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Development and Evaluation of Novel Carbazole Derivatives as Antibacterial Agents: Synthetic Approach and Molecular Docking Studies

Mustafa Kadhum Naeem[1], I. Alrubaie[2], Muhand Dohan Abid[1], Ali Jabbar Radhi[*3]
[1]Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences, Faculty of Medical Science, Najaf, Iraq.
[2]Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences, Faculty of Pharmacy, Najaf, Iraq.
[3]University of Alkafeel, Faculty of Pharmacy, Najaf, Iraq.
[*3]Corresponding author: Email address: alijebar56@gmail.com

Abstract**—***This study focuses on the design, synthesis, and evaluation of novel 1,2,3-triazolylmethyl carbazoles as potential antibacterial agents. The synthesized compounds (2a–2f) were structurally characterized using various spectroscopic techniques, including ¹H NMR, ¹³C NMR, and IR spectroscopy. Their antibacterial activities were assessed against both Gram-positive and Gram-negative bacterial strains using the well diffusion method. Among the tested derivatives, compounds 2b, 2d, 2e, and 2f exhibited the highest antibacterial potency due to the incorporation of electron-withdrawing groups. Molecular docking studies against Staphylococcus aureus DNA Gyrase B enzyme (PDB ID: 2XCT) demonstrated strong binding interactions, particularly for compound 2c, which showed the best binding affinity and stability. These findings suggest that 1,2,3-triazolylmethyl carbazoles hold promise as potential antibacterial agents, warranting further in-depth biological investigations.*

Keywords**—** *Antibacterial, Carbazole, Substituted Pyridine, Click Chemistry, 1,5-tetrazoles.*

I. INTRODUCTION

The simplest member of the group of compounds known as Tetrazoles is a derivative known as tetrazole (CH_2N_4) defined as five-membered heterocyclic organic compounds containing four nitrogen and one carbon atom. There are two tautomeric forms of tetrazole, which include 1H-tetrazole and 2H-tetrazole[1–4]. The only difference between the two is the location of a hydrogen atom bound to the nitrogen atom. Despite being deficient in carbon compounds, tetrazoles have a conjugated electron system which enhances the stability of the molecule and simultaneously facilitates tetrazoles to function as electron rich molecules. They can interact with receptors forming receptor-ligand combinations, which is crucial for biological activity. The internal negative charge of the molecules is primarily attributed to carbon. The carbon negatively charged molecules are stabilized through-electronic delocalization within the molecule[5,6]. Compared to carboxylates, the lipophilicity of tetrazole anions is greater, which means using tetrazole results in enhanced membrane permeability.

The tetrazole compound is more stable metabolically, rendering them more resistant to enzymatic degradation, making them stand out[7–12]. Although pharmacological effectiveness of tetrazole could be lower, the degree of stability offered by the compound augments the pharmacological action time. In the field of medicinal chemistry centrazole along with its derivatizes have been the center of attention due to their effective biological activity proprieties. They possess powerful antihypertensive, analgesic, anti-allergic, and anti-ulcer activities[13–15]. Apart from their medical use, tetrazole based heterocycles have a high synthetic importance by serving as precursors for all kinds of bioactive compounds, various pharmaceuticals, explosives, propellants, and even as alkylating agents[16–21]. It is important that tetrazoles were the first heterogeneous compounds that were discovered to be ligands in the treatment of dopamine D_2 receptors. Furthermore, tetrazole derivatives are very strong antimicrobials and anticancer drugs. Research by Jackman et al confirmed the strong cytotoxic and growth inhibition effects of tetrazole attached compounds, which gives them a better chance in the treatment and development of new drugs[22–25]. The antibacterial activities of several tetrazole derivatives have been the subject of considerable research as they have been found to be effective against a wide range of bacterial pathogens. Antimicrobial activity is enhanced due to the ability to form non-covalent interactions with bacterial enzymes and membranes. Many of the tetrazole-containing compounds exhibited marked inhibition against Gram-positive and Gram-negative bacteria, including some drug-resistant strains[26–30]. With regards to pharmacology, the introduction of the tetrazole moiety is significant because it increases oral bioavailability, improves pharmacokinetics, and increases potency over existing antibiotics. These considerations account for the approval of ceforanide, a second-generation cephalosporin antibiotic with a tetrazole ring. This distinctly emphasizes the possibility of using tetrazole based compounds in treating bacterial infections.

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Given the increasing concern of bacterial resistance to therapies, tetrazole derivatives are an exciting area for research and development of newer antibacterial drugs[15,16,22,23,25,30].

II. EXPERIMENTAL SECTION

Fischer-Johns melting point apparatus was used to determine the uncorrected melting points. A JASCO P2000 polarimeter was used to record optical rotations at 25 °C. The observed absorptions are in cm-1, and the 1H NMR spectra bands of the compounds were acquired as pure liquids or KBr pellets. All generated compounds were recorded at 300 MHz and 75 MHz for 13CNMR in the appropriate solvents, using TMS as an internal standard. The chemical changes were shown using the d scale. The designations for NMR signal multipliers are S (single), d (doublet), t (triplet), and q (quarter). For unresolved lines, the designation is m (multiplet). Analytical thin-layer chromatography (TLC) on GF254 silica gel plates that had been previously coated was used to track each experiment. After elution, the plate was exposed to UV light at 254 nm to check for UV active chemicals. Significantly improved visibility was made possible by PMA staining and charring on a hot plate. After being vacuum-extracted, the solvents were heated to 35 °C in a water bath. Column chromatography was performed using silica gel that was finer than 200 mesh. Before being used, the columns were equilibrated with the proper solvent or solvent mixture and packed as a silica gel slurry in hexane. Using the proper solvent system, the chemicals were loaded either plain or as a concentrated solution. An air pump was used to provide pressure, which helped with the elution. Unless otherwise noted, yields are associated with materials that are homogenous in terms of spectroscopy and chromatography. All of the novel compounds were given their proper names with the assistance of Chem Bio Office 12.0.

Synthesis of 9-(2-acetonitrile)-9H-carbazole (1a)

K_2CO_3 (0.02 mol) was mixed with a solution of carbazole (0.02 mol) in anhydrous DMF (5 mL) and refluxed for 30 minutes. While stirring, acetonitrile (0.035 mol) was added to the boiling liquid. For two more hours, the reaction mixture was refluxed. The solvent was removed using a rotary evaporator once the reaction was finished. Using petroleum ether as an eluent, the crude reaction mixture was purified via silica gel column chromatography to obtain compound 2 in a 75% yield as a white solid. m.p:106–108 C; 1H NMR (300 MHz, CDCl3): d 8.18-7.27 (m, Ar-H), 5.16(s, carbazaole-CH2-CN); 13CNMR (75 MHz, CDCl3139.63, 128.42, 123.81, 120.87, 120.80, 109.24, 114.25 (acetonitrile C2), 33.68 (carbazaole-CH2-CN).

Synthesis derivatives of tetrazolylmethyl carbazole (2a-2f)

In a solution of nitrile2 (0.8 mmol) and azido-pyridine derivatives (2a-2f) (0.8 mmole) DMF (4 mL), $CuSO4.5H_2O$ (115 mole%) and Na-ascorbate (15 mol%) were added. The mixture was stirred for nine to twelve hours at room temperature. The organic solvent layer was separated, cleaned with brine, dried with anhydrous sodium sulfate, and the final product was concentrated under reduced pressure once the reaction was complete (as shown by thin layer chromatography plates). The mixture of reactions was then diluted with ethyl acetate (15 mL) and water (5 mL). Using silica gel column chromatography, the crude residue was refined to get the appropriate 1,5-tetrazoles (2a-2f).

9-((1-(Pyridin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-9H-carbazole (2a) is a brown solid with a melting point of 190–192 °C. The infrared spectroscopy data (in cm^{-1}) shows absorption bands at 3.135 (aromatic C-H), 1.591 and 1.481 (alkene C=C), 1.451 and 1.321 (tetrazole ring C–N), 1.051 and 747 (carbazole ring C–N), and 724. The 1H NMR (300 MHz, CDCl3) spectrum reveals δ 8.31–8.22 (m, 2H, pyridine ring protons at position 2), 7.82–7.23 (m, 11H, aromatic protons), and 5.21 (s, 2H, N–CH2). The 13C NMR (75 MHz, CDCl3) spectrum displays signals at δ 150.07, 139.25, 138.73, 128.11, 122.50, 120.01, 116.90, 109.78 (9C, carbons of aromatic rings), 148.75 (C4 position on the tetrazole ring), and 37.39 (N–CH2).

9-((1-(2-Bromopyridin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-9H-carbazole (2b) is a red-colored solid with a melting point of 168–170 °C. The infrared spectroscopy data (in cm^{-1}) shows absorption bands at 3.110 (aromatic C-H), 1.605 and 1.515 (alkene C=C), 1.460 and 1.345 (tetrazole ring C–N), 1.090, 870, and 750 (carbazole ring C–N), and 680 (C–Br stretching). The 1H NMR (300 MHz, CDCl3) spectrum shows δ 8.42 (d, J = 5.6 Hz, 1H, pyridine ring protons at position 2), 8.03–7.27 (m, 11H, aromatic protons), and 5.26 (s, 2H, N–CH2). The 13C NMR (75 MHz, CDCl3) spectrum exhibits signals at δ 148.56, 147.77, 139.60, 139.25, and 144.10 (C4 position on the tetrazole ring) and 37.77 (N–CH2).

9-((1-(2-Nitropyridin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-9H-carbazole (2c) is a red-colored solid with a melting point of 159–161 °C. The infrared spectroscopy data (in cm^{-1}) shows absorption bands at 3.108 (aromatic C-H), 1.595 and 1.508 (alkene C=C), 1.455 and 1.335 (tetrazole ring C–N), 1.525 and 1.345 (NO_2 asymmetric and symmetric stretching), and 1.075, 865, and 745 (carbazole ring C–N). The 1H NMR (300 MHz, CDCl3) spectrum reveals δ 8.97 (d, J = 5.7 Hz, 1H, pyridine ring protons at position 2), 8.22–7.26 (m, 11H, aromatic protons), and 5.27 (s, 2H, N–CH2). The 13C NMR (75 MHz, CDCl3) spectrum displays signals at δ 158.41, 147.17, 139.25, 137.68, 127.84, 123.00, 122.83, 120.50, 120.14, 116.68, and 109.80 (11C, carbons of aromatic rings), 148.91 (C4 position on the tetrazole ring), and 37.79 (N–CH2).

9-((1-(2-Methoxypyridin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-9H-carbazole (2d) is a brown-colored solid with a melting point of 128–130 °C. The infrared spectroscopy data (in cm^{-1}) shows absorption bands at 3.107 (aromatic C-H), 2.838 (C-H stretching of $-OCH_3$), 1.588 and 1.498 (alkene C=C), 1.448 and 1.338 (tetrazole ring C–N), and 1.078, 858, and 738 (carbazole ring C–N). The 1H NMR (300 MHz, CDCl3) spectrum reveals δ 8.51 (d, J = 5.7 Hz, 1H, pyridine ring protons at position 2), 7.95–7.17 (m, 11H, aromatic protons), and 5.23 (s, 2H, N–CH2). The 13C NMR (75 MHz, CDCl3) spectrum displays signals at δ 165.64, 147.18, 140.30, 139.25, 127.93, 122.83, 120.50, 120.11, 111.28, 109.78, and 102.84 (carbons of aromatic rings), 148.60 (C4 position on the tetrazole ring), 53.75 (O-CH3), and 37.79 (N–CH2).

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9-((1-(2-Chloropyridin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-9H-carbazole (2e) is a white solid with a melting point of 189–191°C. The infrared spectroscopy data shows absorption bands at 3.104 (aromatic C-H), 1.590 and 1.500 (alkene C=C), 1.440 and 1.340 (triazole ring C–N), 1.070, 860, and 740 (carbazole ring C–N), and 750 (C–Cl bond). The 1H NMR (300 MHz, CDCl3) spectrum reveals δ 8.32 (d, J = 5.6 Hz, 1H, pyridine ring protons at position 2), 7.95–7.26 (m, 11H, aromatic protons), and 5.26 (s, 2H, N–CH2). The 13C NMR (75 MHz, CDCl3) spectrum shows signals at δ 150.88, 148.32, 140.05, 139.25, 128.06, 122.83, 120.50, 120.11, 118.25, 113.86, and 109.78 (carbons of aromatic rings), 148.89 (C4 position on the tetrazole ring), and 37.74 (N–CH2).

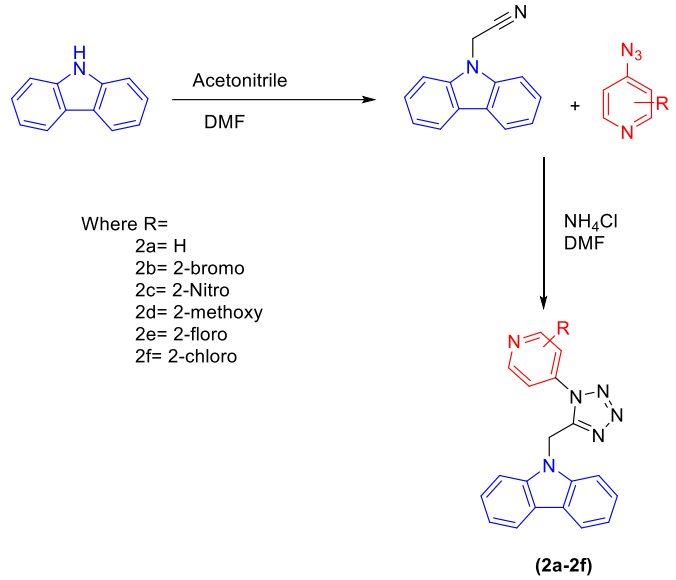
9-((1-(2-Fluoropyridin-4-yl)-1H-1,2,3-triazol-4-yl)methyl)-9H-carbazole (2f) is a brown-colored solid with a melting point of 206–208°C. The infrared spectroscopy data shows absorption bands at 3.105 (aromatic C-H stretching), 1.595 and 1.505 (C=C stretching in aromatic rings), 1.442 and 1.348 (C-N and N=N stretching in the tetrazole ring), 1.078, 870, and 748 (C-N stretching in the carbazole ring), and 1.242 (C-F stretching). The 1H NMR (300 MHz, CDCl3) spectrum reveals δ 8.37 (d, J = 5.7 Hz, 1H, pyridine ring protons at position 2), 8.00–7.26 (m, 11H, aromatic protons), and 5.28 (s, 2H, N–CH2). The 13C NMR (75 MHz, CDCl3) spectrum shows signals at δ 164.49, 161.13, 147.90, 147.72, 142.08, 141.97, 139.25, 128.14, 122.83, 120.50, 120.11, 112.27, 112.23, 109.78, 103.52, and 103.25 (carbons of aromatic rings), 149.18 (C4 position on the tetrazole ring), and 37.74 (N–CH2).

III. Results and Discussion

The structure of an antitubercular drug inspired the design of the new scaffold (Fig. 1). The scaffold consists of three key components: the carbazole unit, which serves as the pharmacophore; the N-functionalized tetrazole, which acts as the core backbone; and a substituted pyridine, introduced to the other side of the N-substituted tetrazole moiety to enhance its pharmacophore properties and increase lipophilicity. The use of aromatic pyridyl azide derivatives allows for variations within the proposed scaffold. The synthesis of substituted tetrazolylmethyl carbazole derivatives (2a-2f) was based on a 1,3-dipolar cycloaddition reaction. Initially, the necessary tetrazoles were synthesized starting from 9-(2-acetonnitrile)-9H-carbazole (1a). Using a modified literature method, early attempts converted carbazole to alkyne (1a) by reacting propargyl bromide with K2CO3 in a solution of carbazole (1) in DMF [30]. This reaction was successfully carried out with high yields by adding acetonitrile after 30 minutes of refluxing, with the reaction continuing for an additional two hours (Scheme 1).

Scheme1 Synthesis and design of new substituted pyridine 1,2,3-triazolylmethyl carbazoles 2a-2f

Using 1H and 13C NMR spectra, the resultant alkyne (1a) was fully characterized. N-methylene's protons at d 4.98 ppm appeared as a doublet (J = 2.4 Hz) (2H), whereas the characteristic proton of acetylenic at d 2.23 ppm appeared as a triplet (J = 2.4 Hz) (1H) in the compound (1a)'s 1H NMR spectra. The splitting pattern of acetylene protons is not new and is in line with information found in the literature on chemical entities that are quite similar [31]. Peaks in the 13C NMR spectra at d 77.7 and 72.4 ppm indicated the acetylenic carbons, whereas a signal at d 32.5 ppm indicated the N methylene carbon. Once the alkyne (1a) and azide derivatives were obtained, we employed a CuSO4 catalyst and Huisgen's (3+2) cycloaddition process.



For example, alkyne building block (1a) interacted with pyridine azide derivatives in tert-butanol and water (1:1, v/v) in the presence of sodium ascorbate and 20 mol% CuSO4 catalyst to get 9-((substituted pyridine-1H-1,2,3-triazol-5-yl)methyl)-9H-carbazole compounds. with a significant output (Scheme 1). All of the products were well characterized using 1H, 13C NMR, and IR data (2a–2f). The singlet resonances from d 5.21 to 5.27 ppm in the 1H NMR were caused by carbazole N-methylene bridge protons, which were present in all synthesized compounds. The IR spectra of compounds (2a-2f) showed that the methylene group's aliphatic C-H stretching occurred between 2,935 and 2,986 cm-1, whereas the aromatic carbon-H stretching frequencies were found between 3108 and 3195 cm-1. All of the new compounds' full spectrum data were provided in the experimental section.

Staphylococcus aureus DNA Gyrase B – Molecular docking studies of Compounds 2a-2f

Analyzed were the molecular docking results pertaining to the binding of the monitored compounds to the Staphylococcus aureus DNA Gyrase B protein (PDB ID: 2XCT) and compare the computed binding affinities of those compounds to the reference ligand. The reference ligand bound with an energy (S) of -7.03427 and showed an RMSD of 1.207259. Thus, these values were used for benchmarking the docking performance of the tested compounds Figure 1.

Among the synthesized compounds, 2c exhibited the greatest binding energy of -7.02886 which is known to interact strongly with the target protein, which explains why its value is closer to that of the reference ligand bearing the binding energy (S) of -7.03427. Additionally, compound 2c recorded the RMSD value of 1.099458, which indicates that its binding

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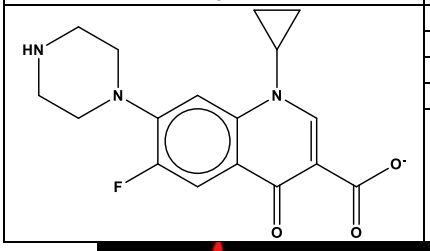
conformation is similar to that of the reference ligand (RMSD = 1.207259).

mol	S	rmsd
	-7.31426	2.166975
	-7.03427	1.207259
	-6.97081	6.713724
	-6.92862	1.128722
	-6.88076	5.505234

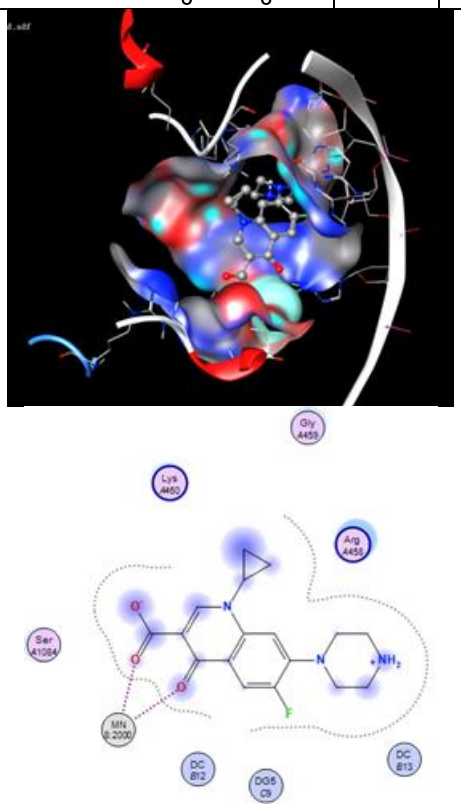


Figure 1: Analysis and visualization of molecular interactions and protein active site with binding energy and root mean square deviation

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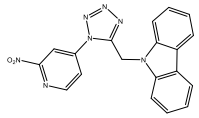
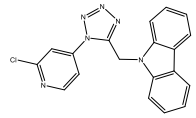
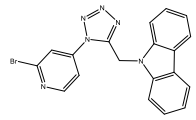
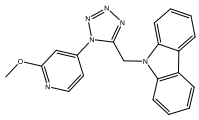
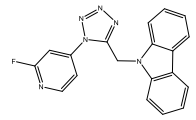
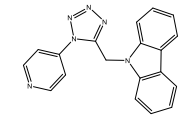
The second-best synthesized compound, 2f had a binding energy score of -6.94594 and an RMSD of 0.802977, indicating acceptable binding and alignment. Other synthesized compounds, such as 2b, 2d, and 2e, had binding scores of -6.73345, -6.72142, and -6.70743 which are lower than 2c and 2f but still suggest some interactions. In comparison with the rest of the results of the reference ligand, compound 2c had the highest affinity and most favorable conformation, thus it is highly suggested for further analysis. On the contrary, compound 2e exhibited the lowest RMSD. While it recorded 0.566583, which implies a stable binding mode, its binding energy was found to be weaker than 2c and 2f. To summarize, these results confirm that compound 2c is the most favorable synthesized candidate while compound 2f demonstrates some substantial ability as well.

TABLE 1. results of 2XCT receptor binding for compounds 2a-2f

mol	code	S	rmsd_refine
	2c	-7.02886	1.099458
	2f	-6.94594	0.802977
	2b	-6.73345	1.904001
	2d	-6.72142	1.035803
	2e	-6.70743	0.566583
	2a	-6.54911	1.323160

This suggests that the first candidate compound has strong and/or stable protein binding that the system is likely to reach. The values turned out to be quite stable with respect to their interactions with the active site of the protein. For the second compound, since its performance is good, it can be regarded as a viable second candidate. Based on this analysis, Compound 2c can be regarded as a potential winner because of the negative 7.02886 kcal mol^1 of binding energy that he has. Also, the other synthesized compounds did not outperform these results. On the other hand, Compound 2f showed sufficient binding affinity but was less effective than Compound 2c. It is suggested that further experimental work, including molecular dynamics simulation and in vitro assays, should be done to prove the biological activity of these compounds against Staphylococcus aureus and to support this work. The interaction of the synthesized compounds with Staphylococcus aureus DNA Gyrase B based on the molecular docking studies was very revealing – especially with regard to how these compounds interact within the active site of the enzyme. The target protein was very well fitted for compound 2c, and stabilized its position within the active site of the protein with hydrogen bonds to key amino acid residues. In addition, the steric bulk of some amino acid residues such as Asp437 aided in the electrostatic stabilization of the compound, while other residues including Ser88 and Cys89 are essential for stabilizing the binding medium. The docking studies of the reference ligand and compound 2c corroborate the binding interactions within the magnesium ion (Mn^{2+}) active site of the Staphylococcus aureus DNA Gyrase B. The reference ligand is known to bind very tightly because of a

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strong coordination bond between Mn^{2+} ions which stabilizes the enzyme-ligand complex within the active site and strengthens the inhibitor's potency and binding. Likewise, compound 2c has been shown to greatly bind with Mn^{2+} ions, strongly suggesting that it is a true antagonist of the reference ligand. This is especially important because magnesium coordination is known to improve ligand binding and increase enzymatic inhibition. This particular metal-ligand interaction contributes to the overall stability of compound 2c and it suggests that it could be a good candidate for DNA Gyrase B inhibition. Additional studies including molecular dynamics, however, would be required to estimate the stability of this interaction over time as well as the effect it has on enzymatic activity Figure 2.

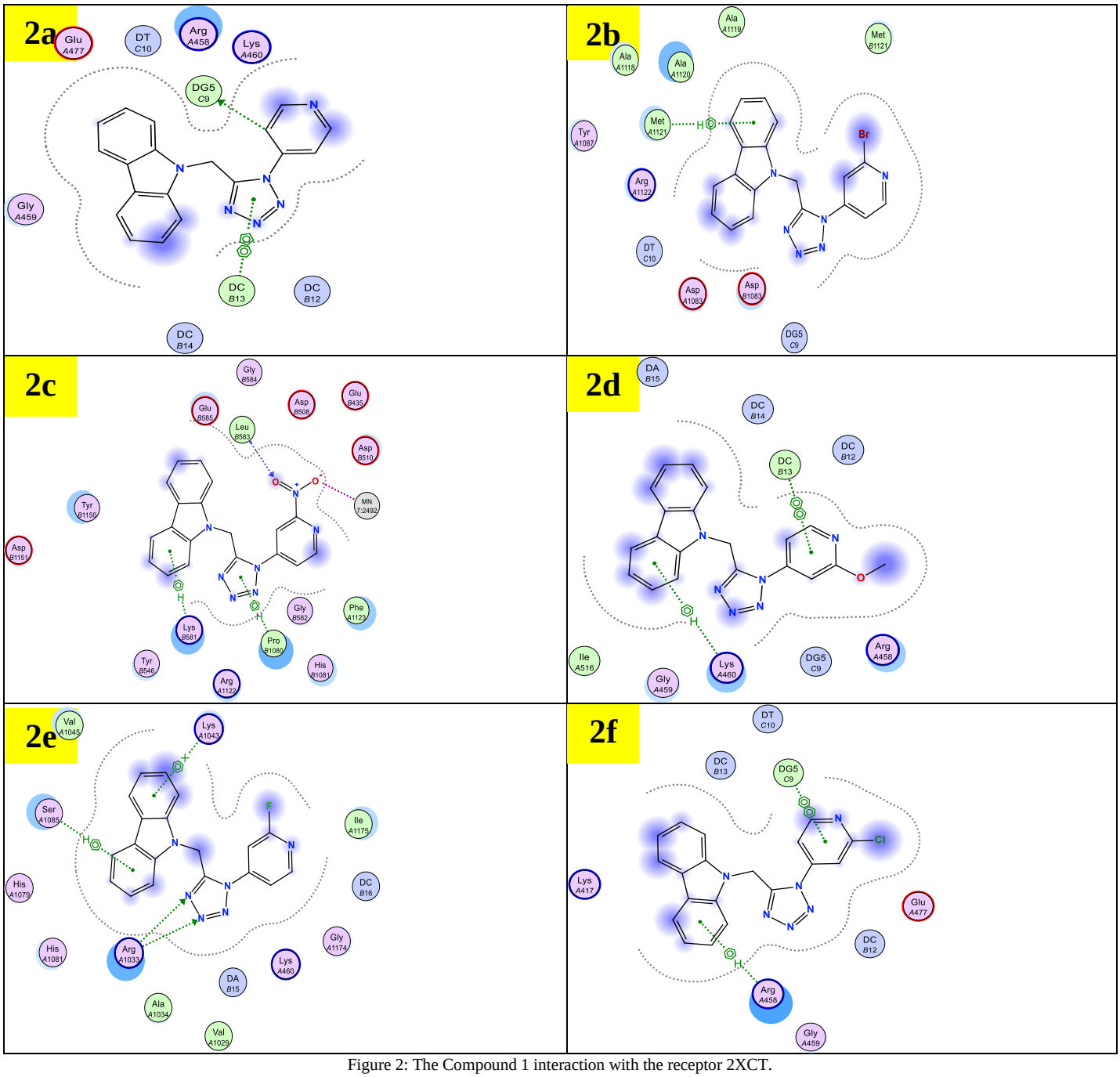

Figure 2: The Compound 1 interaction with the receptor 2XCT.

IV. Conclusion

In this research, a series of novel 1,2,3-triazolylmethyl carbazole derivatives were successfully synthesized and evaluated for their antibacterial properties. The structural analysis confirmed the successful formation of the desired compounds. Biological evaluation revealed that several derivatives displayed significant antibacterial activity,

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particularly against drug-resistant strains. Molecular docking studies further supported these findings, highlighting compound 2c as the most promising candidate due to its high binding affinity and stable interaction with the target bacterial enzyme. The combination of synthetic feasibility, potent antibacterial activity, and strong molecular interactions makes these compounds potential candidates for future drug development. Further studies, including in vitro and in vivo analyses, are recommended to validate their therapeutic potential.

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