AL-Zahraa First International Conference for Medical and Pharmaceutical Sciences (ZICMPS)
Karbala (Iraq), 2nd, 3th March, 2024

# Computational Study of New Nsaids Analogues Bearing Triazole Moiety with Promising Anticancer Activity.

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**Received: 03 April 2024; Revised: 23 April 2024; Published: 30 June 2024**

## Abstract

Computational simulation of five new naproxen analogues bearing 1,2,4-triazole moiety was carried out to evaluate their binding affinities and target the ovarian cancer cells where the topoisomerase I enzyme has been over-expressed. This enzyme was obtained from (PDB code:1K4T). The chemical structure of the molecules was accurately drawn using ChemDraw Professional 12.0 software. The affinity of the designed analogues was checked using Molecular Operating Environment software by calculating the S score and Rmsd. The designed analogues showed good binding interactions with the receptor active site and had a promising activity with these proteins. Va, Vd, Ve yielded the highest S scores.

**Keywords:** In silico, triazole, naproxen analogues, anticancer, MOE, topoisomerase, NSAIDs.

## 1. Introduction

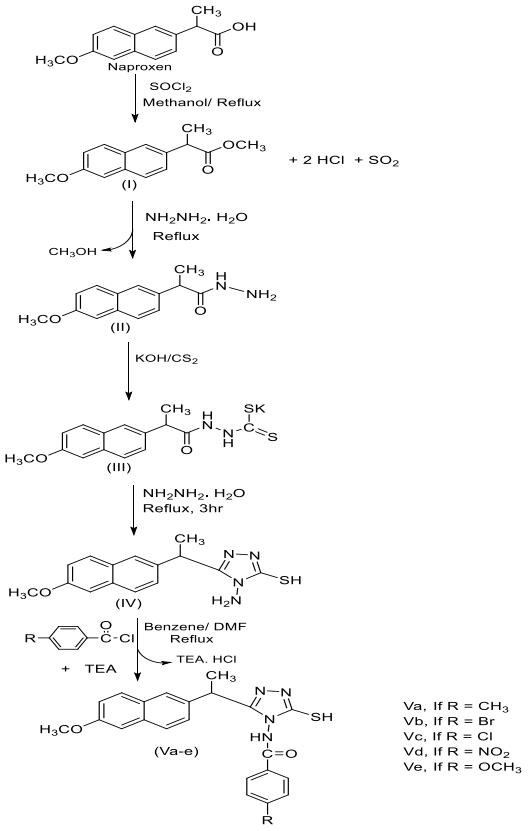
Cancer is a malignant complicated group of diseases, the starting of each is recognized by abnormal cell division with a high potential of metastases to the other parts of the body [1]. Cancer has a high prevalence and growing in scores. In upcoming years, cancer scores as a second cause of death around the world [2]. Many factors affect the prognosis of the disease, such as age, sex, and gender [3,4]. The initiation and survival of the cancer cells and the proliferation of them are dependent on the amount of oxygen, nutrients, and clearance of waste products entering and getting out the cells [5,6]. Widespread issues with cancer therapies include drug resistance, systemic toxicity of given medications, and drug ineffectiveness. The search for an effective therapeutic agent to treat malignancies has also been limited by complex aspects such as the nature of signaling pathways and the propensity of malignant cells to change, requiring an urgent effort to find new anticancer agents as therapeutic leads [7-12]. The combined effects of genotoxicity and resistance to currently available anticancer treatments are the main issues facing modern medicinal chemistry, which has increased the

quest for new small-molecule chemotherapeutic medications that are effective and safe to treat or even prevent cancer, by speeding up the process of finding new compounds, computational techniques like computer-aided drug design (CADD) will potentially reduce the cost of synthesis. [13]. An essential nucleus found in many different compounds is 1,2,4-triazole. There are currently a high number of compounds in the market that contain this nucleus. The 1,2,4-triazole nucleus binds with amino acid residue in the active site of a receptor as hydrogen bonds as it contains H-donor and H-acceptors. By that, it acts as an essential pharmacophore that is stable for metabolism. The triazole nucleus's polar nature can increase the ligand's solubility and considerably enhance the drug's pharmacological profile. Many 1,2,4-triazole containing chemicals possess a variety of biological activities, such as anti-cancer [14-15]. Therefore this hetero-cycle ring is used in many chemical therapeutic compounds, as the sulfur atom will produce many binding interactions that give it therapeutic effectiveness as an anticancer and antimicrobial [16-19]. So, linking the triazole moiety to naproxen aimed to develop a novel anti-cancer nucleus, as the NSAIDs possess inhibitory activity toward cancer through inhibition of COX2 enzyme [20].

## 2. Methodology

### 2.1 Chemical Synthesis [21-22]

The following scheme represents the steps of the chemical synthesis of the target compounds.




**Scheme 1. Chemical synthesis of the naproxen analogues**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### 2.2 Ligand/Receptor Preparation and Molecular Docking Protocol

MOE (Molecular Operating Environment) is the computerized program used to study the binding affinity with the target receptor. Chemdraw used for drawing the designed compounds, which are then input into MOE to prepare and became ready for the docking step.

The ligand protein downloaded from protein data bank PDB website: https://www.rcsb.org/, which are the crystal structures of Human DNA topoisomerase I (PDB code:1K4T) which complexed with the Topotecan and form covalent complex with A22 base pair DNA duplex. This protein input into MOE program and prepared inside it. The preparation step involved addition of protons, bonds, and energy minimization [23, 24].

The final step is Docking process, five poses for each molecule were used and the total was 30 poses that used in the docking process [25].

## 3. Results and Discussion

### 3.1 Chemical Synthesis

The designed chemical compounds were synthesized starting from naproxen that was linked with triazole ring derivatives to give the final five compounds (Va-Ve).

### 3.2 Computational Study and Molecular Docking

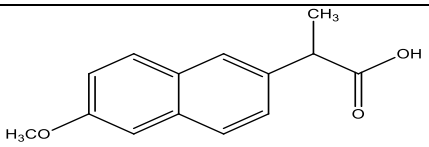
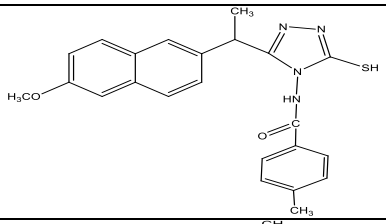
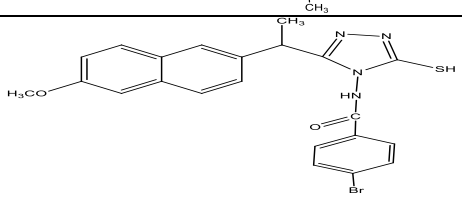
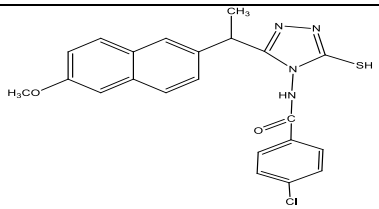
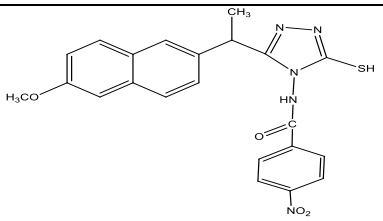
he optimum method for the designed new compound to connect to a target's active site is through using the simulation technique known as molecular docking. The Molecular Operating Environment exhibits the binding affinity of the designed new compounds to the protein Human DNA Topoisomerase I is the same main active site of the poison topotecan. The inhibitory activities of designed compounds were arranged depending on the value of the S score and Rmsd (Root mean square deviation), which shows the average distance between the atoms of the pose and original ligand for the site of the anticancer that was studied, and the similarity in amino acids that entering in the interaction on the same active site.

Topotecan interacts on its site of interaction which consist from: (DA D113, Arg A364, DC D112, Leu429, IIe420, Lys A425, Lys A436, Phe A361, Gln A421, Glu A356, Met A428, Tyr A426, Trp A416, DT B9, Ala A351, Glu A418, Asn A352, DA D114, Lys A532, Thr A718, PTR A723, DT B10, Asn A722, Asp A533).

Table (1) shows the S.score, Rmsd, and the main amino acids that entered the interaction of the naproxen and final products produced in the reaction.

Ve Va, Vd and Naproxen showed the highest similar interaction between all with S.score ( -7.2286, -7.4704, -7.5764 and-5.2376 respectively) and Rmsd are(1.1829, 0.9675, 0.9736 and 0.9069) while the lowest was Vb and Vc they showed less binding affinity compared to the main ligand (topotecan). Va Formed bonding with DA B113, Lys C532, Asp c533. While Vd formed bonding through interaction with Arg C364, DA B113, and Tyr C426. VE also through DT A10, DC B111, DC B112, and DA B113. Naproxen interacts through DA B113, DC B112, and LysC 374.

**Table 1: Binding Properties of designed compounds.**

| Compound | Structure | S-Score | Rmsd | No. of binding sites | Binding amino acids |
|---|---|---|---|---|---|
| **Naproxen** |  | -5.23 | 0.9 | 3 | DA B113, DC B112 and Lys C374. |
| **Va** |  | -7.47 | 0.96 | 3 | DA B113, Lys C532, Asp c533 |
| **Vb** |  | -7.14 | 1.47 | 3 | DC B112, DC B111, DT A10 |
| **Vc** |  | -7.35 | 1.51 | 2 | Arg c364, DA B113 |
| **Vd** |  | -7.57 | 0.97 | 3 | Arg C364, DA B113 and Tyr C426 |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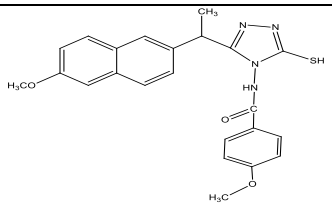
| | | | | | |
|---|---|---|---|---|---|
| **Ve** |  | -7.22 | 1.18 | 4 | DT A10, DC B111, DC B112, DA B113 |

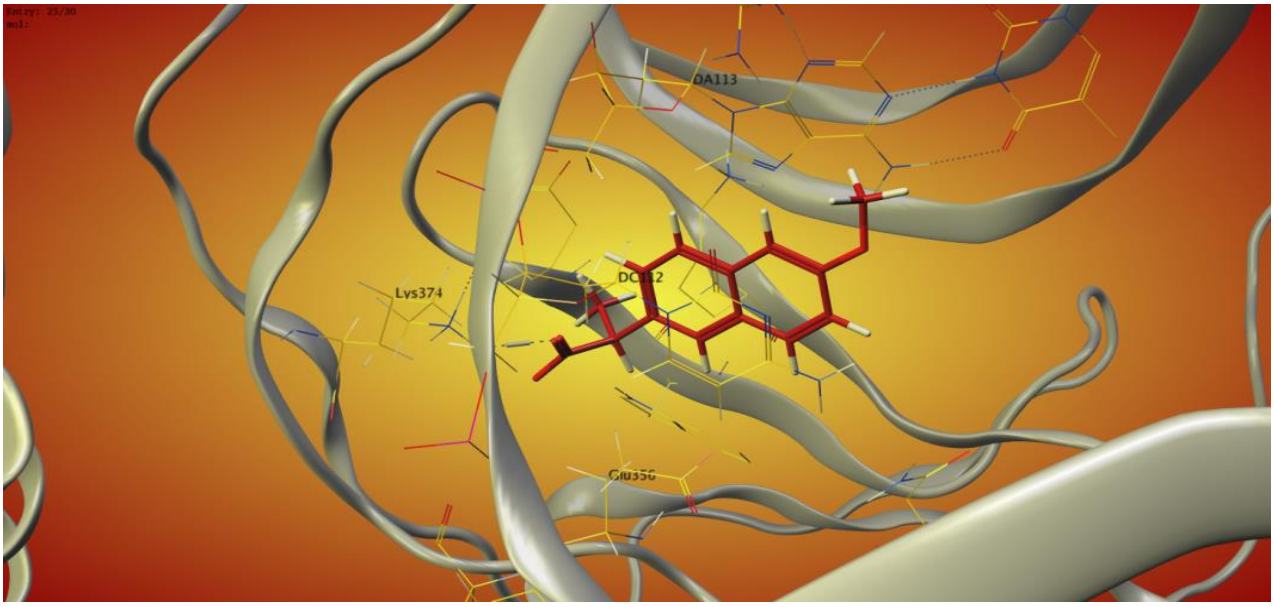



**Figure 1. Naproxen binding with Human DNA Topisomerase I (PDB code:1K4T) (3D).**

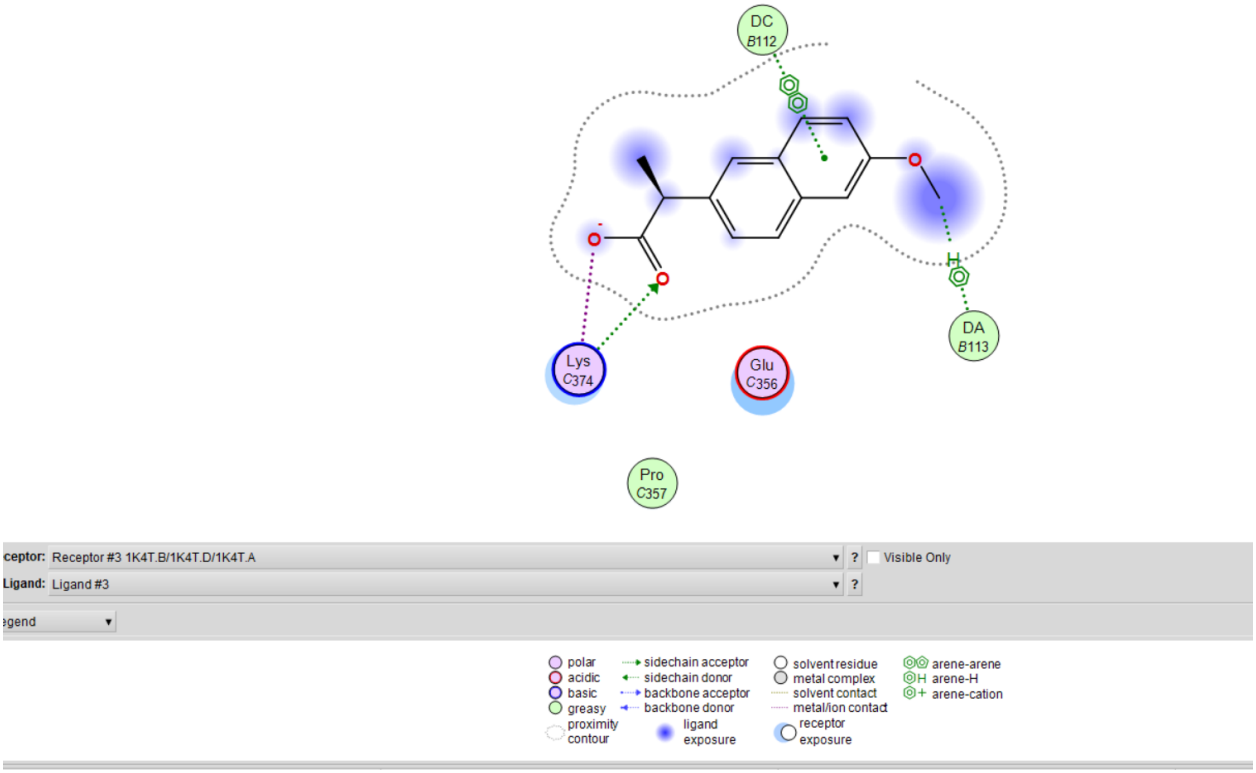



**Figure 2. Naproxen binding with the Human DNA Topisomerase I (PDB code:1K4T) (2D).**

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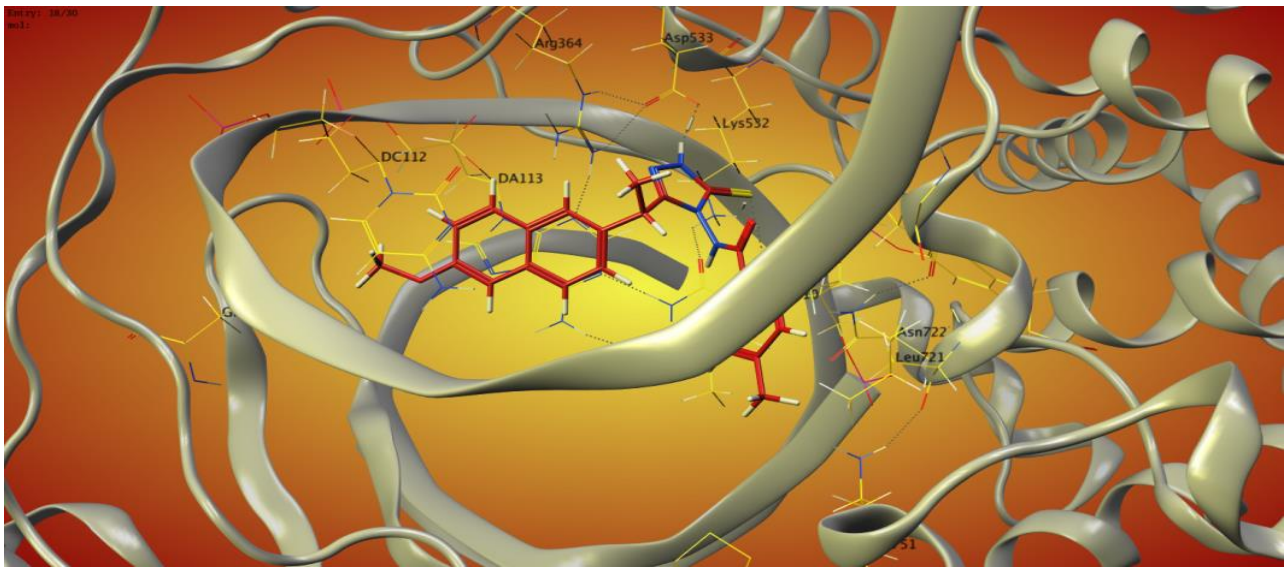


**Figure 3. Va binding with Human DNA Topisomerase I (PDB code:1K4T) (3D).**

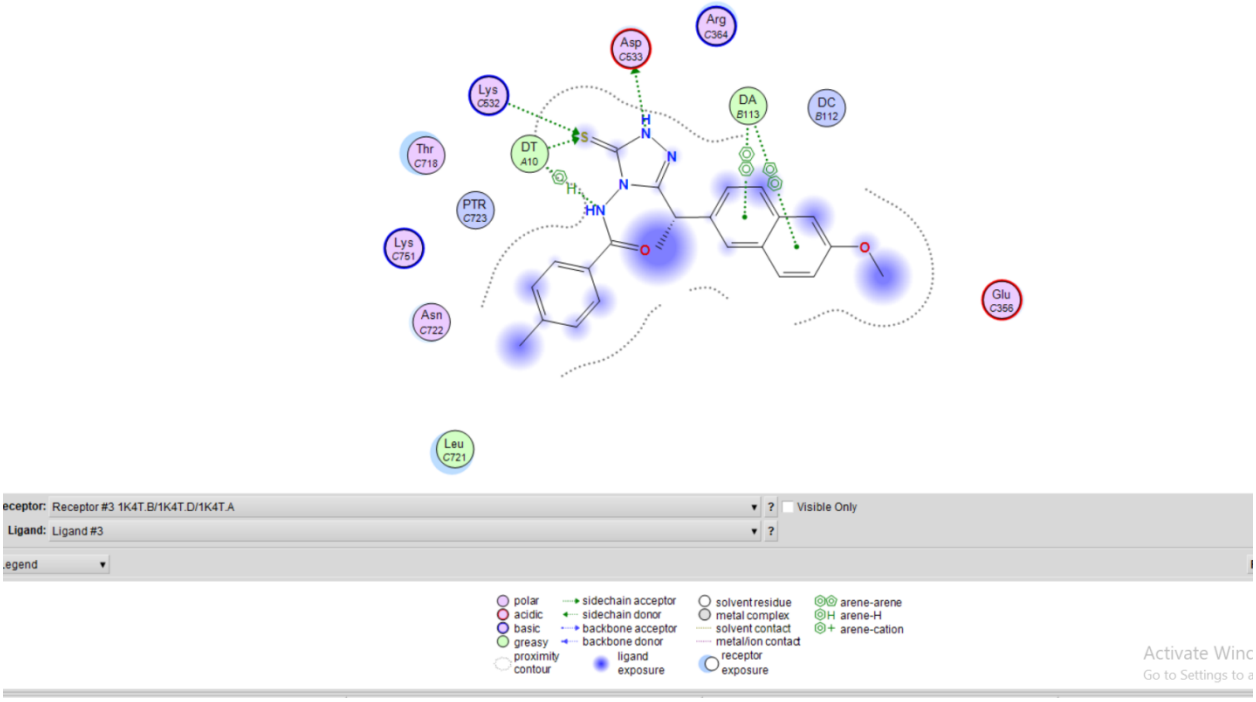


**Figure 4. Va binding with Human DNA Topisomerase I (PDB code:1K4T) (2D).**


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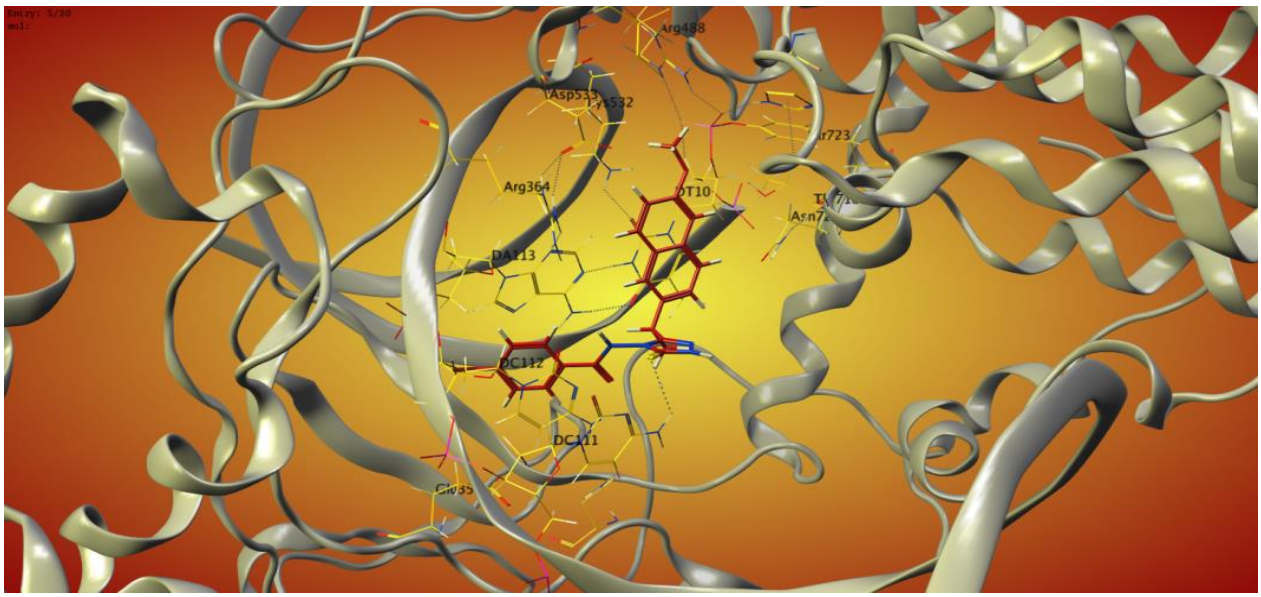


**Figure 5. Vb binding with Human DNA Topisomerase I (PDB code:1K4T) (3D).**

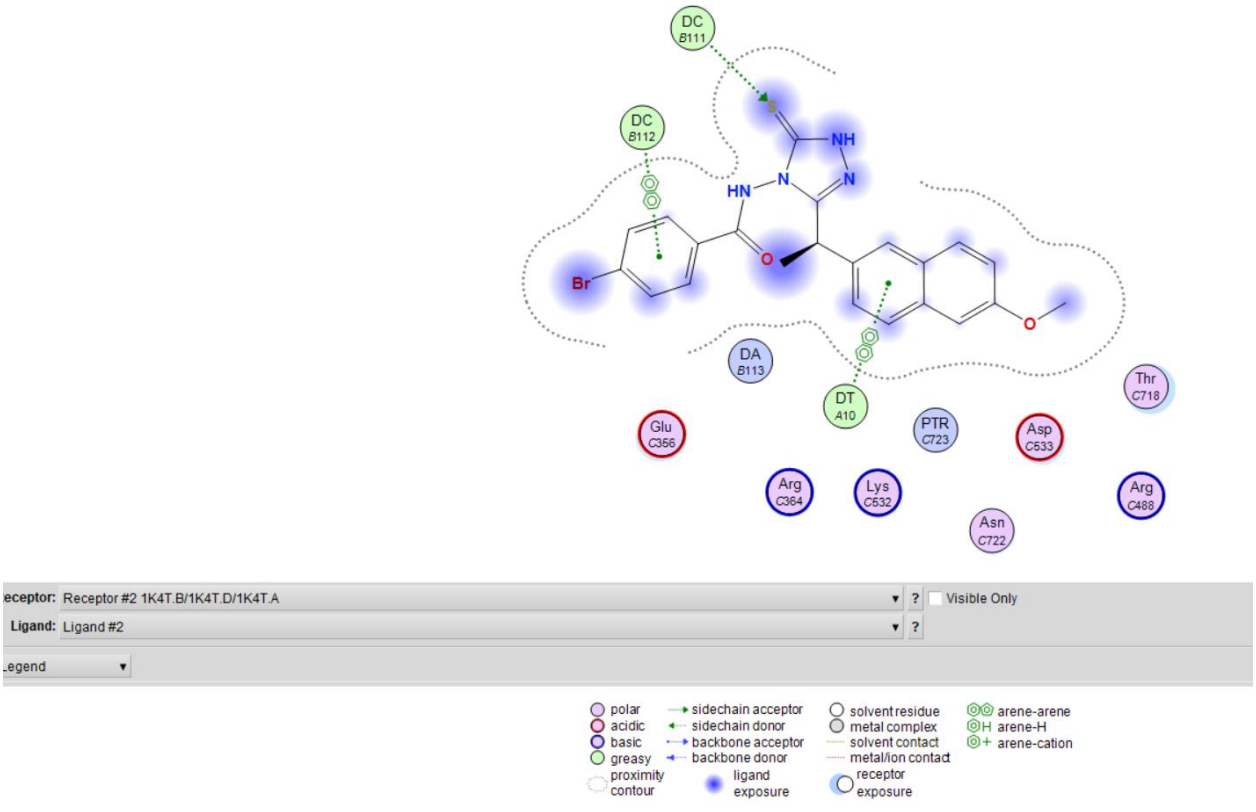


**Figure 6. Vb binding with Human DNA Topisomerase I (PDB code:1K4T) (2D).**


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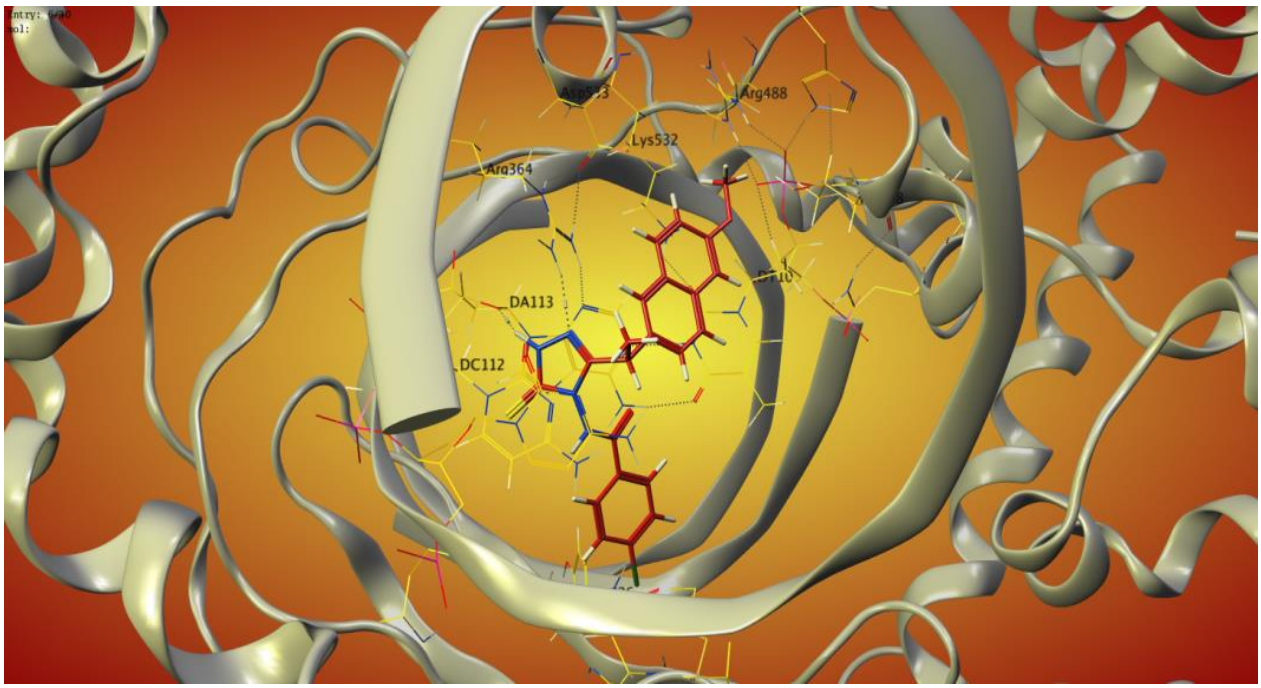


**Figure 7. Vc binding Human DNA Topisomerase I (PDB code:1K4T) (3D).**

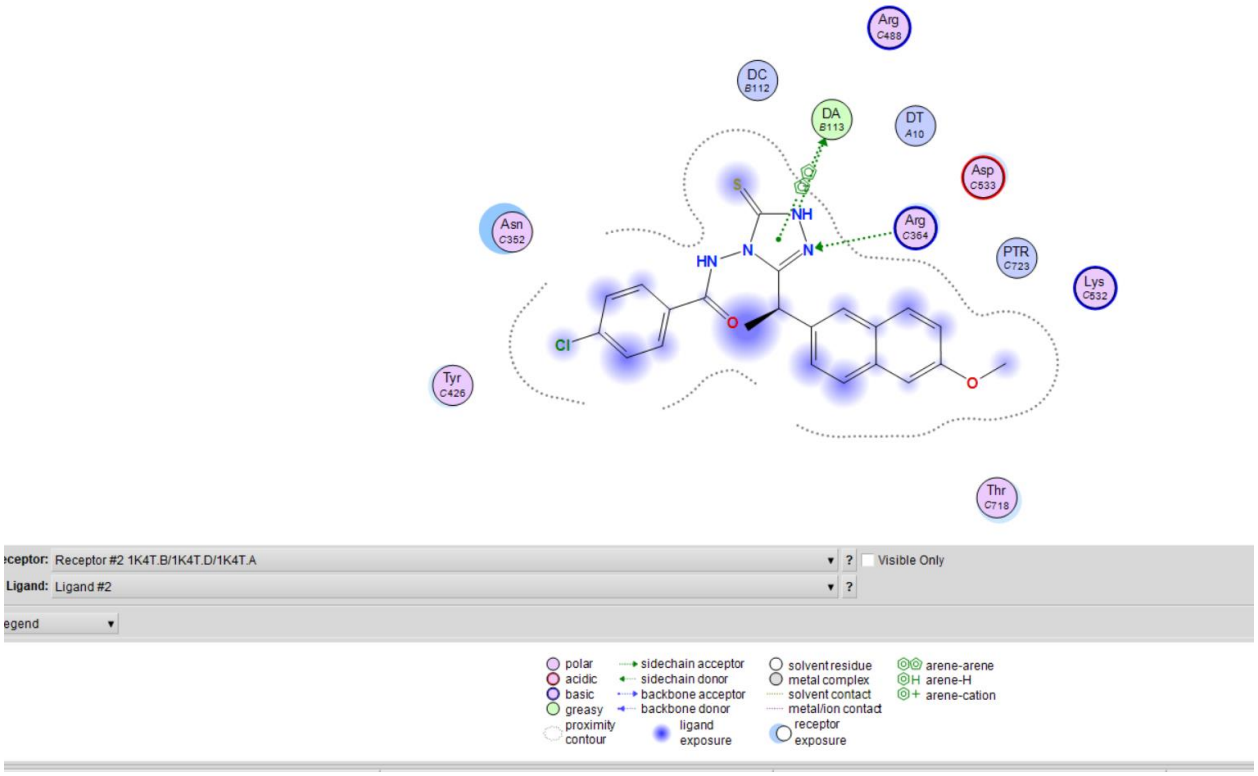


**Figure 8. Vc binding with Human DNA Topisomerase I (PDB code:1K4T) (2D).**


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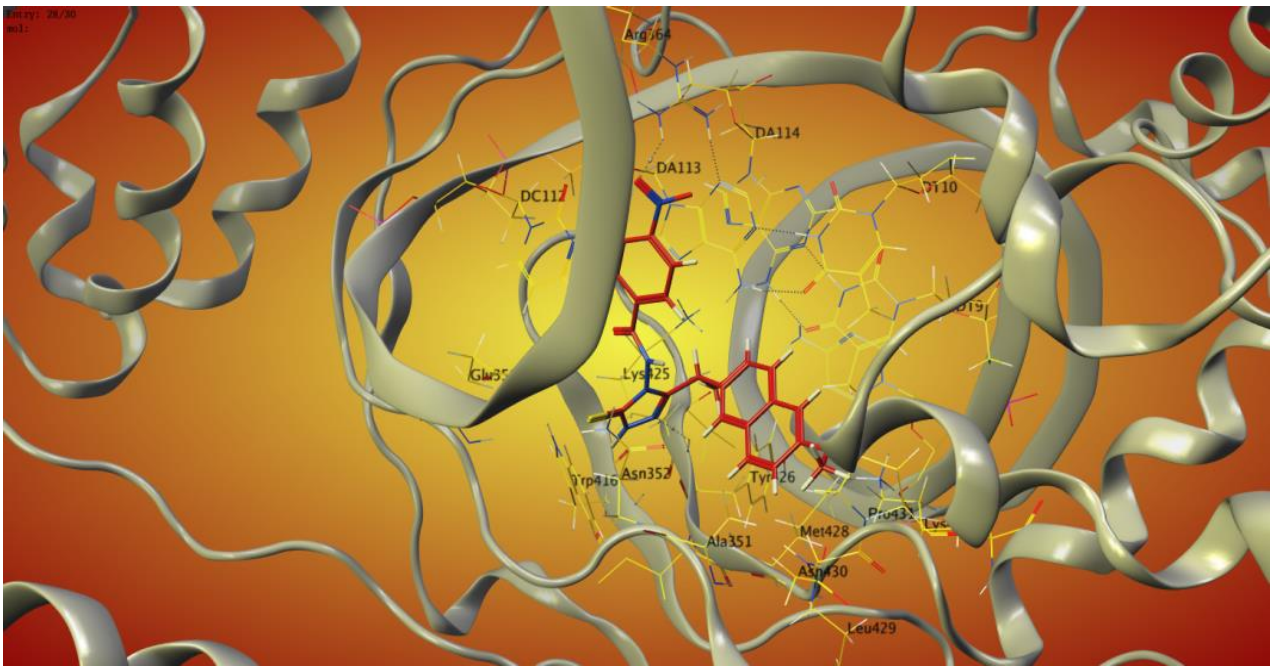


**Figure 9. Vd binding with Human DNA Topisomerase I (PDB code:1K4T) (3D).**

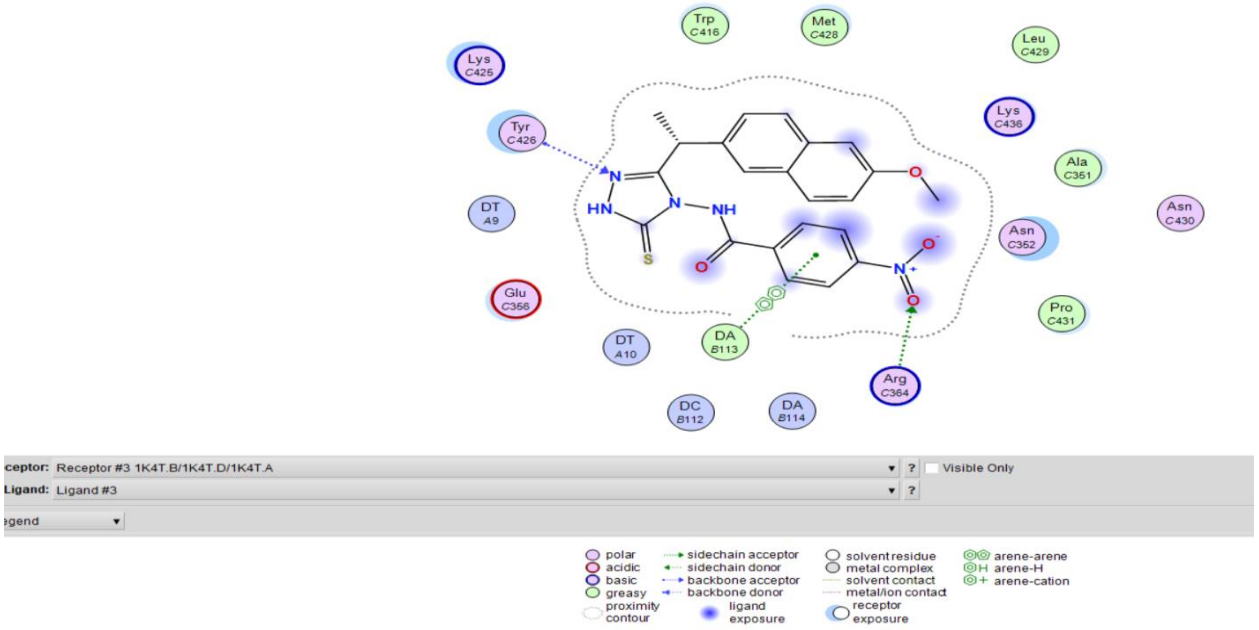


**Figure 10. Vd binding with Human DNA Topisomerase I (PDB code:1K4T) (2D).**


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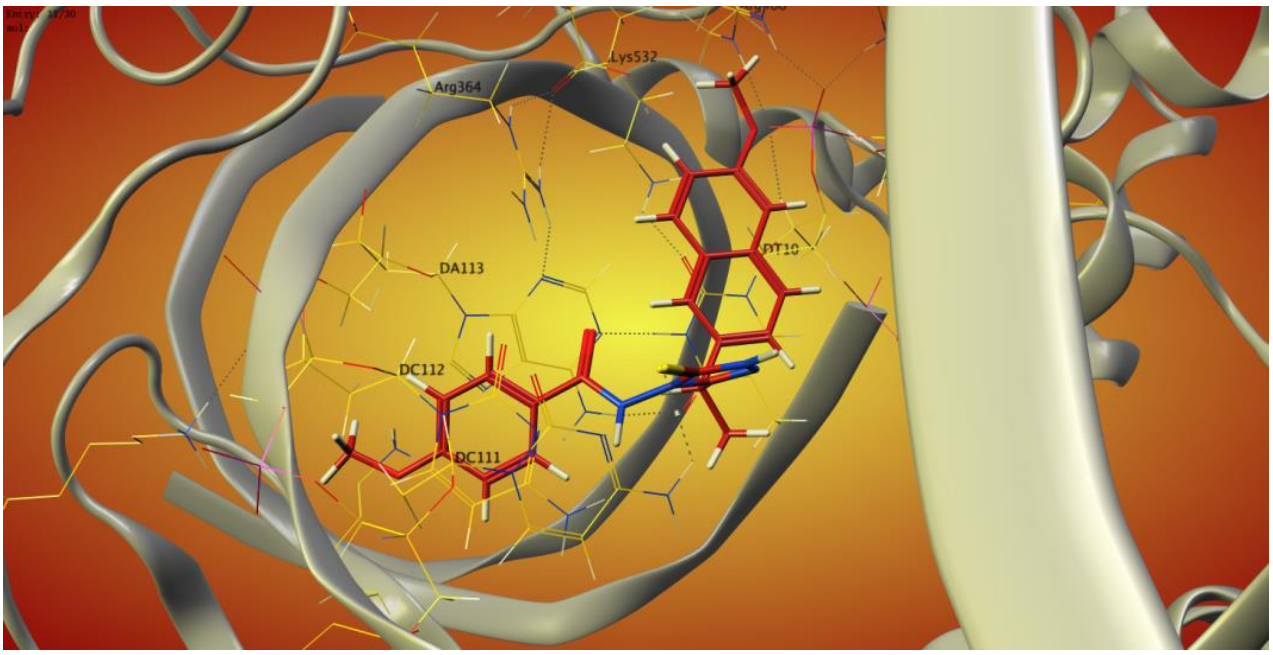


**Figure 11. Ve binding with Human DNA Topisomerase I (PDB code:1K4T) (3D).**

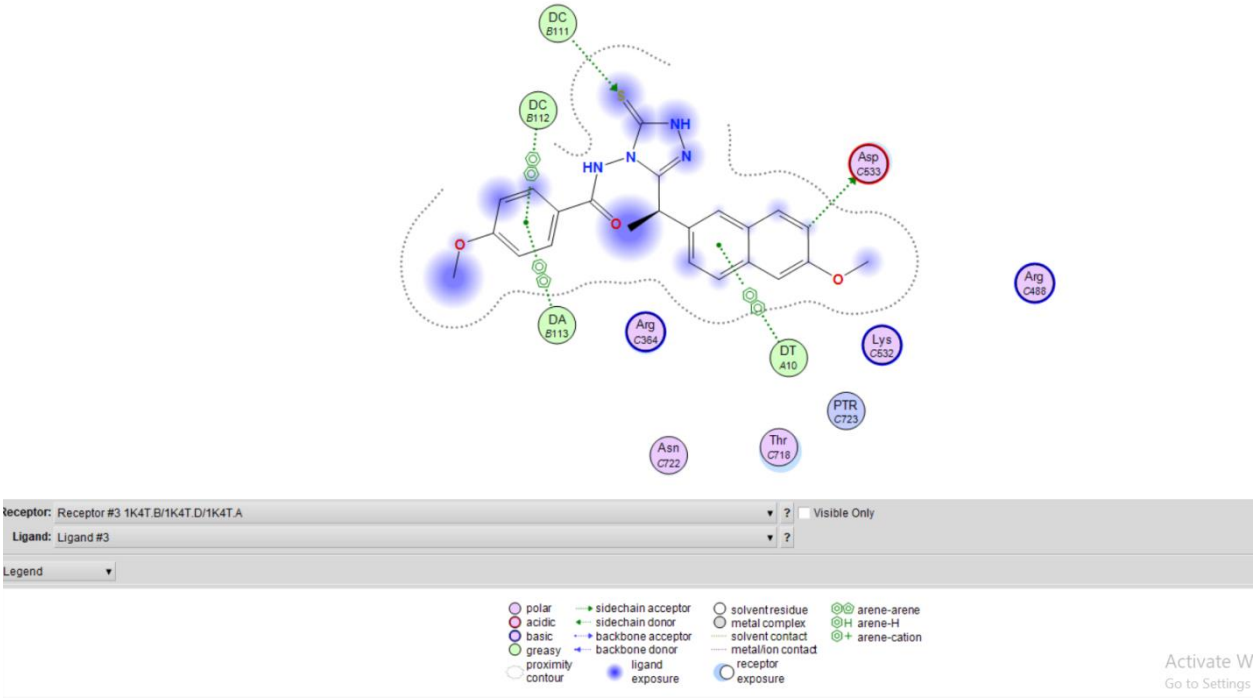


**Figure 12. Ve binding with Human DNA Topisomerase I (PDB code:1K4T) (2D).**

## 4. Conclusions

This study involves the design of the new naproxen analogues bearing 1,2,4-triazole moiety and then evaluation of their anti-cancer activity using in-silico techniques. The Molecular Operating Environment docking results determined that the newly designed analogues have anti-cancer activity towards ovarian cancer, this study was performed using the reference Topotecan. The compounds Va, Vd, and Ve show the highest S score, with the highest binding affinity.

This gives evidence that the triazole ring has an effective and important role in the binding affinity with the receptor, in giving flexibility and increasing the chance of interaction with the receptor active site, also the role of benzoyl chloride derivatives which are affecting the binding orientation depending on the type of substitution at position 4 of benzene ring.

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