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In silico study of novel naproxen derivatives bearing triazole moiety with promising anti-cancer activity

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ABSTRACT— Molecular docking simulation of five (5) compounds synthesized where they are derivatives bearing 1,2,4,triazole moietiy were carried out so as to evaluate their theoretical binding affinities, targeting Overian cancer and also to low scale for other types and the enzyme was Human DNA Topisomerase I (70 KDA) (PDB code:1K4T). The chemical structure of the molecules was accurately drawn using ChemDraw Professional 12.0 software. The designed compounds were checked using Molecular Operating environment software by Checking S.score and Rmsd. The theoretically designed compounds gave good binding interactions with the receptor active pocket and had promising activity with these proteins. Va,Vd,Ve yeilded the highst scores and binding similarity.

KEYWORDS: silicon, triazole moiety, naproxen derivatives

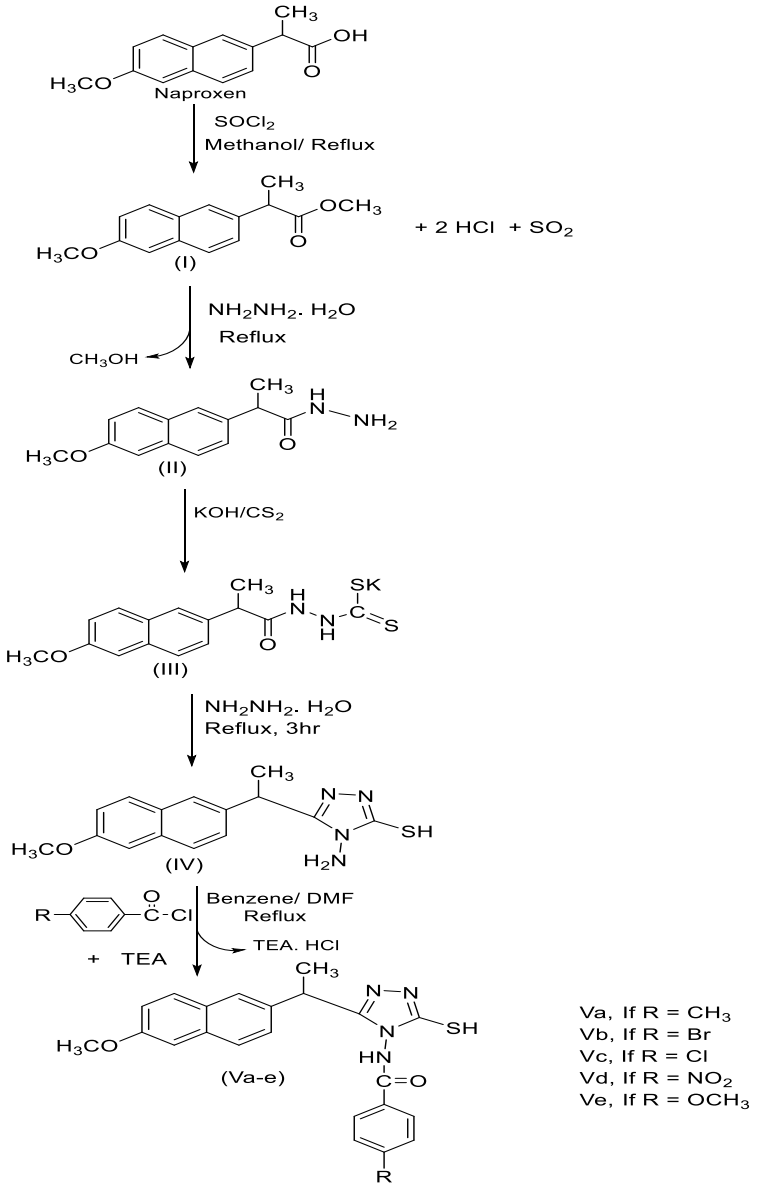
1. INTRODUCTION

Cancer is a complicated group of diseases, the starting of each is recognized by abnormal cell division with high potential of metastaing to the other parts of the body [1]. Cancer has high prevalence and growing in scores. In upcoming years, cancer scores as asecond cause of death around the world and as example, the year 2020 alone, scored 19.3 million new cases with 10 million deaths cases [2]. Sex and age are the most important in cancer susceptibility and treatment, and the male are more subjected to cancer than the female [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 the enter and getting out the cells [5], [6]. Widespread issues with cancer therapies include drug resistance, systemic toxicity of given medications, and drug ineffectiveness. The searching for an effective therapeutic agent to treat malignancies has also been limited by complicating aspects such the numerous signaling nature of pathways and the propensity of most cancer 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 chemistry 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 high number compounds in the market that contain this nucleus. The 1,2,4-triazole nucleus interacts at the active site of a receptor as a hydrogen bond acceptor and as a donor, acting as an essential pharmacophore that is stable to 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 compounds are said to have a variety of bioactivities, such as anti-cancer activity [14]. A great attention has been devoted to the 1,2,4-triazol derivatives because of their biological activities, particularly sulfur-containing ones found to have diverse biological activities such as as anti cancer and anti microbial [15- 18].

2. Methodology

2.1 Chemical synthesis

The following scheme showing the synthesis pathway for compounds (Va-Ve) derived from Naproxen.



Scheme (1): Synthesis of the final compounds and their intermediates

2.2 Computer System and Software

Computer system (Dell), with the following specification properties; CPU Dual@ 0.30 GHz, Intel ® Core i7-6100U, 12 Gigabyte RAM was used throughout the present study. The software download and installed include MOE 2015 and Chemdraw Professional software pro12.0.

2.3. Ligand/Receptor preparation and Molecular docking protocol

Initially, ChemDraw professional (pro12.0) software was used to precisely draw the molecules' chemical structures of the ligand.

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Second, the receptors loaded into the Molecular operating environment(MOE) from the protein data bank PDB website: https://www.rcsb.org/, which are the crystal structures of Human DNA topoisomerase I (70 KDA) (PDB code:1K4T) in complex with the poison Topotecan and covalent cpmplex with A22 base pair DNA duplex.

Then the choosing the right sequence that enter in the interaction and then deleting the un important residues. The next step to add hydrogen boning to get precise ionization and tautomeric positions of amino acid residues then adding the disappeared bonds and then fixation and determing the active site from the whole receptor.

Third step to prepare the ligand, initially by loading into MOE From the saved Data, and then potentiate the ligand in 3D shape, then partial charge, the energy minimization and finally saving the data.

Fourth step is Docking process, five poses for each molecules were used and the total was 30 poses that used in the docking process.

3. Results And Discussion

3.1 Chemical Synthesis

The target compounds that were designed as finals (Va-Ve), they were sythesized from naproxen and in advance steps they react with benzoyl chloride derivatves and the designed and the have been used as anti cancer in vivo (Overian Cancer).

3.2 Molecular Docking and Virtual Screening

The optimum way for a ligand to connect to a target's active site is explored using the simulation technique known as molecular docking [19]. The Molecular operating environment showed that binding selectivity of designed compounds to protein Human DNA Topoisomerase I in the same main active site of the poison topotecan. The inhibitory activities of designed compounds were rated depending on the value of S.score and Rmsd (Root mean square deviation), which is showing the average distance between the atoms of the pose and original ligand for the site of the anti cancer that studied, and the simularity in amino acids that entering in the interaction on the same active site.

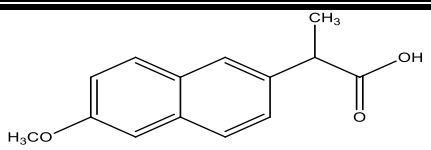
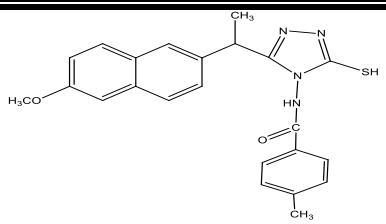
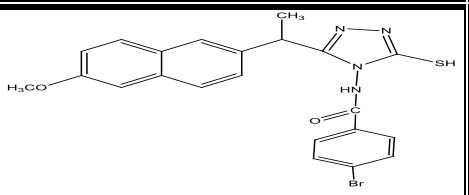
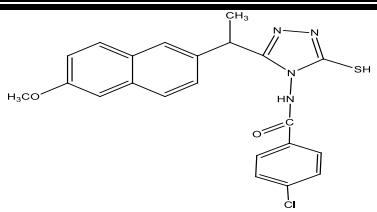
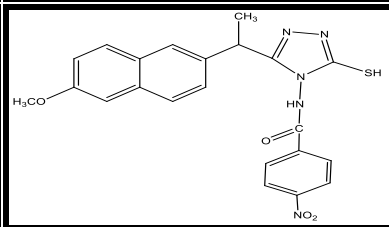
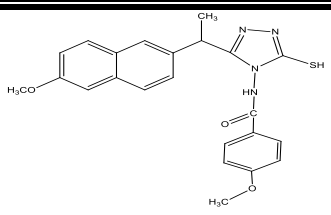
Topotecan interact on its site of interaction which consist from: (DA D113, Arg A364, DC D112, Leu429, IIe420, Lys A425, Lys A436, Phe A361, Gln A421, Glu A356, Met A428, Tyr A426, Trp A416, DT B9, Ala A351,Glu A418, Asn A352, DA D114, Lys A532, Thr A718, PTR A723, DT B10, Asn A722, Asp A533).

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

Ve ,Va, Vd and Naproxen showed the highest similar interaction between the 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 were 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, DA B113. Naproxen interact through DA B113, DC B112 and LysC 374.

Table 1: The Binding Properties of tested 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
Ve		-7.22	1.18	4	DT A10, DC B111, DC B112, DA B113

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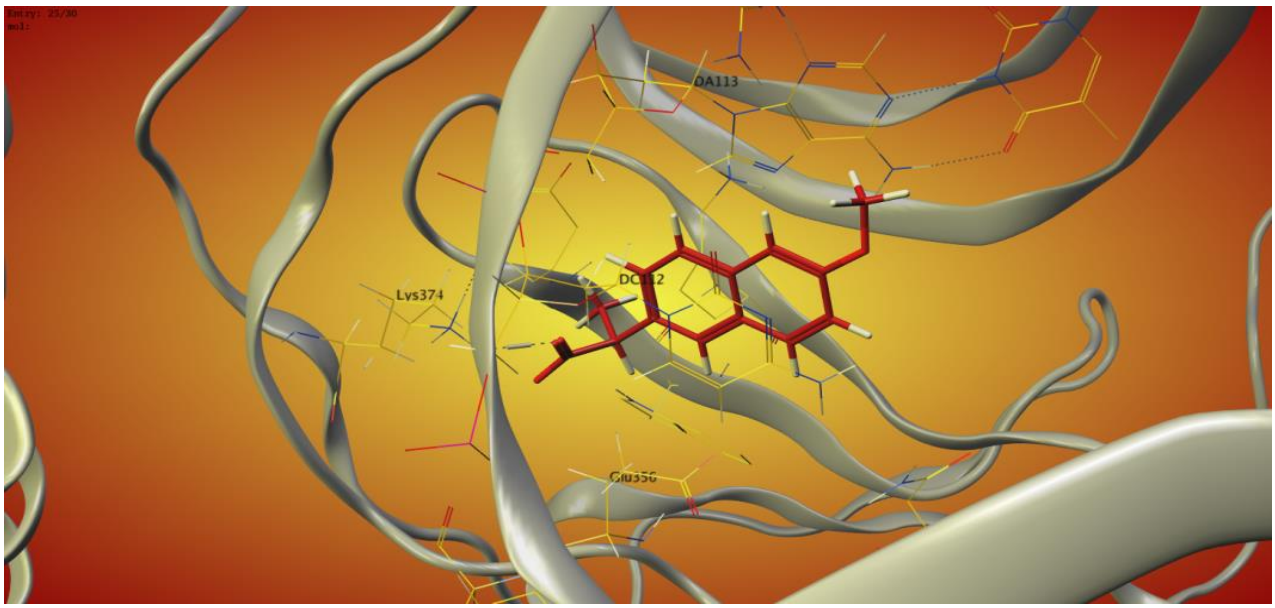

Figure (1) Naproxen with the Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (3D).

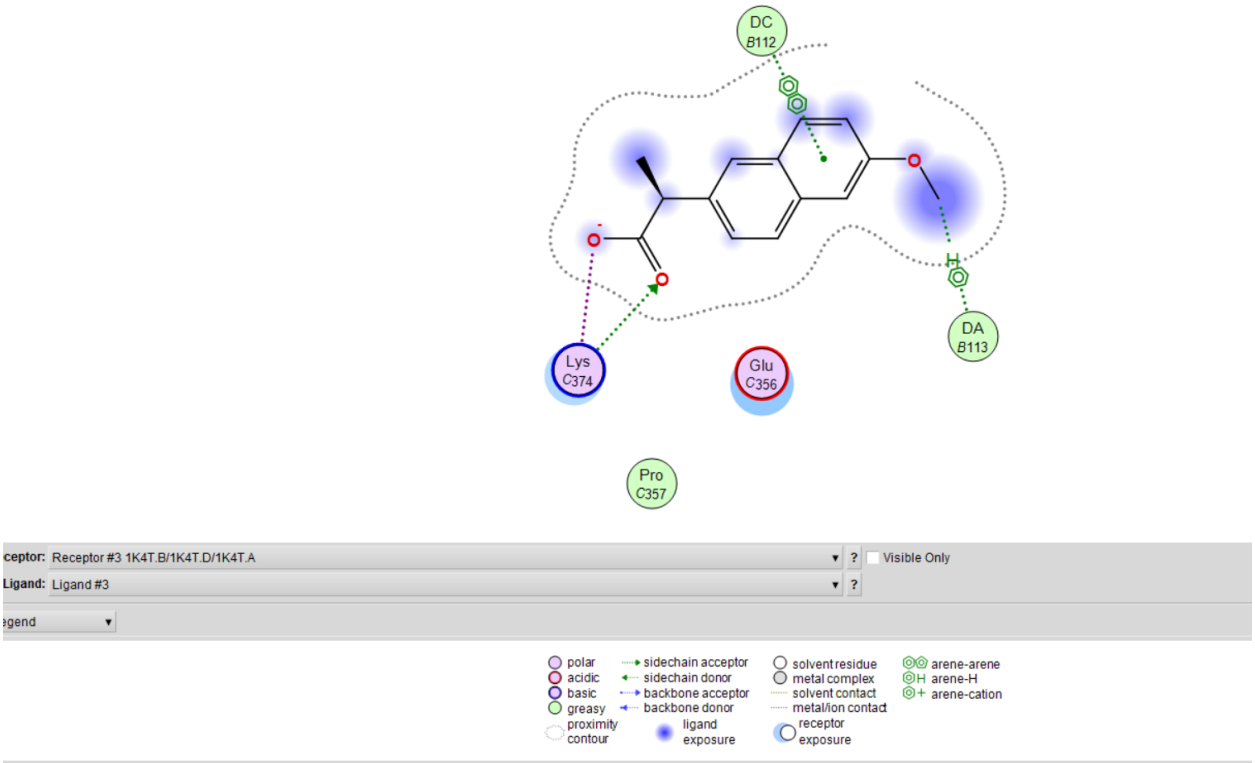

Figure (2) Naproxen with the Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (2D).

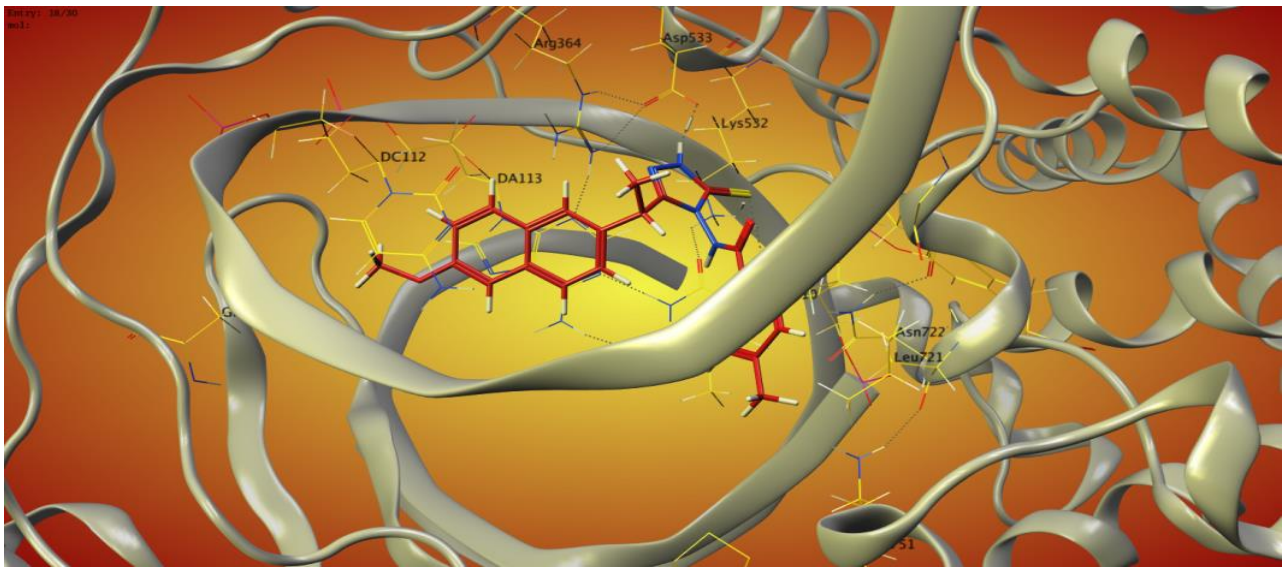

Figure (3) Va Final compound with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (3D).

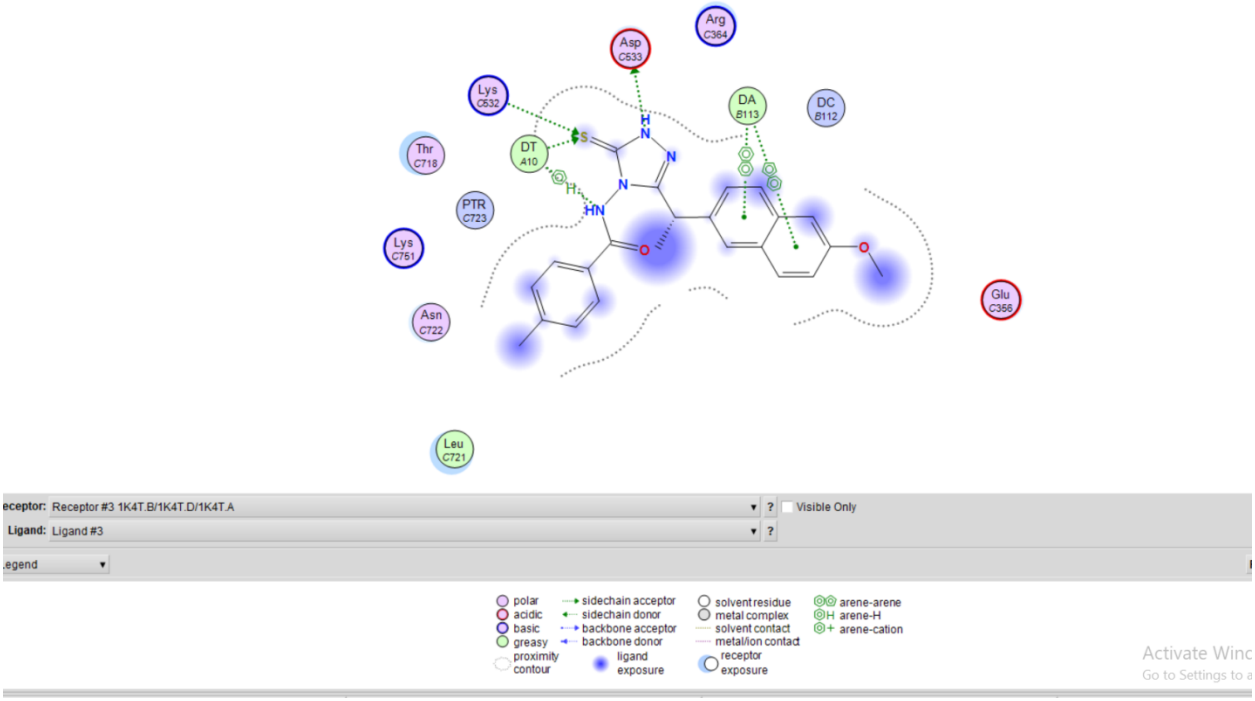

Figure (4) Va Final compound with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (2D).

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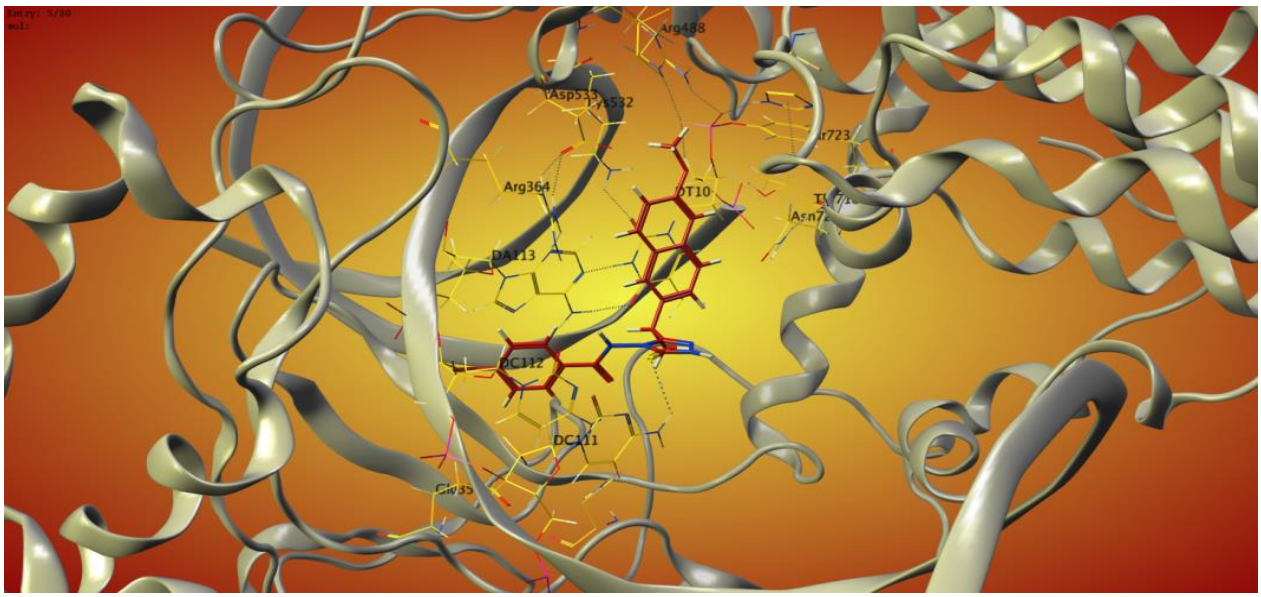

Figure (5) Vb with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (3D).

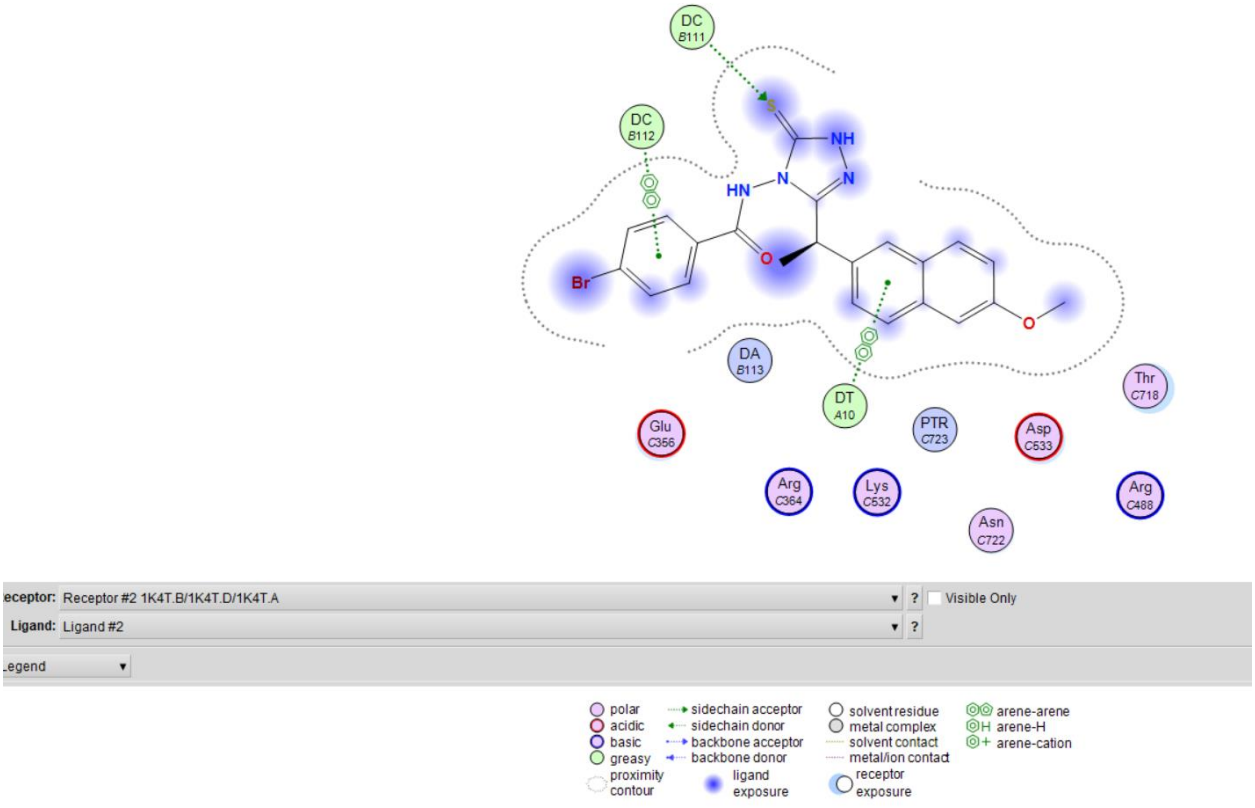

Figure (6) Vb with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (2D).

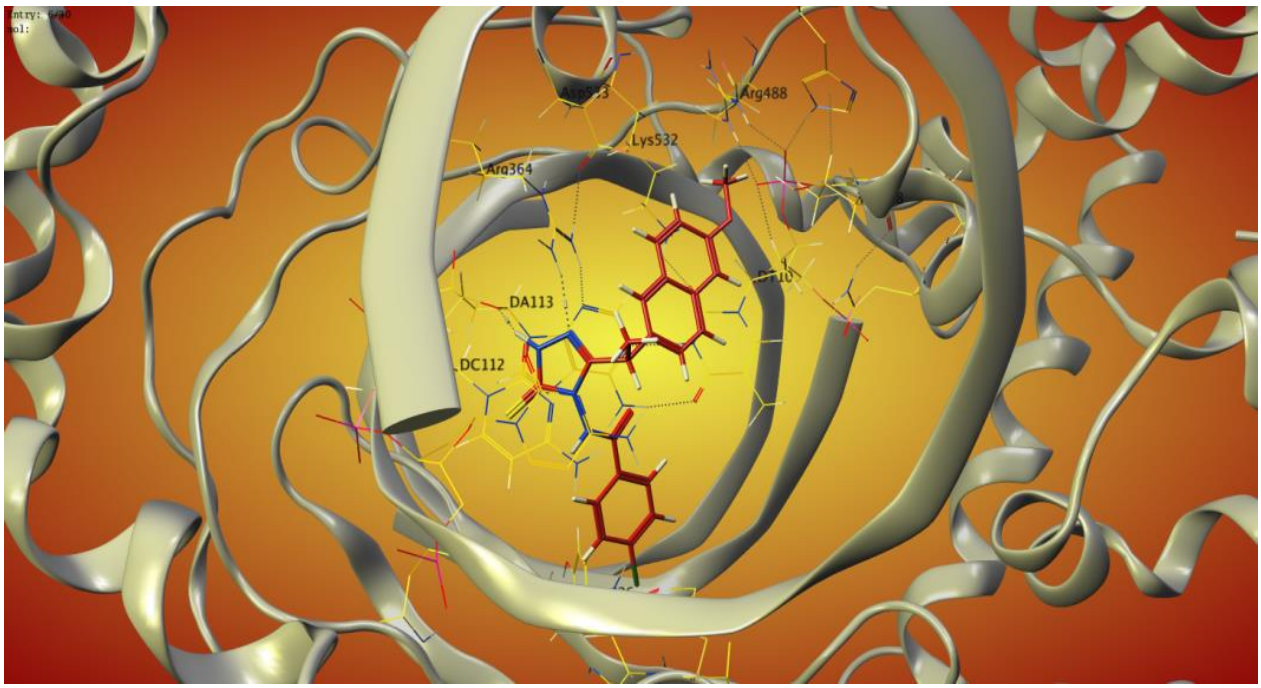

Figure (7) Vc with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (3D).

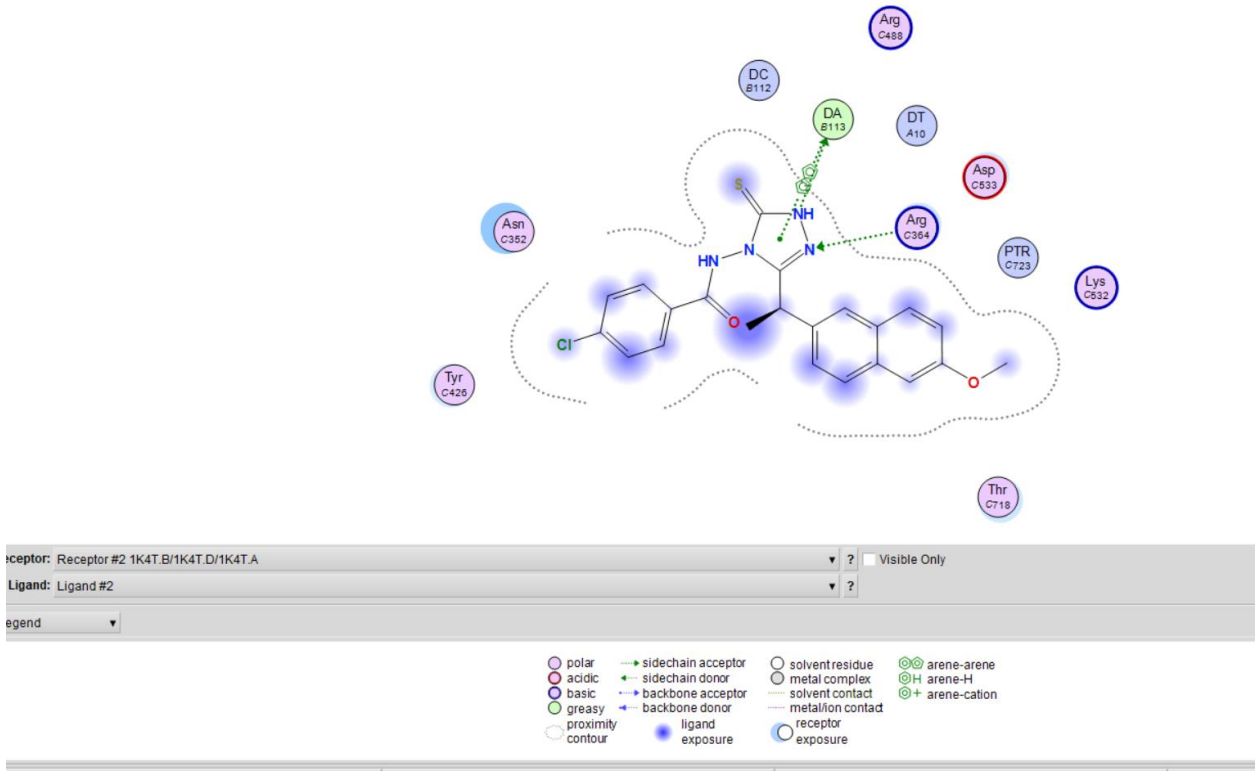

Figure (8) Vc with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (2D).

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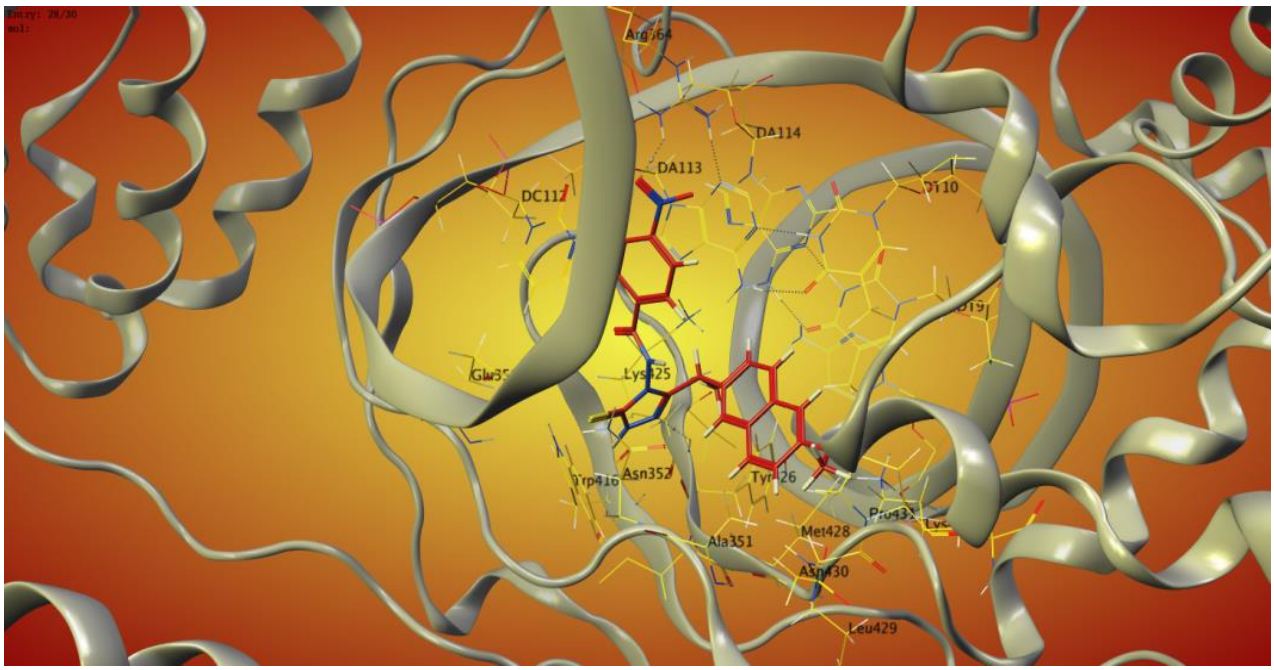

Figure (9) Vd with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (3D).

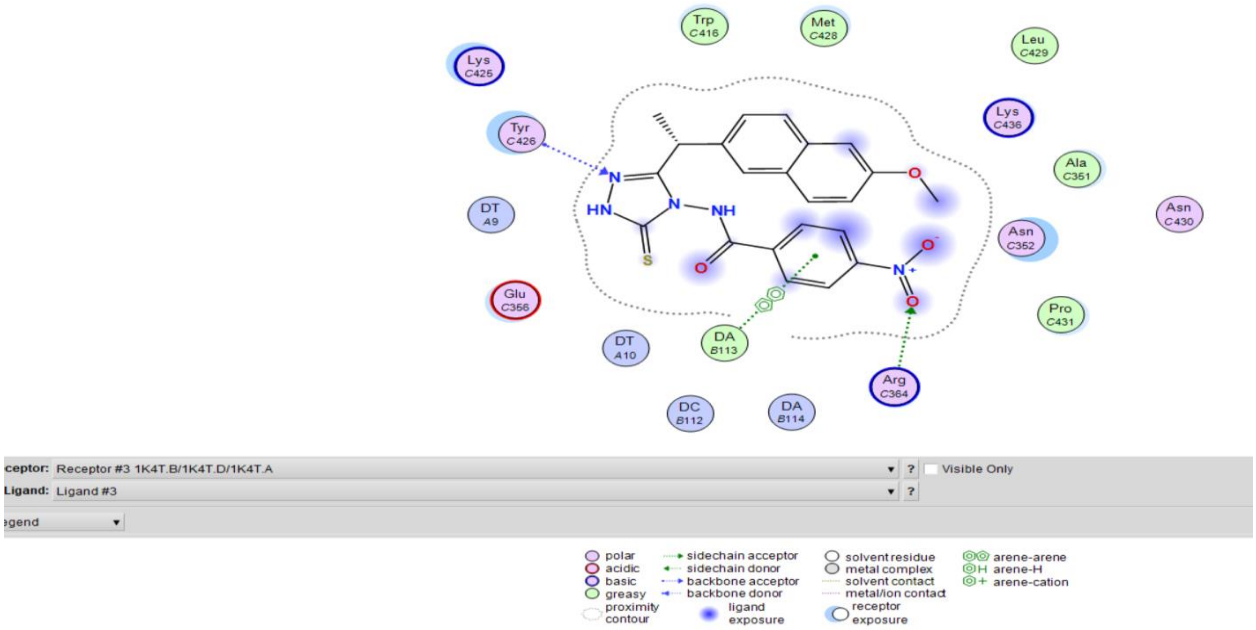

Figure (10) Vd with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (2D).

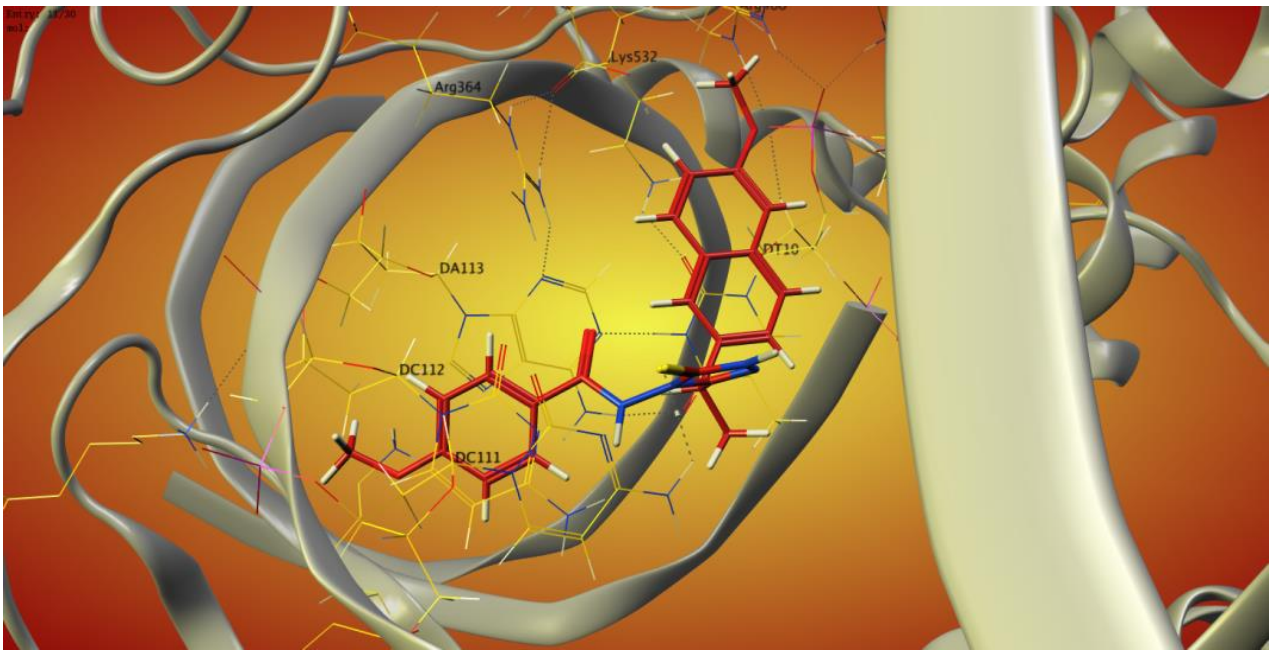

Figure (11) Ve with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (3D).

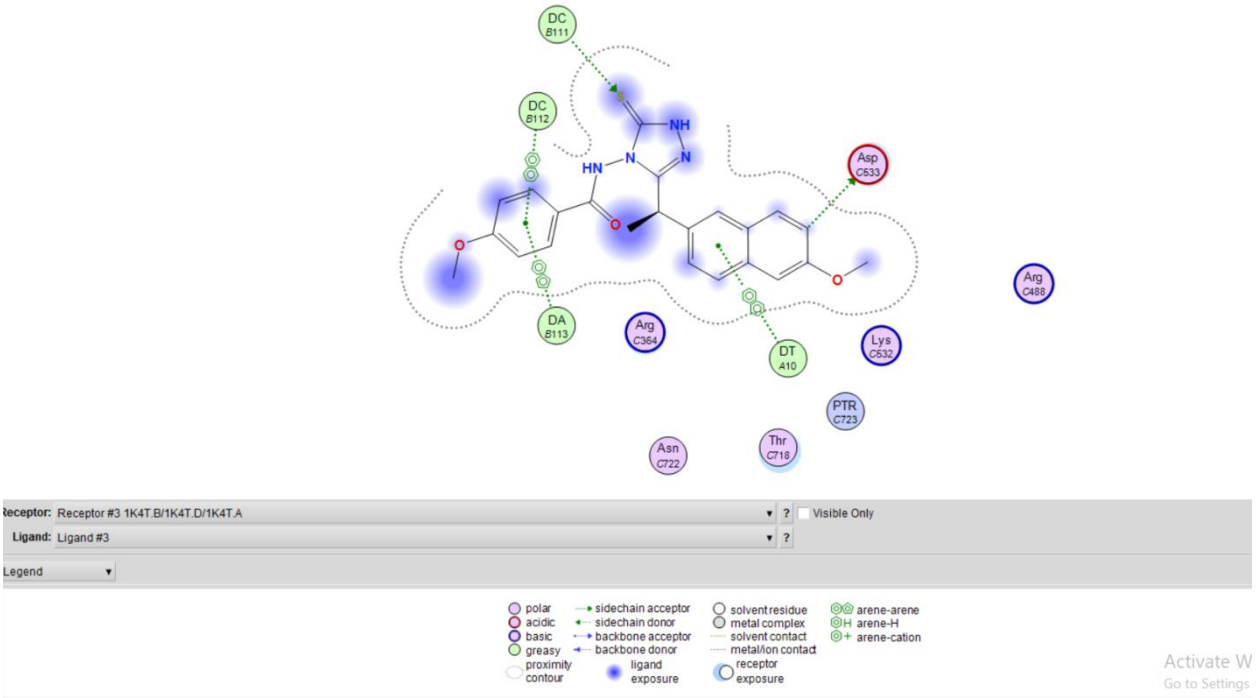

Figure (12) Ve with Human DNA Topisomerase I (70 KDA) (PDB code:1K4T) (2D).

4. CONCLUSION

This study designed Naproxen bearing 1,2,4-traizole moeity and evaluated them by using in-silico techniques. The Molcular Operating Environment docking results determined the potency as anticancer towrds overian cancer, with the most of the tested compounds are showing good binding affinity with target proteins relative to the reference Topotecan. This prove the role of substituted triazole ring and in giving flexibilty and increase the chance of the interaction with the receptor, also the role of benzoyl chloride derivatives where they are differ in the interaction depending on the groups substitued on position 4 on benzen ring.

5. References

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