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ORIGINAL ARTICLE

MOLECULAR DOCKING STUDIES ON THE ANTI-CANCER ACTIVITY OF NOVEL TRI-SUBSTITUTED FLUORO INDOLE DERIVATIVES AGAINST HUMAN TOPOISOMERASE-II ENZYME USING IN-SILICO METHODS

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ABSTRACT

Background: Cancer remains the leading cause of the death worldwide and expected that annual cancer case will rising very rapidly and make the scenario even more troublesome as well as Due to drug resistance makes things even worse.

Method: Auto Dock 4.1 was used to evaluate selected tri-substituted fluoro indole molecules against human topoisomerase II and Discovery studio visualizer and marvin sketch was used to create 3D and 2D structure interaction. Tri-substituted fluoro indole derivatives were docked against the human topoisomerase II enzyme using in-silico methods and various web server was used to determine various parameters.

Results: Docking studies revealed that tri-substituted fluoro indole derivatives could be a good alternate against human topoisomerase II as an anti-cancer agent. Molecular docking score scored by fludarabine [-7.6, -7.6, -8.6, -7.7] kcal/mol with nine hydrogen bonds, S-2 [-8.8, -7.7, -9.6, -8.7] kcal/mol with elveven hydrogen bonds, and S-14 showed [-9.2, -8.2, -8.6, -8.6] kcal/mol with twelve hydrogen bonds respectively in chain-A, B, C, D with excellent drug likeness, good pharmacokinetics parameters, mild toxicity in In-silico model reveals that Tri-substituted fluoro indole derivatives could be a good alternate against human topoisomerase II as an anti-cancer agent.

Conclusion: Among twenty derivatives S-2 and S-14 showed potential inhibitory effect against 4R1F human topoisomerase II with excellent docking score, drug likeness, good pharmacokinetics parameters, mild toxicity in Insilco model.

Keywords: ***Indole, Docking, Cancer, Topoisomerase, DNA-gyrase***

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INTRODUCTION

Indole contain benzenoid nucleus combination of benzene and pyrrole and has 10 pi-electrons system which makes them aromatic in nature. Excessive pi-electrons delocalization on indole readily prone to electrophilic substitution1. Indole is an important heterocyclic system having broad spectrum biological activity, due to this researcher took interest to synthesize various scaffolds of indole for screening pharmacological activity[2]

Cancer remains the leading cause of the death worldwide and expected that annual cancer case will rising very rapidly, Soo discovery of more effective and safer drugs remains urgently needed[3]

Topoisomerases are enzymes that alter the topological state of DNA. These enzymes relax supercoiled DNA. Type II topoisomerases also catenate and decatenate closed circular duplex DNA. As well as implicated in several aspects of DNA metabolism and structure, including replication, sister chromatid exchange, transcription, organization of chromosomal loop domains, and chromosome disjunction at mitosis[4]

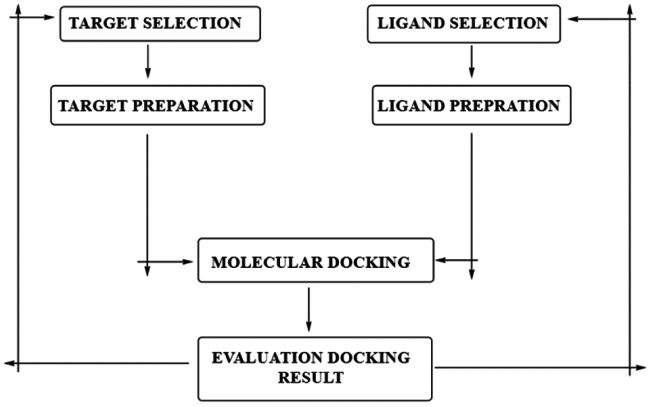
Topoisomerase II is a major target for antineoplastic agents. Topoisomerase II inhibitors are a heterogeneous group of compounds that might interfere with the binding between DNA and topoisomerase II or stabilize non-covalent DNA topoisomerase II complexes or inhibit ATP binding site, Whereas topoisomerase II inhibitors are used solely for their antitumor activities[5]

We hypothesize that tri-substituted fluoro indole derivatives have the better capability to inhibit or alter the human topoisomerase II to prevent cancer. The major objective of the current study was in silico analysis and molecular docking studies pertaining to indole derivatives in relation to human topoisomerase II enzyme. As a result of the current study findings the most potential indole derivatives anticancer agent.

METHODOLOGY

Molecular docking is a key tool in computer-assisted drug design and molecular biology. The major objectives of ligand protein docking are to predict three-dimensional structure of predominant binding sites of a ligand with a protein. docking methods use a scoring function that correctly ranks candidate docking ligands. It is used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization. Auto-dock 4.2 is a software designed to predict how small molecules either substrates or drug candidates, bind to a receptor/protein of known 3D structure. Molecular docking study was performed for the Tri-substituted Fluoro-indole derivatives to find activity against biological target for the newer compounds and then validated it experimentally by in-silico studies methods[6]

Figure 1: Process of Molecular Docking:



Preparation of Ligand:

Pub-Chem was used to obtain the SDF files of tri-substituted fluoro indole derivatives, Marvin sketch was used for the construction of novel fluoro indole derivatives in SDF format and discovery visualizer was utilized for converting the SDF files into PDB files. SDF files cannot be used directly for docking studies[7,8]

Figure 2: Parent molecule [Tri-substituted fluoro indole]

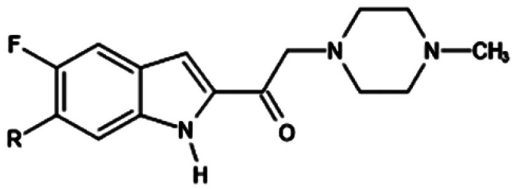
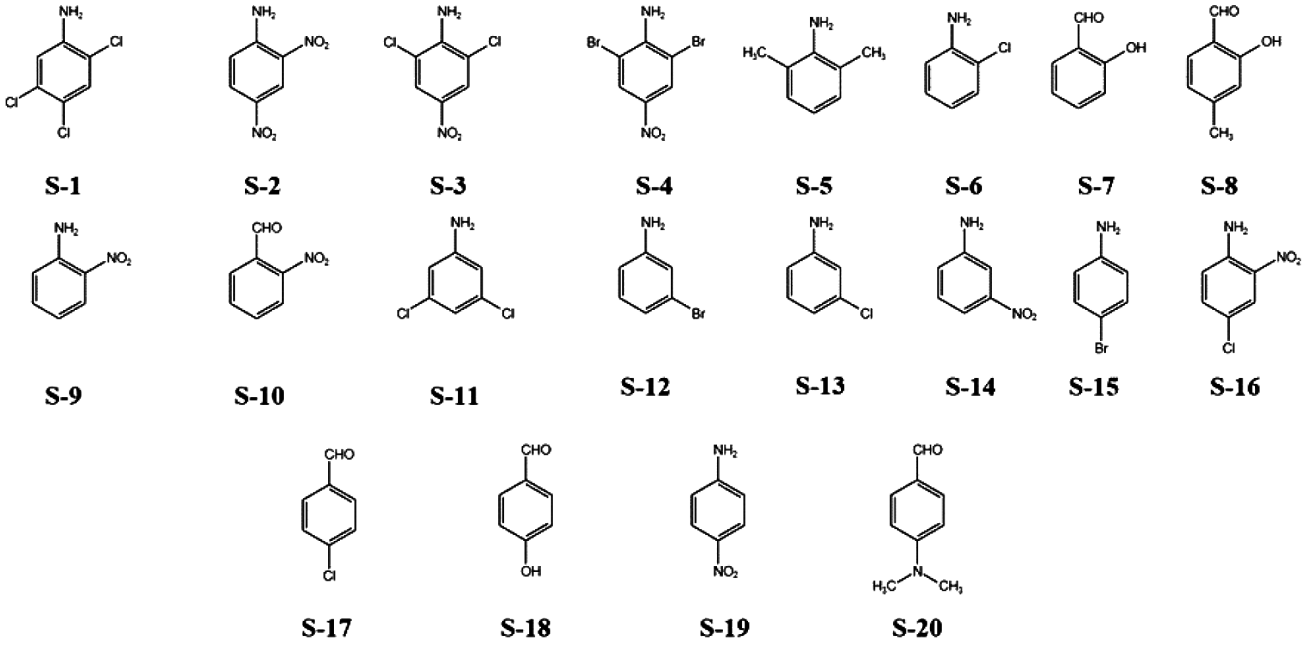
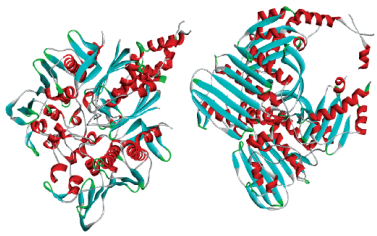


Figure 3: Substituted [R = Aryl Aldehyde and Amines groups]



Preparation of protein molecule

PDB web citation (https://www.rcsb.org/) was used to obtain X-ray crystal structures of human topoisomerase II (PDB ID: 4R1F). First, the Auto Dock Tool (ADT) was used to remove all H2O molecules from the protein, assign hydrogen polarities, and add Kollman charges and polar hydrogen atoms. Gasteiger charges were also applied to the prepared protein and the 4R1F protein structure file from PDB to PDBQT format 9



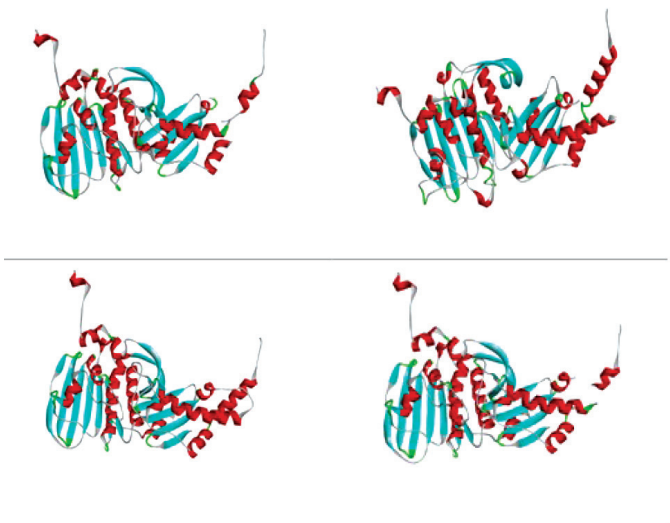


Figure 4: 4R1F protein [chain-A, B, C, D]

Validation of target 4RIF protein:

The inbound ligand present in 4R1F protein was isolated and redocked with the same protein. All the other docking results of the ligand were validated with the redocking results.

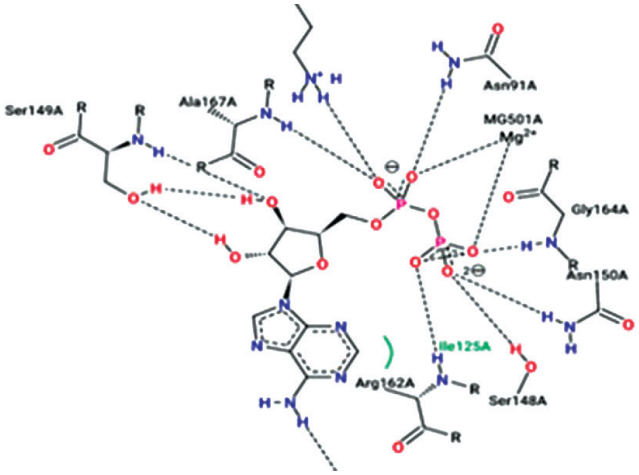


Figure 5: 2D interaction of 4R1F and inbounded ligand

Identification of binding pockets:

Cast-p server was used to identify the active binding pocket of 4R1F protein.[10]

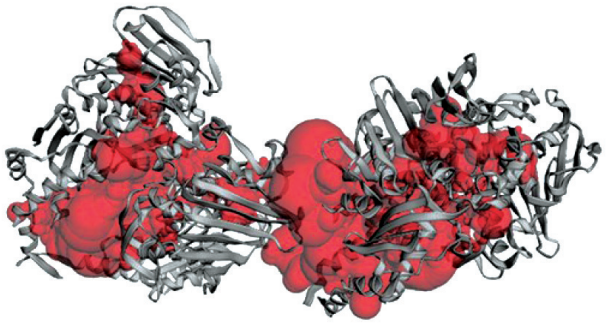


Figure: 6 - Active binding pocket of 4R1F protein.

Table 1: 148 active binding pockets of 4R1F protein.

33 ILE, 34 TYR, 46 ARG, 48 ASP, 49 THR, 50 TYR, 51 ILE, 52 GLY, 53 SER, 54 VAL, 55 GLU, 56 LEU, 57 VAL, 58 THR, 59 GLN, 60 GLN, 61 MET, 62 TRP, 64 TYR, 65 ASP, 66 GLU, 68VAL, 69 GLY, 70 ILE, 71 ASN, 72 TYR, 73 ARG, 74 GLU, 77 PHE, 79 PRO, 82 TYR, 83 LYS, 86 ASP, 87 GLU, 88 ILE, 90 VAL, 91 ASN, 92 ALA, 94 ASP, 95 ASN, 97 GLN, 98 ARG, 99 ASP, 101 LYS, 102 MET, 118 ILE, 120 ASN, 121 ASN, 122 GLY, 123 LYS, 124 GLY, 125 ILE, 126 PRO, 141 ILE, 142 PHE, 147 THR, 148 SER, 149 SER, 150 ASN, 153 ASP, 157 LYS, 159 THR, 160 GLY, 161 GLY, 162 ARG, 163 ASN, 164 GLY, 165 TYR, 166 GLY, 167 ALA, 168 LYS, 169 LEU, 183 SER, 184 ARG, 185 GLU
186 TYR, 212 GLU, 213 ASP, 215 THR, 217 ILE, 227 LYS, 233 LYS, 238 LEU, 241 ARG, 245 ASP, 270 TYR, 273 MET, 274 TYR, 275 LEU, 276 LYS, 304 SER, 305 GLU, 306 LYS, 307 GLY, 308 PHE, 309 GLN, 310 GLN, 311 ILE, 312 SER, 313 PHE, 317 ILE, 318 ALA, 319 THR, 320 SER, 321 LYS, 322 GLY, 323 GLY, 324 ARG, 326 VAL, 327 ASP, 331 ASP, 334 VAL, 337LEU, 338 VAL, 354 HIS, 355 GLN, 356 VAL, 357 LYS, 358 ASN, 359 HIS, 361 TRP, 369 GLU, 370 ASN, 371 PRO, 372 THR, 373 PHE, 374 ASP, 375 SER, 376 GLN, 377 THR, 378 LYS, 379 GLU, 380 ASN, 381 MET, 382 THR, 383 LEU, 384 GLN, 387 SER, 407 ILE, 408 VAL, 409 GLU, 410 SER, 412 LEU, 413 ASN, 415 VAL, 416 LYS, 418 LYS, 420 GLN.

Pharmacokinetic and toxicity prediction

The GI absorption, distribution, metabolism, and excretion of all ligands were predicted by SWISS ADMETlab web server (http://www.swissadme.ch/).11 Toxicity was predicted by a virtual toxicity prediction web server for small molecule, ProTox-II (https://tox-new.charite.de/).[12]

Biological activity prediction

To validate our docking results, we used the biological activity prediction tool pass web server (https://www.way2drug.com/passonline/)[13] and predicted the anticancer activity of all bioactive compounds. The probability to be active (Pa) value of all the bioactive compounds were greater than their probability to be inactive (Pi) values. This finding indicated that all these compounds can show anticancer activity.

Docking standard

MGL tools autodock 4.2 software were used to predict the interaction energy between ligand (Tri-substituted fluoro indole derivatives) and protein (human topoisomerase II) where autodock use the method below to compute the ligand and receptor interaction binding energy[14]

ΔG (BINDING) = ΔG (GAUSS) + ΔG (REPULSION) + ΔG (H-BOND) + ΔG (HYDROPHOBIC) + ΔG (TORS)

Where the dispersion of two Gaussian functions is referred to as ΔG gauss. ΔG repulsion: the square of the distance is repelled if the distance is larger than a threshold value. ΔG H-bond: a ramp function that may be used to model metal ion interactions. ΔG hydrophobic ramp function, ΔG tors proportional to the number of rotatable bonds[15]

3D structure of native PDB file of human topoisomerase II (4R1F) was modified by removing water molecules, ligand and unwanted chain and addition of hydrogen atoms, Kollman unified charge, Gasteiger charge, default solution parameter was added (14). Docking experiment, the grid box was intended to enclose the maximum area of the protein resulting in the blind docking. The value of x, y, z axes of grid point were set to 69.57◦ X 59.28◦ X 105.62◦. The Lamarckian genetic algorithm (LGA) was utilized to calculate flexible docking calculations between protein and ligand. The obtain conformation of protein and ligand were subjected to additional analysis and were thoroughly examined by using discovery studio 2021 molecular visualization software.

RESULT

Molecular docking analysis: in this study all ligands are docked with 4R1F (Human Topoisomerase II) protein to predict the potential anti-cancer activity. The binding energy, and amino acid responsible for interaction were evaluated. The unit of binding free energy is Kcal/mol and the lowest energy of ΔG was taken as the best ligand for further investigation.

Docking analysis

The standard ligand fludarabine having purine ring substituted by halogen, hydroxy group showed the moderate binding energy with this protein. The best binding energy (ΔG = -7.6, -7.6, -8.6, -7.7 kcal/mol) was exhibited by standard ligand fludarabine purine derivatives with five H-bonds THR-215, ASP-94, ASM-91, SER-148, THR-147 with distance 3.22, 2.48, 2.52, 2.55, 2.03 angstroms in chain A, no interaction in chain B, three H-bonds ASP-94, GLY-164, ALA-167 with 2.34, 2.59, 2.06 angstroms in chain C, one H-bond ASN-150 with distance 3.10 angstroms in chain D respectively.

The ligand having 2-4 dinitro aniline substituted derivatives showed the best binding energy with this protein. The best binding energy (ΔG = -8.8, -7.7, -9.6, -8.7 kcal/mol) was exhibited by 2-4 dinitro aniline fluoro indole derivatives with four H-bonds SER-149, LYS-168, ALA-167, ASN-91 with distance 2.34, 2.54, 2.28, 1.91 angstroms in chain A, one H-bond SER-320 with 2.50 angstroms in chain B, four H-bonds ASN-150, SER-149, LYS-168, ASN-91 with 1.95, 2.10, 2.36, 1.82 angstroms in chain C, two H-bond TRP-62, SER-320 with distance 2.05, 2.17 angstroms in chain D respectively.

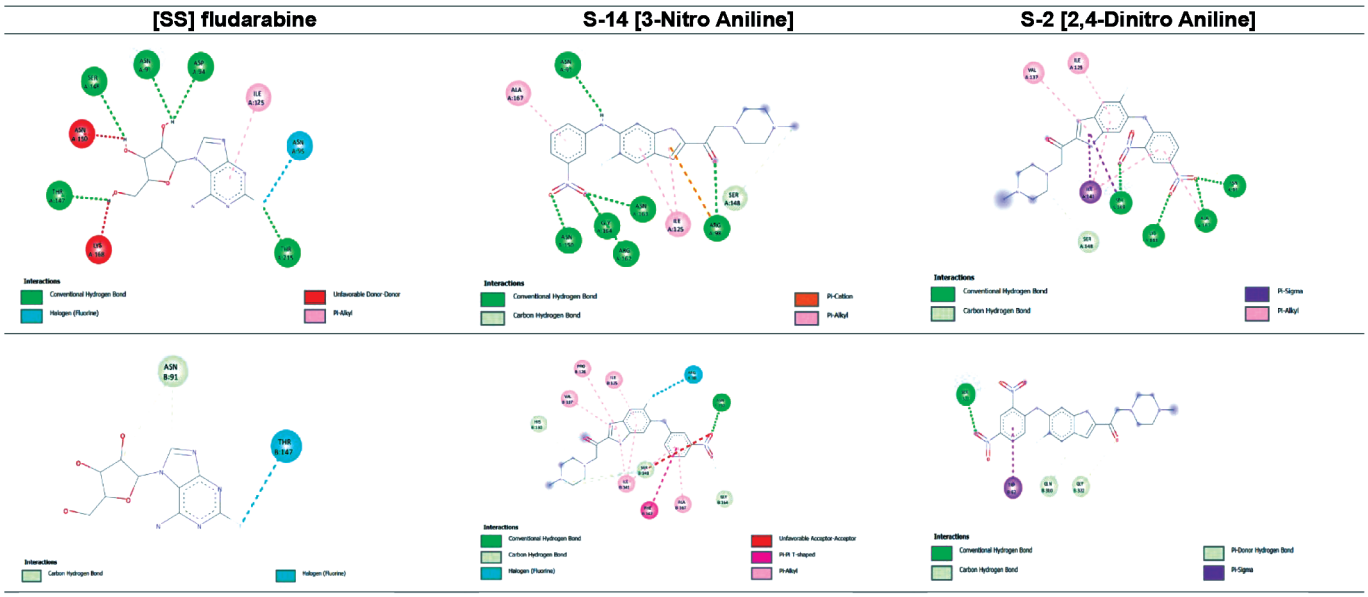
The ligand having nitro substituted aniline showed the best binding energy with this protein. The best binding energy (ΔG = -9.2, -8.2, -8.6, -8.6 kcal/mol) was exhibited by 3-nitro aniline fluoro indole derivatives with six H-bonds ASN-91, ASN-150, ARG-162, ASN-163, GLY-164 with distance 2.69, 1.86, 2.64, 2.28, 2.60, 1.88 in chain A, one H-bond ASN-150 with 2.53 angstroms in chain B, two H-bonds GLN-310, GLN-309 with 2.07 and 1.94 angstroms in chain C, three H-bond ASN-120, ARG-98, LYS-157 with distance 1.74, 2.52, 2.15 angstroms in chain D respectively.

The 2D and 3D interaction was represented in figure – 7,8 and Table - 2 shows the binding energy ranging from -7.3 kcal/mol to -10.3 kcal/mol.

Table 2: Binding energy of substituted fluoro indole derivatives

SN	CHAIN-A	CHAIN-B	CHAIN-C	CHAIN-D
SS	-7.6	-7.6	-8.6	-7.7
S1	-7.8	-8.4	-8.7	-7.8
S2	-8.8	-7.7	-9.6	-8.7
S3	-7.5	-8.4	-8.0	-7.5
S4	-7.9	-7.7	-8.7	-8.9
S5	-7.5	-7.9	-9.0	-7.7
S6	-7.7	-7.7	-8.5	-7.6
S7	-8.3	-7.9	-8.9	-8.3
S8	-7.7	-8.3	-8.3	-7.7
S9	-7.6	-8.9	-8.6	-8.4
S10	-7.7	-9.3	-8.4	-8.5
S11	-7.4	-7.8	-8.4	-7.4
S12	-8.5	-8.1	-8.6	-7.5
S13	-7.8	-7.3	-8.5	-7.9
S14	-9.2	-8.2	-8.6	-8.6
S15	-7.6	-7.9	-8.5	-8.1
S16	-7.7	-7.5	-8.2	-7.6
S17	-8.3	-8.3	-9.0	-8.3
S18	-8.6	-8.7	-8.8	-8.6
S19	-7.6	-8.1	-8.6	-8.9
S20	-8.1	-7.5	-8.8	-7.9

Figure: 7 - Images were created by using BIOVIA discovery studio visualizer 21.1.0.0 and showing the 2D interaction between 4R1F and [SS] [S-14] and [S-2]



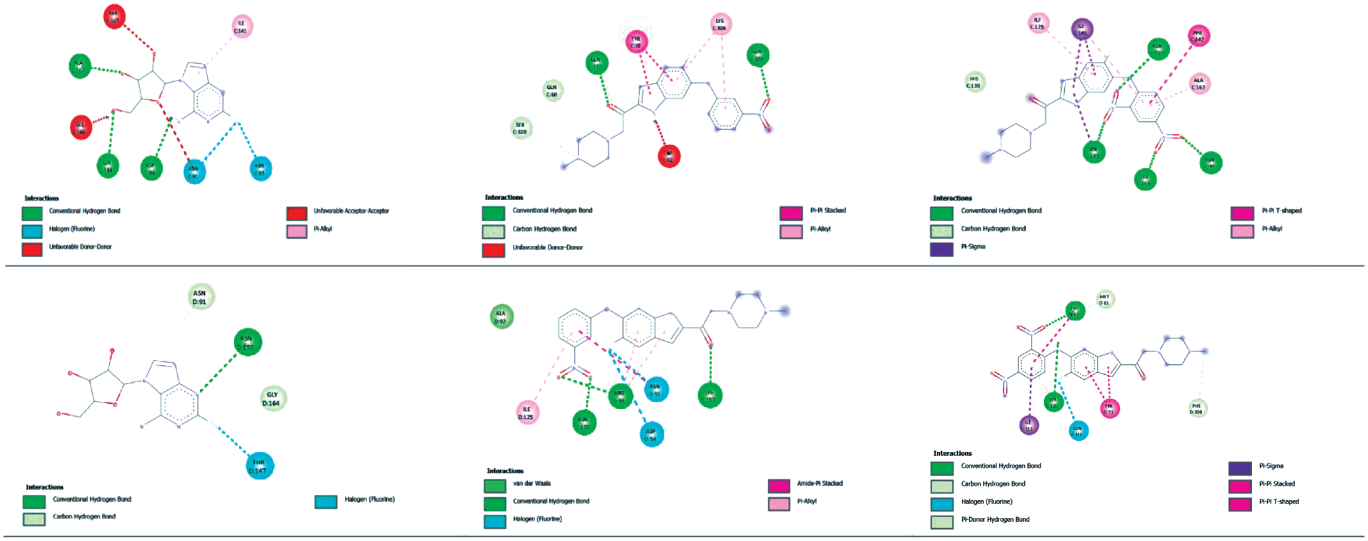
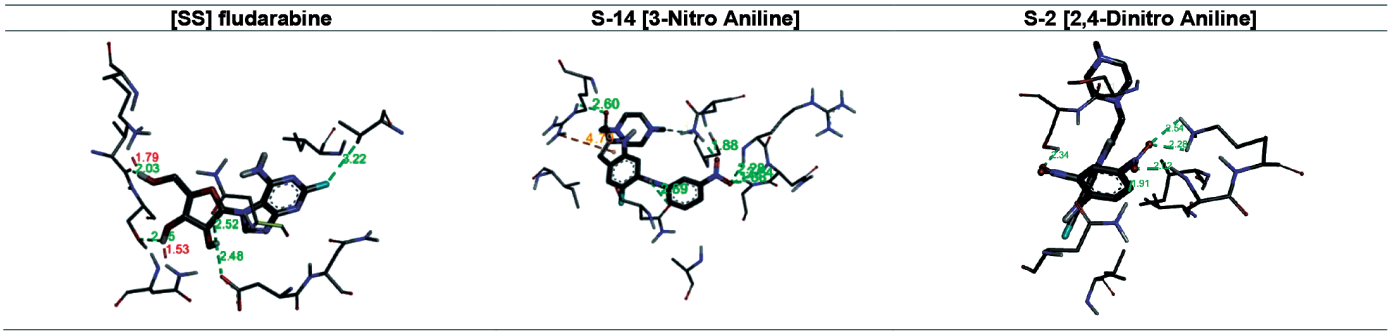


Figure: 8 - 3D interaction between 4R1F and [SS] [S-14] and [S-2]



ADME Analysis:

Docking data are not enough to select any drug for further development. The (ADME) absorption, distribution, metabolism, and excretion properties of the drug, toxicity of the drugs, and Lipinski's rule of five (LRO5) parameters should be good. Good Pharmacokinetic and toxicity profile is the key parameter for drug development. Therefore, the ADME properties of all derivatives were determined by swissADME web server[11] as shown in [Table 3]. We analysed all derivatives and found that none of them violated the Lipinski's rule of five which filters the candidate to define the draggability and drug likeness. All the derivatives have good lipophilic parameters, high intestinal absorption value and low skin permeability parameters.[11]

Biological activity prediction:

Docking parameters and pharmacokinetic parameters is further supported by biological activity prediction tool and predicted the anticancer activity of all derivatives [Table–4]. The probability to be active [Pa] value of all derivatives was greater than their probability to be inactive [Pi] values which indicated that all these compounds can show anticancer activity.[13]

Table 3: ADME properties and LRO5 parameters.

Note: log-S scale [Insoluble < -10 < poorly < -6 < moderately < -4 < soluble < -2 very soluble < 0 <highly soluble]

Compound	Lipinski's rule of five					ADMET properties				
SN	MW	RB	HBA	HBD	Log-P	Water solubility	BBB	Intestinal absorption	Skin (Permeation)	Drug likeness
SS	285	2	8	4	0.96	-0.88	No	Low	-9.08	Yes
S1	469	5	4	2	3.73	-6.24	Yes	High	-5.28	Yes
S2	456	7	8	2	2.27	-4.94	No	Low	-6.39	Yes
S3	480	6	6	2	2.90	-5.71	No	High	-5.91	Yes
S4	569	6	6	2	3.17	-6.34	No	High	-7.48	Yes
S5	394	5	4	2	3.46	-5.06	Yes	High	-7.36	Yes
S6	400	5	4	2	3.22	-5.05	Yes	High	-7.19	Yes
S7	395	5	6	2	3.09	-4.61	Yes	High	-5.90	Yes
S8	425	6	7	2	3.57	-4.68	No	High	-6.00	Yes

S9	411	6	6	2	2.38	-4.87	No	High	-5.95	Yes
S10	424	6	7	1	2.35	-4.46	No	High	-5.83	Yes
S11	435	5	4	2	3.55	-5.64	Yes	High	-7.78	Yes
S12	445	5	4	2	3.27	-5.36	Yes	High	-7.39	Yes
S13	400	5	4	2	3.25	-5.05	Yes	High	-7.19	Yes
S14	411	6	6	2	2.60	-4.52	Yes	High	-6.38	Yes
S15	445	5	4	2	3.21	-5.36	Yes	High	-7.39	Yes
S16	445	6	6	2	2.67	-5.46	No	High	-5.75	Yes
S17	413	5	5	1	2.88	-4.99	Yes	High	-5.97	Yes
S18	395	5	6	2	2.54	-4.25	Yes	High	-6.56	Yes
S19	411	6	6	2	2.61	-4.52	No	High	-6.38	Yes
S20	422	6	5	1	2.89	-4.63	Yes	High	-6.39	Yes

Table 4: Predictions Of Biological Activity.

SN	Biological activity [Pa>-Pi]	[Pa] value	[Pi] value
SS	Anti-cancer activity	0.887	0.005
S1	Anti-cancer activity	0.268	0.173
S2	Anti-cancer activity	0.489	0.075
S3	Anti-cancer activity	0.248	0.187
S4	Anti-cancer activity	0.242	0.192
S5	Anti-cancer activity	0.299	0.153
S6	Anti-cancer activity	0.293	0.157
S7	Anti-cancer activity	0.268	0.173
S8	Anti-cancer activity	0.336	0.132
S9	Anti-cancer activity	0.454	0.086
S10	Anti-cancer activity	0.126	0.080
S11	Anti-cancer activity	0.336	0.132
S12	Anti-cancer activity	0.466	0.082
S13	Anti-cancer activity	0.350	0.125
S14	Anti-cancer activity	0.423	0.096
S15	Anti-cancer activity	0.446	0.088
S16	Anti-cancer activity	0.380	0.112
S17	Anti-cancer activity	0.151	0.032
S18	Anti-cancer activity	0.274	0.169
S19	Anti-cancer activity	0.394	0.106
S20	Anti-cancer activity	0.281	0.164

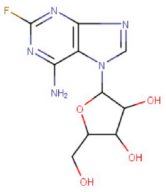
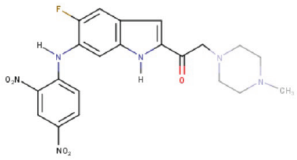
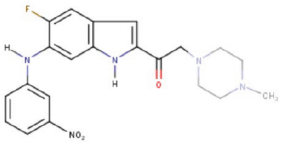
	**[SS] Toxicity class**	**II**
	LD-50	13 mg/kg
	Hepatotoxicity	Inactive
	Cytotoxicity	Inactive
	Carcinogenicity	Inactive
	Mutagenicity	Inactive
	Immunotoxicity	Inactive
	**[S-2] Toxicity class**	**IV**
	LD-50	1420 mg/kg
	Hepatotoxicity	Inactive
	Cytotoxicity	Inactive
	Carcinogenicity	Active
	Mutagenicity	Active
	Immunotoxicity	Active
	**[S-14] Toxicity class**	**IV**
	LD-50	1300
	Hepatotoxicity	Inactive
	Cytotoxicity	Inactive
	Carcinogenicity	Active
	Mutagenicity	Active
	Immunotoxicity	Active

Table 5: Predictions Of Biological Activity.

Toxicity prediction:

The acute toxicity of all derivatives was predicted. The toxicity profile of standard fludarabine [SS] belongs to class-II with lethal dose [(5 < LD50 ≤ 50)] and shows neurotoxicity, nephrotoxicity and respiratory toxicity but inactive at other toxicity figure-9. Toxicity profile of all derivatives indicated that none of them showed cytotoxicity and hepatotoxicity. Derivatives S-2, S-3, S-4, S-6, S-9, S-10, S-14, S-16, S-19 are Mutagenicity, Immunotoxicity, Carcinogenicity in nature. All derivatives except S-6 belongs to toxicity class IV with lethal dose [(300 < LD50 ≤ 2000)] and S-6 belongs to toxicity class III with lethal dose [(50 < LD50 ≤ 300)]. Hence S-6 is more toxic than other derivatives [Table-5].[12,16,17]

Note: LD50 values are given in [mg/kg]: Class I: fatal if swallowed (LD50 ≤ 5), Class II: fatal if swallowed (5 < LD50 ≤ 50), Class III: toxic if swallowed (50 < LD50 ≤ 300), Class IV: harmful if swallowed (300 < LD50 ≤ 2000), Class V: may be harmful if swallowed (2000 < LD50 ≤ 5000) and Class VI: non-toxic (LD50 > 5000).

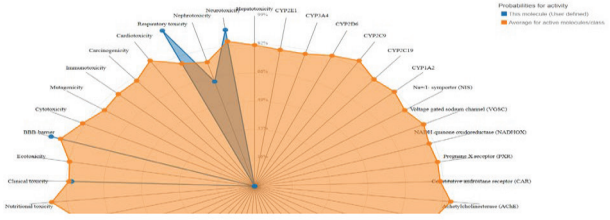


Figure: 9 - The toxicity radar chart of fludarabine [SS]

DISCUSSION

Cancer remains the leading cause of the death worldwide and expected that annual cancer case will rising very rapidly and make the scenario even more troublesome as well as Due to drug resistance makes things even worse. our investigation suggested that Tri-substituted fluoro indole derivatives have a good impact against human topoisomerase-II, we believed that this study would be a huge help in discovering and developing new anti-cancer agents. DNA gyrase and topoisomerase-II are the key target for the discovery and development of anti-cancer agents. Our research indicate that substituted fluoro indole derivatives have remarkable impact on DNA gyrase and topoisomerase-II.

Docking studies revealed that tri-substituted fluoro indole derivatives could be a good alternate against human topoisomerase II as an anti-cancer agent. The ligand having 2-4 dinitro [S-2] and 3-nitro aniline [S-14] showed the best binding energy with 4R1F protein. The docking score of indole derivatives are relatively high as compared to standard. In chain-A fludarabine score -7.6 kcal/mol with five hydrogen bonds whereas 2-4 dinitro aniline indole derivatives score -8.8 kcal/mol with four hydrogen bond and 3-nitro aniline indole derivatives score -9.2 kcal/mol with six hydrogen bonds. In chain-B fludarabine score -7.6 kcal/mol with zero hydrogen bonds whereas 2-4 dinitro aniline indole derivatives score -7.7 kcal/mol with one hydrogen bond and 3-nitro aniline indole derivatives score -8.2 kcal/mol with one hydrogen bonds. In chain-C fludarabine score -8.6 kcal/mol with three hydrogen bonds whereas 2-4 dinitro aniline indole derivatives score -9.6 kcal/mol with four hydrogen bond and 3-nitro aniline indole derivatives score -8.6 kcal/mol with two hydrogen bonds. In chain-D fludarabine score -7.7 kcal/mol with one hydrogen bonds whereas 2-4 dinitro aniline indole derivatives score -8.7 kcal/mol with two hydrogen bond and 3-nitro aniline indole derivatives score -8.6 kcal/mol with three hydrogen bonds. Docking scores reveals that substituted indole derivatives have better binding affinity with higher number of hydrogen bonds against fludarabine. In chain-A and chain-B 3-nitro aniline derivatives shows excellent docking score with seven hydrogen bonds where as in chain-C and chain-D 2-4 dinitro aniline derivatives shows excellent docking score with six hydrogen bonds. On the basis of docking score and number of hydrogen bond indole derivatives are better alternative against fludarabine. [Table-2 and Figure-7,8]

ADME parameters gives additional evidence supports the docking evaluations. All derivatives show the drug likeness properties and don't violets the Lipinski rules of five. Optimal molecular weight less than 500 Dalton, hydrogen bond acceptor ≤ 10 and hydrogen bond doner ≤ 5, log-p value (2.27, 2.60) slightly greater than standard (0.96), fludarabine (SS) is soluble in water (-0.88) compared with indole derivatives S-2 (-4.94) and S-14 (-4.52) which is moderately soluble. most of synthesized indole derivatives cross the BBB, high intestinal absorption and low skin permeability. [Table - 3]

Insilco biological activity prediction reveals that fludarabine shows highest Pa/Pi ratio (0.887/0.005) whereas all indole derivatives show moderate activity S-2 (0.489/0.075) S-14 (0.423/0.096) and Insilco taxological profile shows fludarabine belongs to class-II and active neurotoxic, nephrotoxic, and respiratory toxic but inactive Hepatotoxicity, Cytotoxicity, Carcinogenicity, Mutagenicity, Immunotoxicity activities. Most of the indole derivatives show class-III and active Carcinogenicity, Mutagenicity, Immunotoxicity but inactive Hepatotoxicity, Cytotoxicity. Comparing with fludarabine only S-6 show high toxicity rest derivatives are moderately toxic. [Table-5, Figure-9]

Zhuang et al.18 designed, synthesized, and evaluated a series of 2,4-disubstituted fluoro indoles in vitro for anticancer activity. Compound 10a which contain basic indole it skeleton, which demonstrated the best anticancer activity among the tested compounds hence support our investigation. From the medicinal chemistry viewpoint, compound 10a, S-2, S-14 presents new possibilities for optimizing analogues and warrants further investigation.

CONCLUSION

Indole derivatives containing nitro group S-2 and S-14 showed potential inhibitory effect against 4R1F human topoisomerase II with excellent docking score, drug likeness, good pharmacokinetics parameters, mild toxicity in Insilco model. However, detailed and in-depth research is required to explore the anticancer activity of tri-substituted fluoro indole derivatives.

FUTURE PRESPECTIVE

Wet lab and further studies can be conducted to explore the potential mechanisms of action and their impact is needed to determine the potency, efficacy and safety of compounds S-2 and S-14 in preclinical and clinical trials. The objective of these future studies will be to determine the feasibility and viability of S-2 and S-14 as new treatments for cancer which critical in advancing the development of these compounds and contributing to the global efforts to combat cancer.

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COMPETING INTERESTS

All the authors declare no competing interests.