INSILICO STUDY OF NOVEL TOPOISOMERASE II INHIBITORS AS ANTICANCER AGENTS

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ABSTRACT:

A molecular docking study was employed to investigate their binding and functional properties as TOP2a inhibitors, using the iGEMDOCK version 2.1, where they showed very interesting ability to intercalate the DNA–topoisomerase complex. Compound **2** showed high energy values/highest docking score (−123.4) and revealed the highest enzyme inhibition activity. The best hit compounds exhibited highly potent TOP2a inhibitors compared to the reference ciprofloxacin. DNA topoisomerases play a major role in DNA relaxation. Hence these enzymes are important targets for cancer drugs. DNA topoisomerase inhibitors bind to the transient enzyme–DNA complex and inhibit DNA replication. Molecular docking studies showed that ciprofloxacin has shown formation of hydrogen bond and good binding affinity with human Topo2a. Hence proposed molecules may inhibit the activity of enzyme topoisomerase by binding at its active site. Compound 2, compound 7, compound 6 and compound 8 are predicted to be the most potent inhibitors among the ten proposed molecules docked. GLN773, ASN770, LYS723 and TRP931 amino acid residues of Topo2a are involved in binding with proposed molecules. Our in silico study suggests that proposed molecules could be repositioned as DNA topoisomerase II inhibitors hence can be used as anticancer drugs. In vitro and in vivo experiments need to be done to confirm their efficacy.

Keywords: Docking, Chroman derivatives, Topoisomerase IIa inhibitors, Anti-cancer activity.

1. INTRODUCTION :

Cancer is group of diseases in which unwanted or uncontrolled grow of cells with the potential to spread to other parts of the body.[1][2] They form a subset of neoplasms. A neoplasm or tumor is a group of cells that have undergone unregulated growth and will often form a mass or lump, but may be distributed diffusely.[3][4]

1.1 TYPE OF TUMORS: Table no.1 indicates two types of tumors [5].

Table (1) Type of Tumors

Benign	Malignant
In this tumor rate of growth of tumor is slow and consistent.	In this tumor rate of growth of tumor is faster and irregular.
This tumor is small in size.	This tumor is larger in size.
This is well differentiated.	This is poorly differentiated.
In this type of tumor necrosis is not observed.	In this type of tumor necrosis is observed.
Eg.:adenomas(epithelial tissue that covers gland) Papillomas (skin, breast, cervix)	Eg.:Sarcomas(connective tissue, muscle) Carcinomas(organ and gland tissue)

1.2 Type of cancer:

- **Carcinoma**

  They are formed by epithelial cells, which are the cells that cover the inside and outside surfaces of the body.

- **Sarcoma**

  Sarcomas are cancers that form in bone and soft tissues, including muscle, fat, blood vessels, lymph vessels, and fibrous tissue.

- **Leukemia**

  Cancers that begin in the blood-forming tissue of the bone marrow are called leukemia. These cancers do not form solid tumors. Instead, large numbers of abnormal white blood cells (leukemia cells and leukemic blast cells) build up in the blood and bone marrow, crowding out normal blood cells.

- **Lymphoma**

Lymphoma is cancer that begins in lymphocytes (T cells or B cells). These are disease-fighting white blood cells that are part of the immune system. **[6]**

1.3 SIGNS AND SYMPTOMS :

Generally, no symptoms, it appears on ulcerates. It is a great imitator. There is chances to become anxious and depressed post-diagnosis.[7] Generally produce mass of tumor it can block bronchus resulting cough and pneumonia. Difficult to swallow.[2] tumors in breasts or testicles can observable as lumps. In that blood in urine. Generally observed pain, weight loss, fatigue etc. [9] it can produce Hodgkin disease, leukaemia, liver and kidney cancer and sometimes seen fever. Sometimes maybe myasthenia gravis in thymoma and also clubbing in lung cancer. It can spread locally in skin and other organ. It depend on the tumor location and maybe enlarged lymph nodes, enlarge spleen, enlarged lever etc. there is also neurological symptoms. [8]

1.4 CAUSES:

There is more chances to produce cancer (90-95%). There are so many factors like, genetic mutations, environmental factors etc.[10] There is less chances by heredity.[11] Generally produce by chemicals (like alcohols, smokes can damage oesophagus and pancreas)[14] , obesity (in that includes colon cancer, gastric cancer etc.)[10][15], infections (viruses like oncoviruses, human pappiloma viruses, epstain-barr virus, hepatitis B & C etc.)[16][17], stress, radiation (in that generally skin cancer by UV radiation, gamma radiation etc.)[10][12][18] And lack of physical agents (like asbestos, cobalt, nickel etc my produce oesophageal and broche cancer) [10][19]. There is can't identify the actual reason of particular cancer. There is rare transmission in pregnancy and occasional organ donors. It is not transmissible disease. [13]

1.5 STATISTIC OF CANCER :

Cancer is widely distributed in the 21st century. It is a most death causing in worldwide. According to WHO there are 12 million deaths yearly. In 2000 there is a changing in lifestyle and precaution is a right way to prevent and treat cancer. According to research there is 635000 deaths from cancer in 2008 and 395400 in 2010. There are 1,735,350 new cases diagnosed and 609,604 peoples die in United States. According to 2018 the most common like breast cancer, lung cancer, bronchus cancer, colon cancer, rectum cancer, skin cancer and rectum cancer. There is also included leukaemia, pancreatic,

thyroid and liver cancer. In the world 12.7 million cancer cases and 7.6 million deaths in 2008. There are most frequently diagnosed cancers are breast cancer in women and lung cancer in males. There are 439.2 per 100,000 men and women cases in 2011-2015. In the United States there were 15.5 million cases of cancer estimated in 2016. As per research 20.3 million cases expected in 2026. In 2013-2015 the data is shown approximately 38.4%men and women will be diagnosed from the studies there were 15,270 children (age: 0-19) diagnosed and 1,790 children died in 2017. [20]

1.6 CELL LIFE CYCLE:

Every cell in the body goes through a life cycle. Cell grow and divide to replace cells that are lost because of normal and tear injury. Some cell such as epithelial cell. Making the surface of body (skin) & lines of hollow organs and gland reproduce quickly. Other cell like never cells, grows slowly.

Both normal cell &cancer cell goes through a sequence of steps, or phases, when they form a new cell, this is called cell cycle. [21]

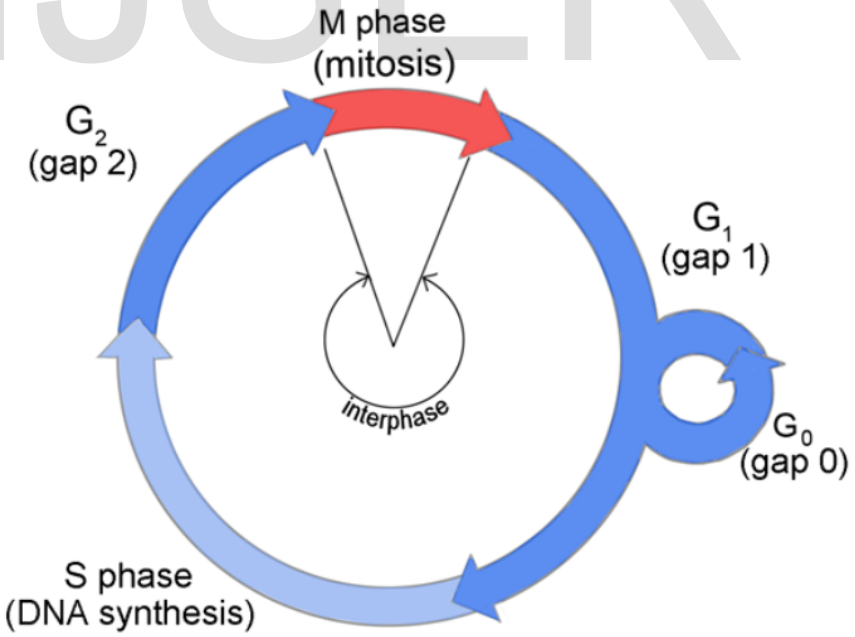


Figure (1) Cell cycle

Table (2) cancer cell cycle[21]

PHASE		DESCRIPTION
Interphase	G_0	This phase is resting phase (also called dormant phase.) The cells perform all of its normal functions but are not preparing to divide. Some cells divide often and either are G_0 for short amount of time or skip G_0 other cells do not divide very often and are in the G_0 phase for many years. When the cells receive the signal to divide, it moves in to G_1 phase of the cell cycle.
	G_1	G_1 is first growth phase. The cells prepare to undergo cell division. The cell still performs all of its normal function, but starts to get bigger. The cells begin to make copy of parts (organelles). It also begins to make more protein to ready to get divide. The time for this phase varies from about 8 hours to several days, weeks or months.
	S	This phase is synthesis phase. The cell copy its DNA (DNA synthesis) to make 2 sets of chromosomes – 1 set for each new cell. This phase last about 6-8 hours.
	G_2	Gap 2 is second growth phase. The cell makes more protein in preparation for cell division. This phase last about
Prophase Metaphase Anaphase Telophase	M	This phase is mitosis phase. The cell divides in to two new cells, which occurs in four stages (Prophase, Metaphase, Anaphase, telophase). The mitosis phase last about 1-3 hours.
After mitosis, a cell either re-enter the G_1 phase or goes into the resting phase(G_0) where it may later re-enter the cell cycle.		

1.7 CANCER TREATMENT BEASED ON CELL CYCLE :

The cell cycle is important in cancer treatment because some therapies work best when cell are actively or quickly dividing.

For example, some chemotherapy drug work by attacking cells in particular phase of the cell cycle (such as G_0, S, or G_2), while radiation therapy seems to be most effective when cells are undergoing cell division (in the M-phase). [21]

1.8 ROLE OF TOPOISOMARESE II RECEPTOR:

After the cut, the ends of the DNA are separated and the second double DNA passes through the gap. After passage, the truncated DNA is recombined. This reaction allows type II topoisomerases to increase or decrease by two units the number of DNA loop beams and promotes the removal of chromosomes. Reactions associated with an increase in excess stretching require two ATP molecules. For example, DNA gyrase, a type II topoisomerase, found in E. coli and most other prokaryotes, introduces negative hyperpigmentation and reduces the number of bands by 2. The gyrase is also able to eliminate the knots from the bacterial chromosome. Along with gyrase, most prokaryotes also contain a second type IIA topoisomerase, called topoisomerase IV. The Gyrase and the topoisomerase IV differ in their C-terminal regions, which as expected, dictates the substrate specificity and functionality of these two enzymes. A fingerprint indicates that gyrase, which forms a 140-pair trace and surrounds DNA, introduces a negative supersaturation, while topoisomerase IV, which forms a trace of 28 base pairs, does not surround DNA. Eukaryotic type II topoisomerase cannot introduce supercoils of DNA. Can only relax them.The function of type IIB topoisomerases are less understood. Unlike type IIA topoisomerases, type IIB topoisomerases cannot simplify DNA topology (see Below), but have several structural features with type IIA topoisomerases.

Type IIA topoisomerases are required to separate the involved daughter strands during replication. This function is considered to be performed topoisomerase II in eukaryotes and topoisomerase IV in prokaryotes. Failure to separate these clones leads to cell death. Type IIA topoisomerases have a special ability to relax DNA in a state at thermodynamic equilibrium different from topoisomerases of formulas IA, IB and IIB.This ability is known as topology simplification. it was first identified by Rybenkov et al. (Science 1997). ATP hydrolysis is the drived this simplification, but there is still a lack of

a clear molecular mechanism. Various models have been proposed to explain this phenomenon, including two models which rely on the ability of type IIA topoisomerases to recognize curved DNA duplexes (Vologodskiy, Proceedings of the National Academy of Sciences 1999). Biochemistry, electron microscopy and recent DNA topoisomerase II structures show that type IIA topoisomerases are linked to DNA apices, supporting this model. [22]

1.9 TOPOISOMERASE II INHIBITOR:

Topoisomerase inhibitor is one of the best target for anti-cancer activity. Topoisomerase inhibitors are chemical compounds that block the fuction of topoisomerase(topoisomerase I and II), which is a type of enzyme that controls changes in DNA structure by catalytic cleavage and binding of the phosphodiester ligand of DNA strands during the normal cell cycle. In last few years, topoisomerases have become popular targets for cancer chemotherapy treatments. Topoisomerase inhibitors are believed to block the ligation of the cell cycle, creating single and double-stranded fragments that affect the integrity of the genome. The introduction of these holidays leads to apoptosis and cell death.

Topoisomerase inhibitors can also function as antibacterial agents.eg.: quinolones (including nalidixic acid and ciprofloxacin) have this function. Quinolones is bind with these enzymes and inhibit them from decatenation replicating DNA.

These inhibitors are divided into main two classes: 1. Topoisomerase poisons in which target the topoisomerase-DNA complex, and 2.topoisomerase inhibitors in which intercept catalytic turnover.

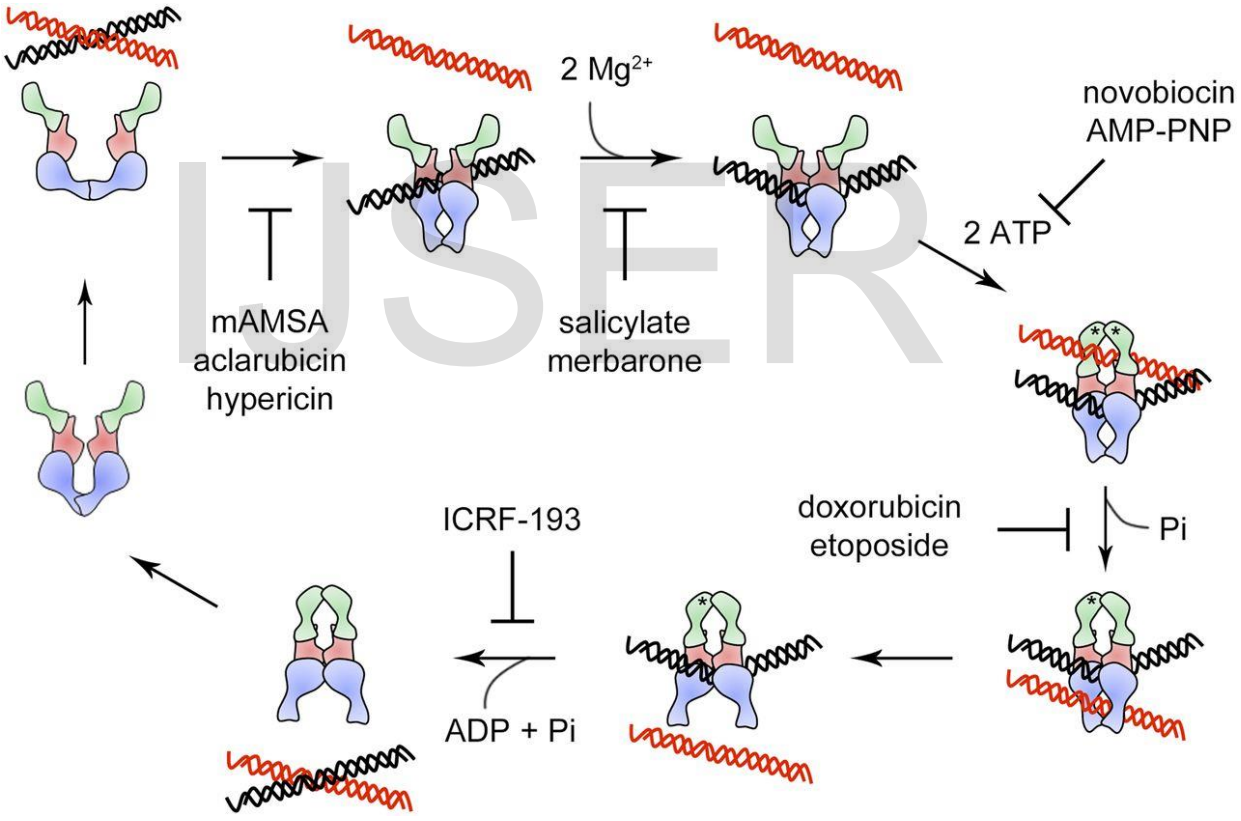
1. **Topo II poisons**

➢ Examples of topoisomerase poisons following:

- *eukaryotic* type II topoisomerase inhibitors (topo II): amsacrine, etoposide, etoposide phosphate, teniposide and doxorubicin. These drugs are used in anti-cancer therapies.
- *bacterial* type II topoisomerase inhibitors (gyrase and topo IV): fluoroquinolones. These drugs are use in antibacterials and include fluoroquinolones such as ciprofloxacin.

Some type of these poisons encourages the forward cleavage reaction like fluoroquinolones, while other poisons inhibit the re-ligation of DNA like etoposide and teniposide.

Topoisomerase IIA-poisons can preferably target prokaryotic and eukaryotic enzymes, making them attractive to drug candidates. Ciprofloxacin targets prokaryotes more than a thousand times more than placebo II eukaryotes. However, ciprofloxacin is a dose-dependent potent type II poison, which explains the enormous destruction of tissue cells. This low safety profile is one of the reasons why the FDA has reported that fluoroquinolones are used only as a last resort. [23]



Figer (2) Topoisomareaes II inhibitors[24]

2. Topo II inhibitors

These inhibitors target on the N-terminal ATPase domain of topo II and prevent topo II from turning over.

- Examples of topoisomerase inhibitors:

- ICRF-193-Classen (Proceedings of the National Academy of Sciences, 2004) solves the structure of this compound associated with ATPase, which indicates that the drug binds uncompetitive and blocks the dimerization of the ATPase domain.
- genistein.

1.10 MOLECULAR DOCKING :

Drug exerts its biological activity by binding to the pocket of receptor molecule (usually protein). In their binding conformations, the molecules exhibit geometric and chemical complementarily, both of which are essential for successful drug activity. The computational process of searching for a ligand that is able to fit both geometrically and energetically into the binding site of a protein is called molecular docking.

Molecular docking helps in studying drug/ ligand or receptor/ protein interactions by identifying the suitable active sites in protein, obtaining the best geometry of ligand - receptor complex and calculating the energy of interaction for different ligands to design more effective ligands.

The target or receptor is either experimentally known or theoretically generated through knowledge based protein modeling or homology modeling. The molecular docking tool has been developed to obtain a preferred geometry of interaction of ligand - receptor complexes having minimum interaction energy based on different scoring functions viz. only electrostatics, sum of steric and electrostatic (parameters from MMFF force field) and Dock Score. This utility allows one to screen a set of compounds for lead optimization. [25]

2 MATERIALS AND METHODOLOGY

2.1 PROTOCOL FOR DOCKING STUDY

1] PREPARATION OF LIGANDS

The compounds involved in this study, ligands were studied for their binding activities to 2xct receptor were sketched in Chem Draw ultra 8.0 software [Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2003)]

These structures were converted to 3D structures using Chem3D ultra 8.0 software and the constructed 3D structures were energetically minimized by energy minimization technique Allinger's Molecular Mechanics (MM2) force fields followed by geometry optimization using semi empirical Quantum mechanics based on AM-1 (Austin Model-1).

2] GENERATION OF RECEPTOR

The X- ray structure of topoisomerase II inhibitor from cancer with ciprofloxacine resolution of 2.1 A˚ reported Cellitti, S.E. et.al was retrieved from the protein Data Bank (Entry code) and used as target for modeling studies.

Since the position of most water molecules in the crystal structure complex are unlikely to be conserved, water molecules were excluded before the docking protocols.

In the receptor, binding site was defined by amino acid included into 2.1 A˚. The mode of interaction of substituted Chroman derivatives to 2xCT was used as standard docked model.

3] DOCKING OF LIGAND AND RECEPTOR

- Export receptor which was prepared in last step into iGEMDOCK version 2.1 docking software.
- Select prepare binding site.
- Set the population size 200 with 20 generation and two number of solutions.
- Now select ligand in mol file from where saved and select apply and dock, so docking process will start.
- In the result of docking, there is total binding energy.
- Save the interaction analysis and interaction profile and exported in excel. [26]

2.2 Ramachandran plot:

The Ramachandran diagram is also known as the Ramachandran diagram or [φ], originally developed in 1963 by G. N. Ramachandran, K. Ramakrishnan and V. Saseiseharan. The ramachandran plot is a wey to show the energetically allowed regions for backbone dihedral angles ψ against φ of amino acid residues in protein structure, it is called as φ and φ' by Ramachandran. The peptide bond is normally 180^o at the ω angle, since the partial double-stranded character retains the planar peptide. The figure in top right shows the allowed φ, ψ backbone conformational regions from the Ramachandran et al. in 1963 and 1968 hard-sphere calculations: the full radius in solid outline, reduced radius in dashed, and relaxed tau (N-Cα-C) angle in dotted lines. Because dihedral anglevalues are circular and 0° is the same as 360°, the edges of the Ramachandran plot "wrap" right-to-left and bottom-to-top. For instance, the small strips of allowed values along the lower-left edge in the plot are a continuation of the large, extended-chain region at upper left.

A Ramachandran plot is also can be used in two somewhat different ways. first is the top right site in show the theory which values, or conformations, of the ψ and φ angles are possible for an amino-acid residue in a protein. A second is to show the empirical distribution of datapoints observed in a single structure at the plot in right, here in usage for structure validation, or else in a database of many structures as in the lower 3 plots at left. Either case is usually shown against outlines for the theoretically favored regions.

To see the correctness of protein we were used ramachandran plot (fig. 3) which gives ψ and φ angles allow as analysing the structure of protein. We found more than 90 % of amino acids in the range. [27]

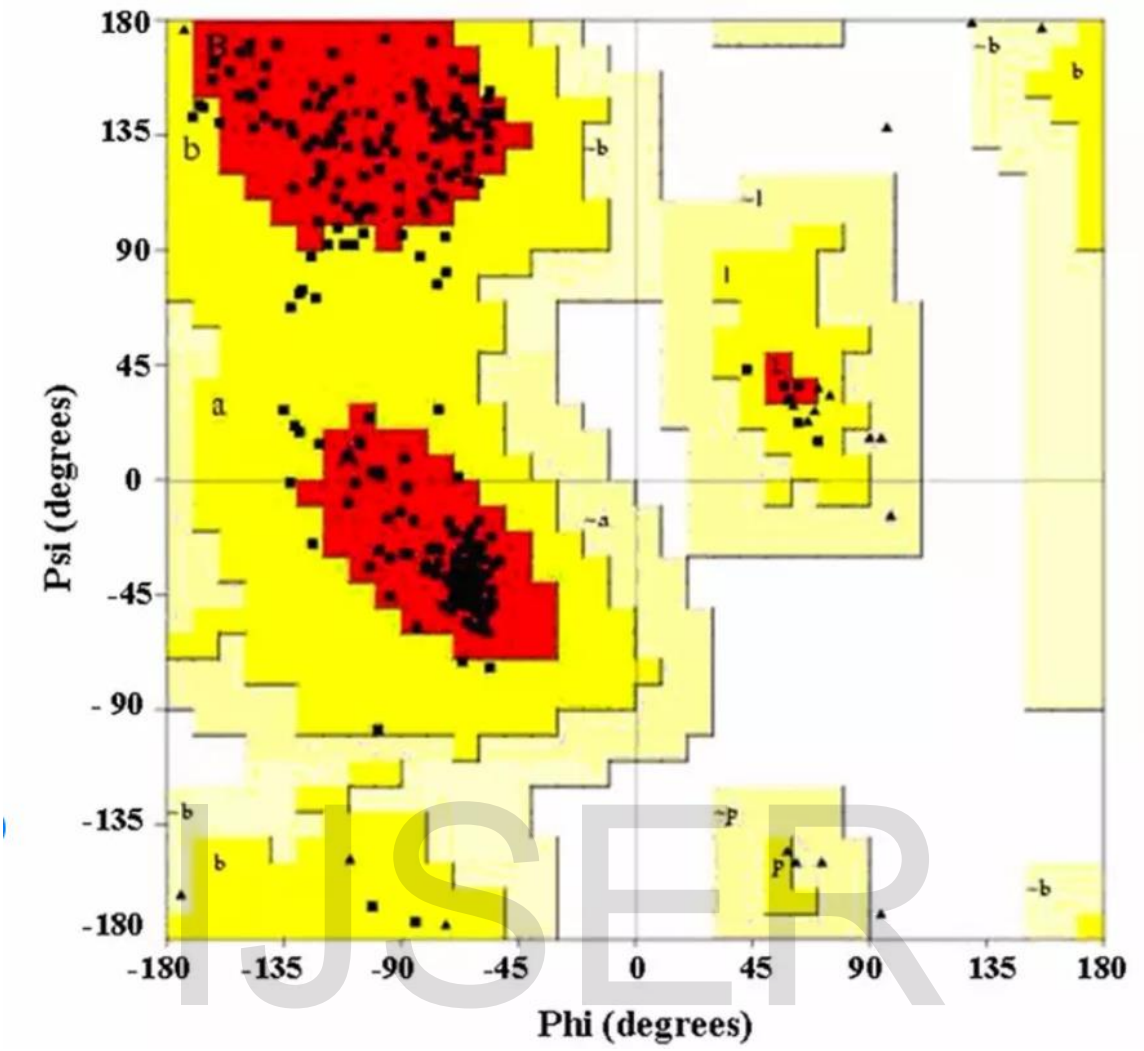
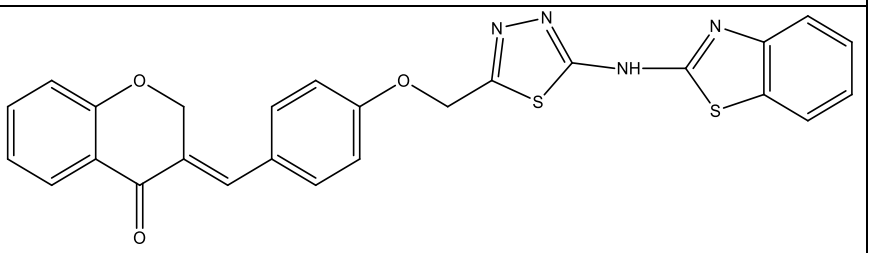
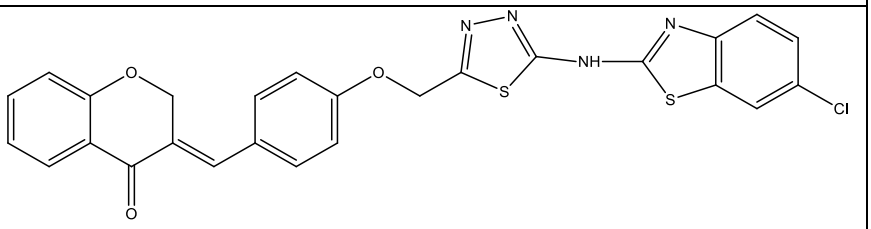
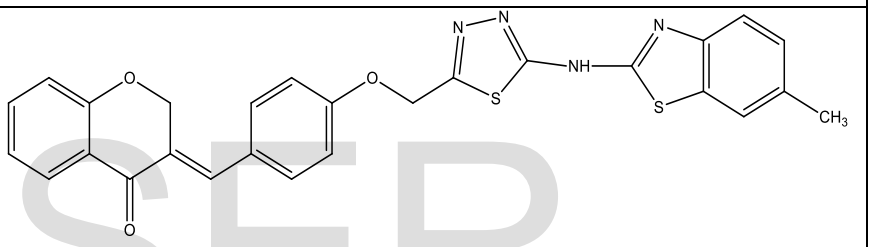
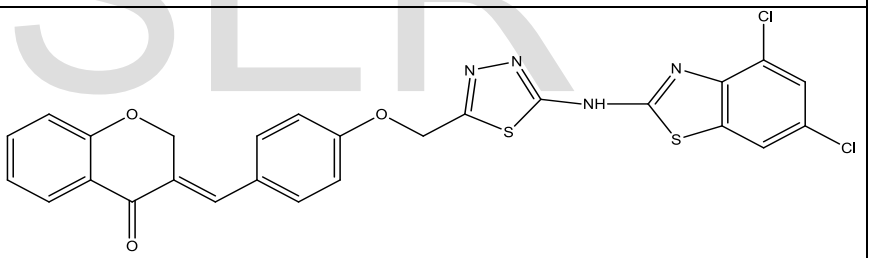
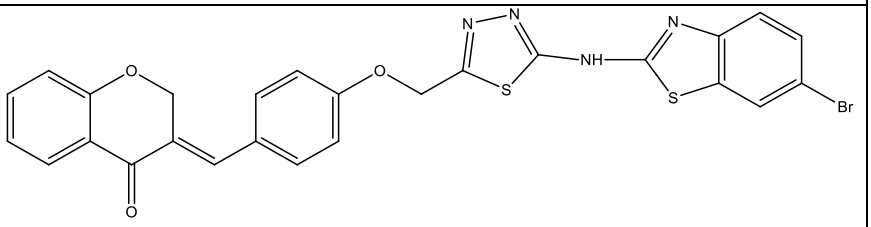
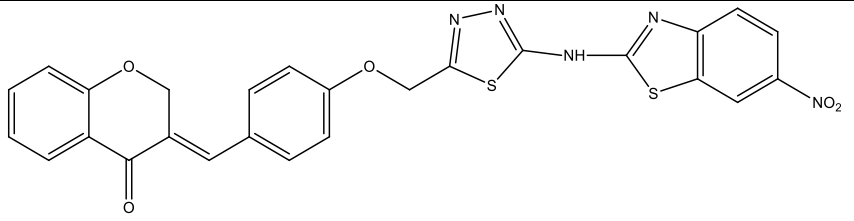


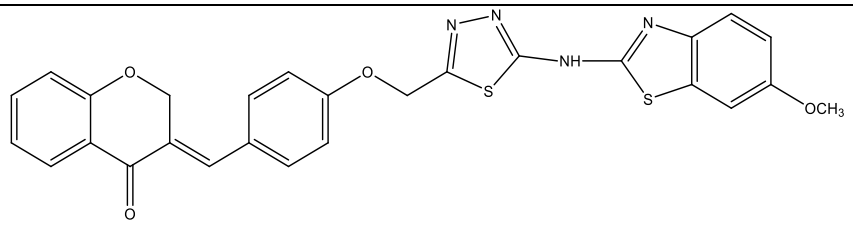
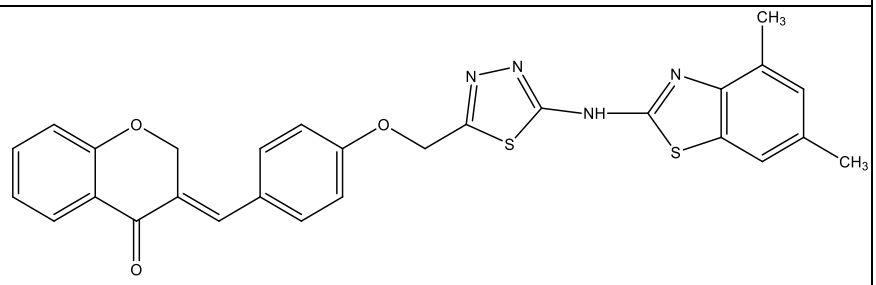
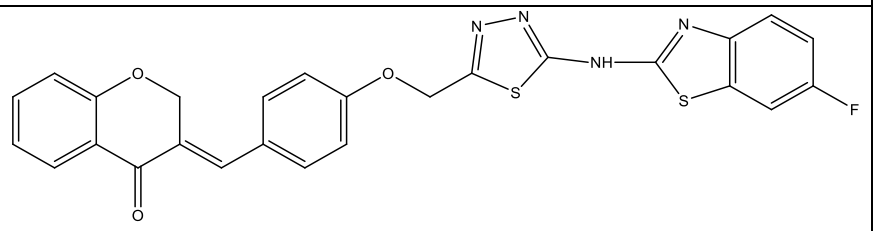
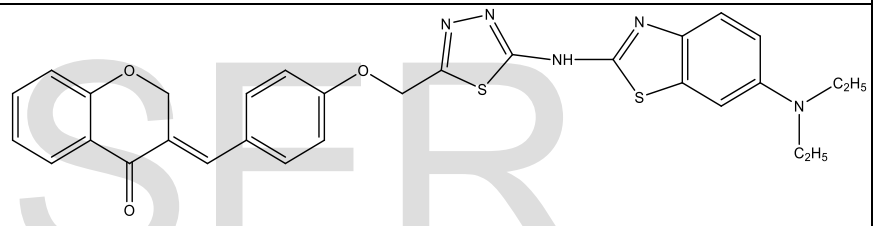
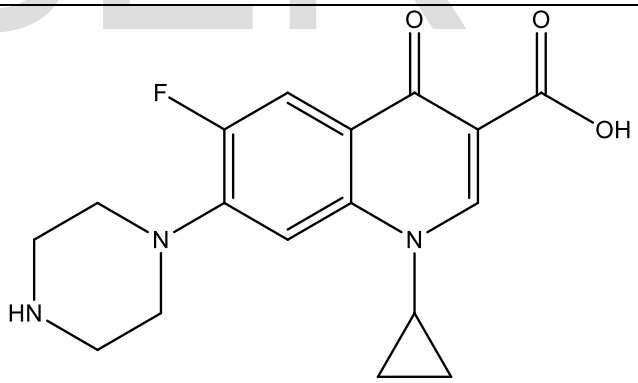
Figure (3) Ramachandran plot of PDB: 2XCT

2.3 LIST OF COMPOUNDS

For the present study we were designed some compounds based on the literature survey and analysed for in sillico topo II an inhibitory potency by comparing with active site ligand i.e. ciprofloxacin. The designed molecules contain various fragments like chroman, thiadiazole, benzothiazole, which are well known fragments of anticancer drugs. [28] ,[29], [30], [31]

Table (3) List of compounds

SR NO.	STRUCTURE NAME	STRUCTURE
1	R1	
2	R2	
3	R3	
4	R4	
5	R5	
6	R6	

7	R7	
8	R8	
9	R9	
10	R10	
11	S1	

2.4 PHYSICOCHEMICAL PARAMETER

To be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery

process, at a stage when considered compounds are numerous but access to the physical samples is limited.

SwissADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILEDEgg, iLOGP and Bioavailability Radar.[32]

2.5 Lipinski Rule of five :

The first thorough analysis of the impact of physicochemical parameters was performed by Christopher Lipinski at Pfizer in the late 1990s. The rule of five analyses helped to raise awareness about properties and structural features that make more or less drug-like. The rule describes molecular properties important for drug's phanacokinetics in the human body, including their **absorption, distribution, metabolism and excretion ("ADME").** However, the rules do not predict whether a compound is pharmacologically active or not. The rule is important for drug development where a pharmacologically active lead structure is optimized step-wise for increased activity and selectivity as well as drug-like properties as described by Lipinski's rule.

The Lipinski's Rule of Five (Lipinski ***et al., 1997)*** states that an orally active drug should obey the following criteria:

1. Maximum 5 hydrogen bond donors.
2. Maximum 10 hydrogen bond acceptors.
3. **A** maximum molecular weight 500g/mol.
4. **A** partition coefficient log **P** less than 5.
5. Number of rotatable bonds not less than 10. [33]

3 RESULTS AND DISCUSSION:

3.1 Calculated Physicochemical Parameters

Table (4) Calculated Physicochemical Parameters

Sr No.	Compound Code	Molecular Weight	H-Bond Donors	H-bond Acceptors	clogp	Lipinski Alert
1	R1	498.58	1	6	3.11	0
2	R2	533.02	1	6	3.58	1
3	R3	512.60	1	6	3.23	1
4	R4	567.47	1	6	4.05	1
5	R5	577.47	1	6	3.68	1
6	R6	543.57	1	8	3.08	1
7	R7	528.60	1	7	2.80	1
8	R8	526.63	1	6	3.51	1
9	R9	516.57	1	7	3.48	1
10	R10	569.70	1	6	3.38	1
11	S1	331.34	2	5	1.28	0

Table (5) Docking score/energy obtained for all the molecules.

Sr no.	Compound Code	Total energy	VDW	H Bond	Electrostatic
1	R1	-103.706	-91.933	-11.7728	0
2	R2	-123.392	-107.48	-15.9124	0
3	R3	-114.66	-99.0206	-15.6392	0
4	R4	-120.055	-99.2811	-20.7737	0
5	R5	-110.399	-104.54	-5.85881	0
6	R6	-121.539	-102.02	-19.281	-0.237466
7	R7	-121.638	-93.3674	-28.2706	0
8	R8	-120.421	-108.392	-12.0286	0
9	R9	-113.512	-90.0616	-23.45	0
10	R10	-116.234	-97.7236	-18.5108	0
11	S1	-84.9209	-61.3367	-21.8668	-1.71742

3.2 INTERACTION OF MOLECULES WITH AMINOACIDS PRESENT IN PDB ID:2xCT

Table (6) Binding interaction observed between all designed molecules and topo IIa enzyme (pdb id: 2XCT)

Sr no.	Compound code	Energy	Name of H-BOND Amino acid	Name of vanderwaals Bond amino acid
1	R1	-103.6	Glu-1295, Aeg-1299	Asp-448,Trp-592, Glu-1295,Ser-1297, Arg-1299,Asg-1303, Asn-587,Asp-1096, Phe-1097,Met-1113, Asp-1114,Thr-1296
2	R2	-116.2	Asp-508, Asp-510, Asp-512, Asn-1109	Phe-1123,Asp-512, Arg-1033,Hig-1079, His-1081,Ser-1085
3	R3	-106.5	-	Asp-448,Agr-450, Trp-592,Arg-1293, Glu-1295,Leu-1298
4	R4	-130.4	Asp-1109, Ser-1112	Asp-1096,Phe-1097, Pro-1102,Phe-1110, Met-1113,Leu-1298, Arg-1485
5	R5	-108.8		Asp-1096,Phe-1097, Met-1113,Asp-1114, Thr-1296
6	R6	-117	Ser-445, Asn-587, Asn-1109	Phe-1110,Leu-1298

7	R7	-113.7	Asp-1096, Ser-1112, Asn-587	Asp-1096,Phe-1096, Phe-1110,Met-1113, Leu-1298,Arg-1485, Asn-587
8	R8	-106.7	Ser-1112	Asp-1096,Phe-1097, Phe-1123,Ser-1297, Leu-1298,Arg-1485, Ser-445,Asp-589, Trp-592
9	R9	-120	Asn-587, Asp-1114, Lys-1270, Asp-448	Asn-587,Asp-1096, Phe-1097, Met-1113, Asp-1114,Thr-1296
10	R10	-118.1	Asp-1096, Ser-1112, Asp-1114, Ser-445	Asp-1096,Phe-1097, Met-1113,Ser-1297, Leu-1298,Arg-1485, Ser-445,Asp-589, Trp-592
11	**S1**	-84.90	Asp-512, His-1081, Arg-1033	Glu-435,Phe-1123, Asp-512,Asp-508

Docking results obtained is reported in table no. (6) to know my best model of interaction with topoisomerase we re-docked ciprofloxacin and observed energy of -84.90 and hydrogen bond with (Asp-512,His-1081,Arg-1033), vander waals bond with(Glu-435,Phe-1123,Asp-512,Asp-508).

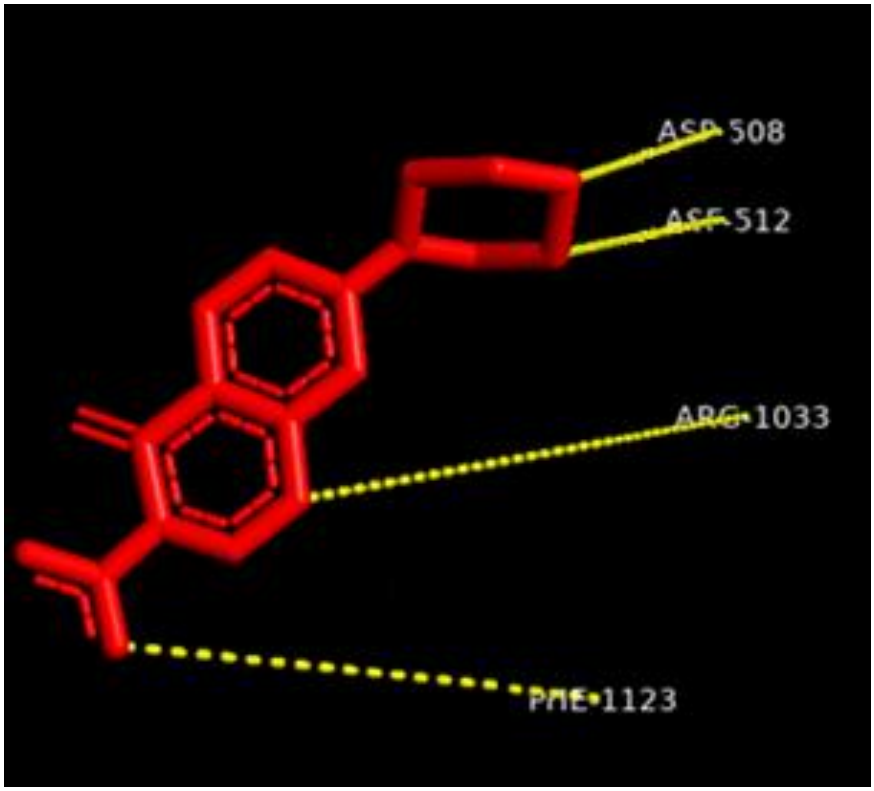


Figure 4. Standard molecule

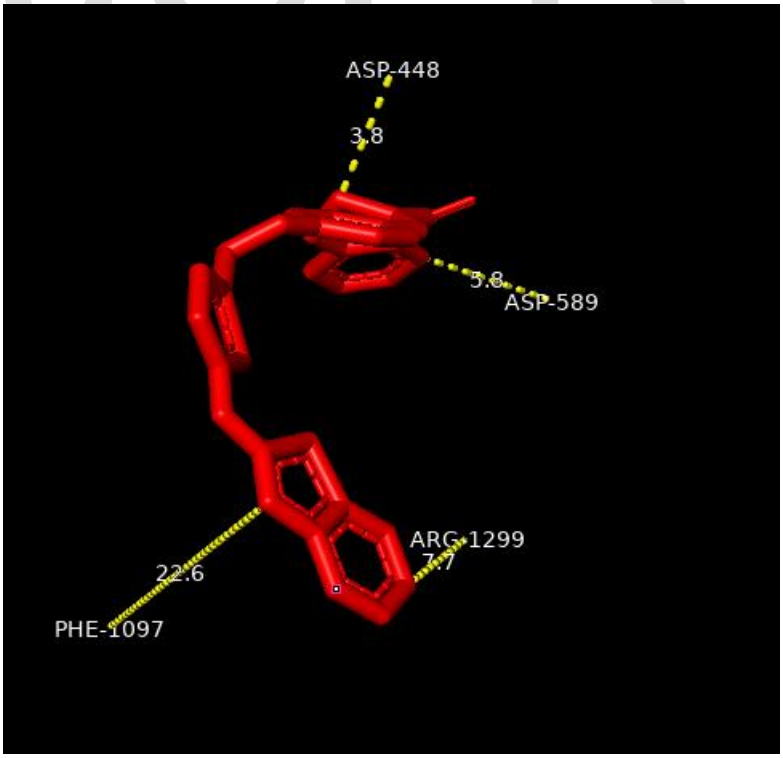


Figure 5. Compound-1

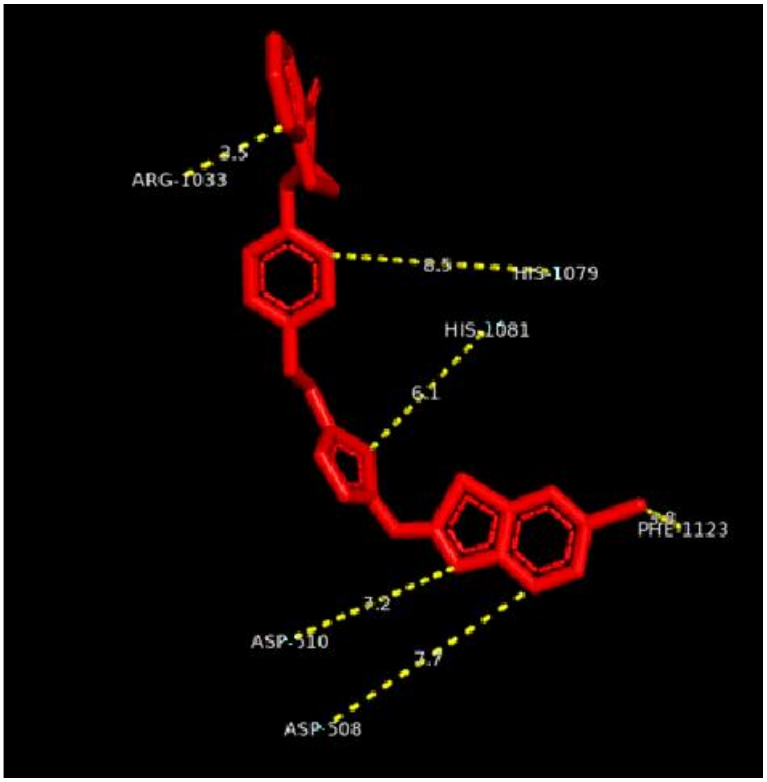


Figure 6.Compound-2

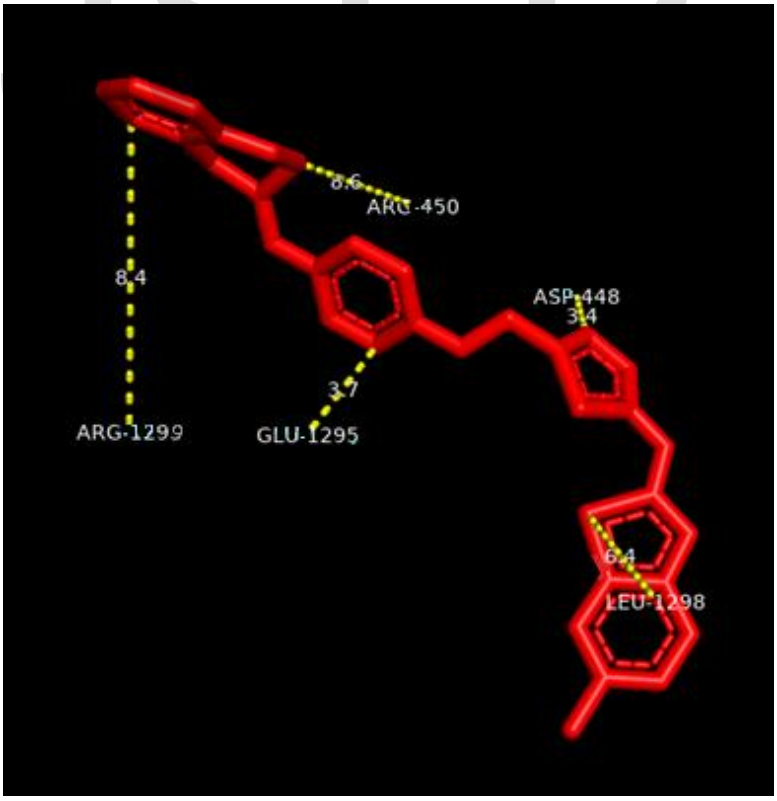


Figure 7. Compound-3

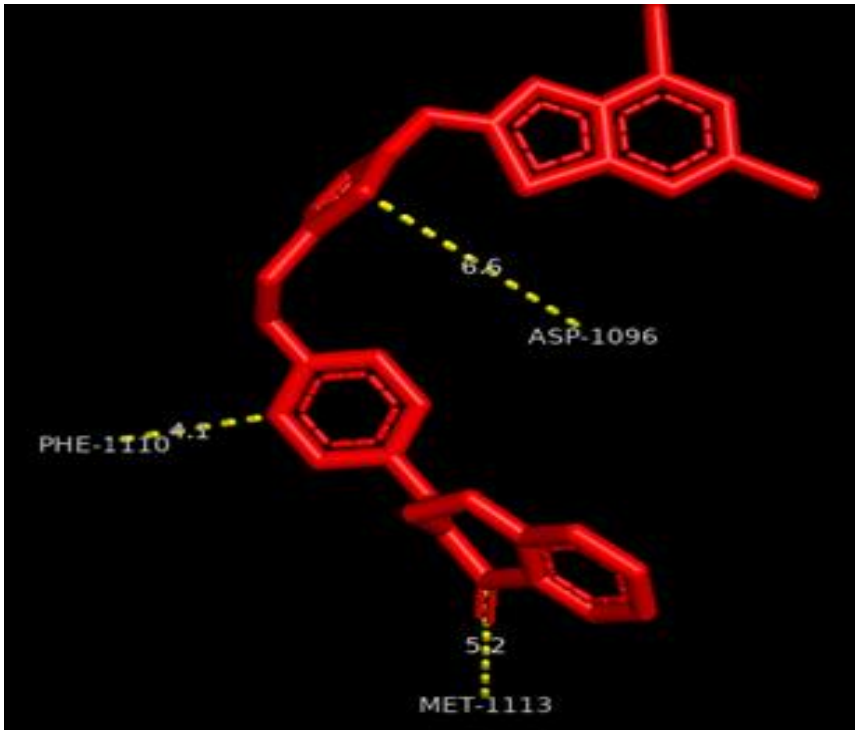


Figure 8. Compound-4

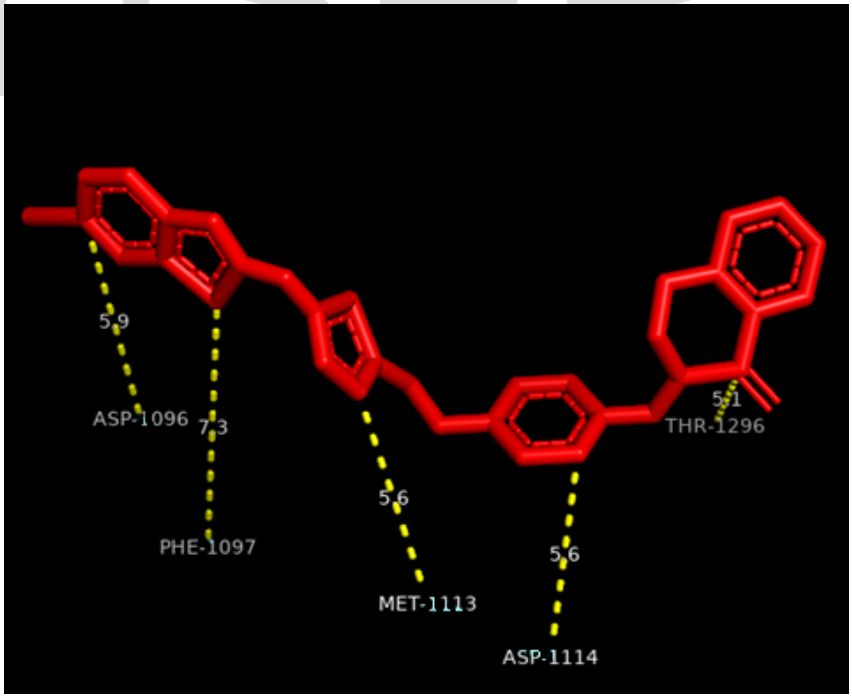


Figure 9. Compound-5

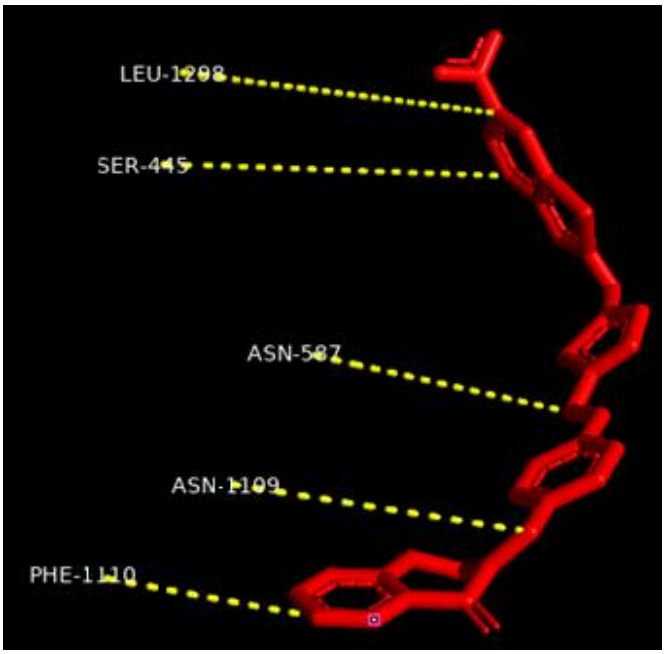


Figure 10. Compound-6

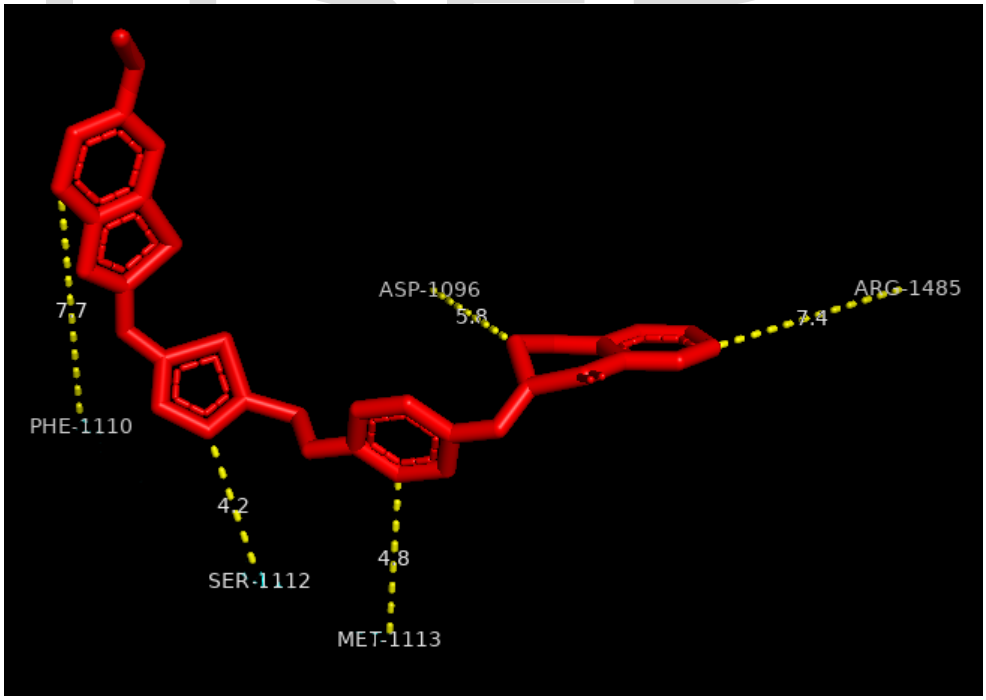


Figure 11.Compound-7

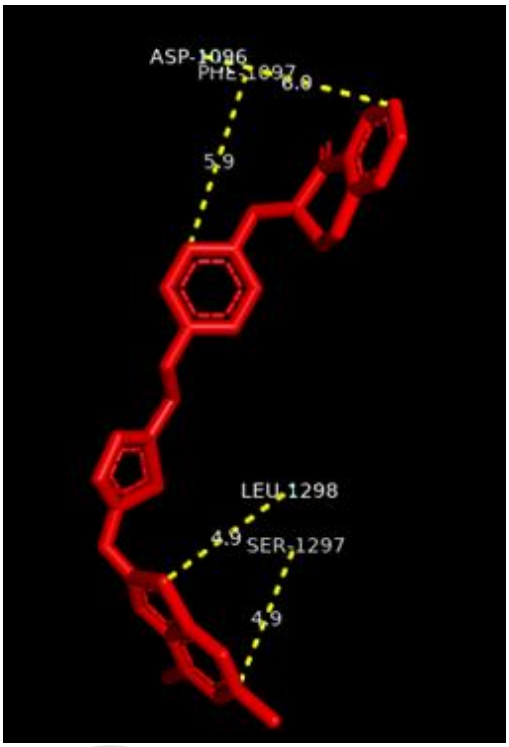


Figure 12.Compound-8

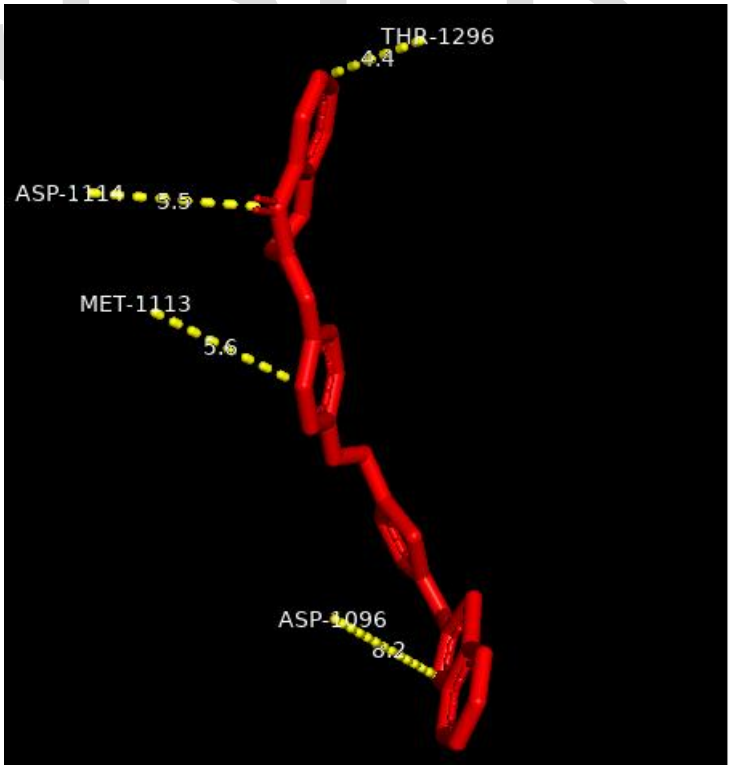


Figure 13.Compound-9

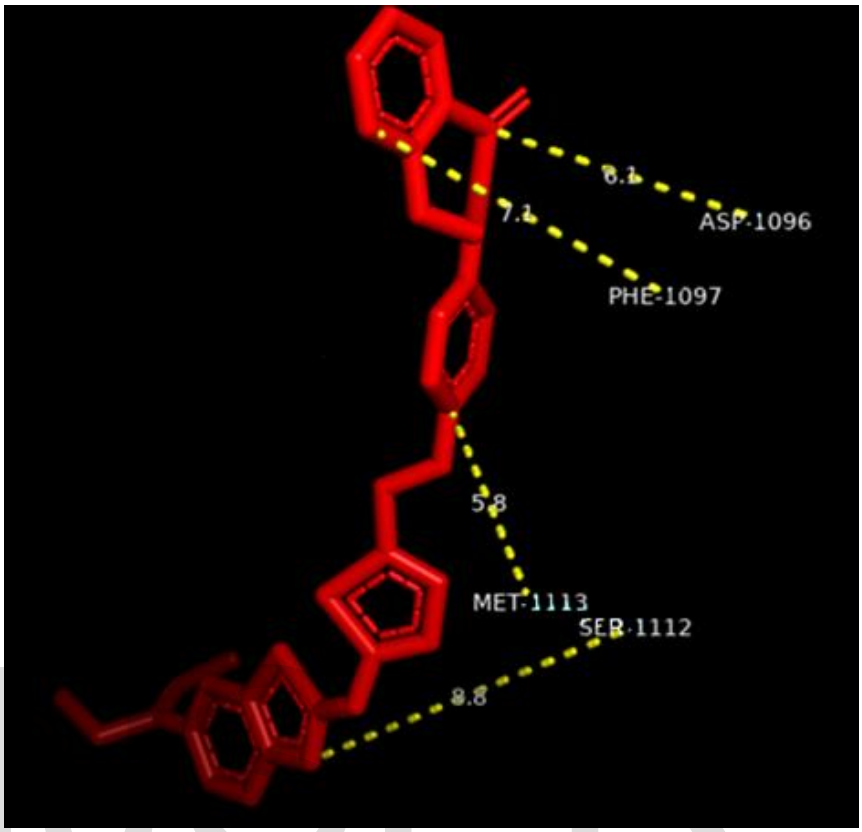


Figure 14.Compound-10

We were purposed 10 molecules all they are showing higher or batter energy then standard molecule. The molecule (2) showed highest energy in the series that is -123.40 and it showed hydrogen bond interaction with (Asp-508,Asp-510,Asp-512,Asn-1109) and also showed vander waals interaction with (Ahe-1123,Asp-512,Arg-1033,His-1079,His-1081,Ser-1085).while looking at other molecules in the series, single / double substituted molecule are good in energy for electron windrowing and electron donating group influence on energy is not observed.

4 CONCLUSION:

The present investigation compiles design of new topo IIa inhibitors, to do this we performed some literature survey and designed a 10 molecules, then this designed molecules were docked using the PDB ID 2XCT i.e. the twinned 3.35A structure of *S. aureus* Gyrase complex with Ciprofloxacin and DNA, obtained from https://www.rcsb.org/structure/2xct. Looking at results, we found that proposed molecules may inhibit the activity of enzyme topoisomerase by binding at its active site. Compound 2, compound 7, compound 6 and compound 8 are predicted to be the most potent inhibitors among the ten proposed molecules. The amino acids involved in binding with compound 2 are (hydrogen bond-Asp-508,Asp510,Asp512,Asn-1109, and vander waals bond Phe-1123, Asp-512, Arg-1033, His-1079, His-1081, Ser-1085), compound 7(hydrogen bond-Asp-1096, Ser-1112, Asn-587and vander waals bond-Asp-1096, Phe-1096, Met-1113, Leu-1298, Arg-1485, Asn-587), and compound 6(hydrogen bond- Ser-445, Asn-587, Asn-1109 and vander waals bond- Phe-1110, Leu-1298) Our in silico study suggests that proposed molecules could be repositioned as DNA topoisomerase II inhibitors hence can be used as anticancer drugs. In vitro and in vivo experiments need to be done to confirm their efficacy.

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