using click chemistry. Springerplus. 2016;5(1):1–15.
13. Mady MF, Awad GEA, Jørgensen KB. Ultrasound-assisted synthesis of novel 1, 2, 3-triazoles coupled diaryl sulfone moieties by the CuAAC reaction, and biological evaluation of them as antioxidant and antimicrobial agents. Eur J Med Chem. 2014;84:433–43.
14. Chinthala Y, Thakur S, Tirunagari S, Chinde S, Domatti AK, Arigari NK, et al. Synthesis, docking and ADMET studies of novel chalcone triazoles for anti-cancer and anti-diabetic activity. Eur J Med Chem. 2015;93:564–73.
15. Al-Smaisim RF, Sharba AHK, Al-Bayati RI. Synthesis of 1, 2, 3-Triazole Compounds Derived from 4-Amino Benzoic Acid. Al-Mustansiriyah J Sci. 2010;21(5).
16. Sheng C, Zhang W. New lead structures in antifungal drug discovery. Curr Med Chem. 2011;18(5):733–66.
17. Neu HC, Fu KP. Cefatrizine activity compared with that of other cephalosporins. Antimicrob Agents Chemother. 1979;15(2):209–12.
18. Soltis MJ, Yeh HJ, Cole KA, Whittaker N, Wersto RP, Kohn EC. Identification and characterization of human metabolites of CAI [5-amino-1-1 (4’-chlorobenzoyl-3, 5-dichlorobenzyl)-1, 2, 3-triazole-4-carboxamide. Drug Metab Dispos. 1996;24(7):799–806.
19. Higashitani F, Hyodo A, Ishida N, Inoue M, Mitsuhashi S. Inhibition of β-lactamases by tazobactam and in-vitro antibacterial activity of tazobactam combined with piperacillin. J Antimicrob Chemother. 1990;25(4):567–74.
20. Evans WJ, Montalvo E, Champagne TM, Ziller JW, DiPasquale AG, Rheingold AL. Organolanthanide-based synthesis of 1, 2, 3-triazoles from nitriles and diazo compounds. J Am Chem Soc. 2008;130(1):16–7.
21. Amantini D, Fringuelli F, Piermatti O, Pizzo F, Zunino E, Vaccaro L. Synthesis of 4-aryl-1 H-1, 2, 3-triazoles through TBAF-catalyzed [3+ 2] cycloaddition of 2-aryl-1-nitroethenes with TMSN3 under solvent-free conditions. J Org Chem. 2005;70(16):6526–9.
22. Sharba AHK. Synthesis Of New 1, 2, 3-Triazole And 1, 2, 3-Triazoline Derived From Unsaturated D-Fructose Via 1, 3-Dipolarcyclo addition Reaction. Al-Mustansiriyah J Sci. 2011;22(2).
23. Appukkuttan P, Dehaen W, Fokin V V, Van der Eycken E. A microwave-assisted click chemistry synthesis of 1, 4-disubstituted 1, 2, 3-triazoles via a copper (I)-catalyzed three-component reaction. Org Lett. 2004;6(23):4223–5.
24. Rostovtsev V V, Green LG, Fokin V V, Sharpless KB. A stepwise huisgen cycloaddition process: copper (I)-catalyzed regioselective “ligation” of azides and terminal alkynes. Angew Chemie. 2002;114(14):2708–11.
25. Harkala KJ, Eppakayala L, Maringanti TC. Synthesis and biological evaluation of benzimidazole-linked 1, 2, 3-triazole congeners as agents. Org Med Chem Lett. 2014;4(1):1–4.
26. Khattab M, Galal SA, Ragab FAF, El Diwani HI. Different synthetic routes to 4-(1H-benzo [d] imidazol-2-yl) aniline. Res Chem Intermed. 2013;39(7):2917–23.
27. Kuntala N, Telu JR, Banothu V, Nallapati SB, Anireddy JS, Pal S. Novel benzoxepine-1, 2, 3-triazole hybrids: synthesis and pharmacological evaluation as potential antibacterial and anticancer agents. Medchemcomm. 2015;6(9):1612–9.
28. Al-Blewi FF, Almehmadi MA, Aouad MR, Bardaweel SK, Sahu PK, Messali M, et al. Design, synthesis, ADME prediction and pharmacological evaluation of novel benzimidazole-1, 2, 3-triazole-sulfonamide hybrids as antimicrobial and antiproliferative agents. Chem Cent J. 2018;12(1):1–14.

29. Omran SM, Abd Razik BM, Mahdi MF. Density Functional Theory and Molecular Modeling Studies of New 4-(Furan-2-yl) Thiazol-2-Amine Derivatives as Cyclooxygenase Inhibitors. Egypt J Chem. 2021;64(9):4833–41.
30. Cobanoglu MC, Liu C, Hu F, Oltvai ZN, Bahar I. Predicting drug–target interactions using probabilistic matrix factorization. J Chem Inf Model. 2013;53(12):3399–409.
31. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov. 2004;3(11):935–49.
32. Daina A, Zoete V. A boiled-egg to predict gastrointestinal absorption and brain penetration of small molecules. ChemMedChem. 2016;11(11):1117–21.
33. Palm K, Stenberg P, Luthman K, Artursson P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. Pharm Res. 1997;14(5):568–71.
34. Klebe G. Virtual ligand screening: strategies, perspectives and limitations. Drug Discov Today. 2006;11(13–14):580–94.