Section A -Research paper
ISSN 2063-5346

Molecular Docking, ADMET Prediction and Pharmacophore Mapping of Purines as Anticancer Agents

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Abstract

Purines are chief components for building of DNA and RNA and provides high energy for cell proliferation and survival, so antimetabolites are prescribed for blocking the synthesis of DNA and cell growth in various cancerous condition. CADD is referred an *in silico* screening technique which hasten the process of drug discovery through molecular docking, ADMET Prediction, and pharmacophore hypothesis or mapping. Molecular docking technique predominantly used to study the molecular interactions among the designed ligands and surface of target receptors. ADMET prediction data is considered as vital part of developing and discovery of new drugs. Pharmacophore mapping is used to characterize the pharmacophoric features like HBA, HBD, partial charge, acidic and basic groups etc. of dataset of compounds in which molecules are divided into test and training set.

Keywords: Purines; docking; Pharmacophore mapping

Introduction

Purines are chief components for building of DNA and RNA and provides high energy for cell proliferation and survival, so antimetabolites are prescribed for blocking the synthesis of DNA and cell growth in various cancerous condition (Yin *et al*., 2018). Purine ring has various activities (Dinesh *et al*., 2012) like antifungal (Hu *et al*., 2010), antitumor (Raic-Melis *et al*., 1999), phosphodiesteraseinhibiton (c*et al*., 1999), antibacterial, antiprotozoal (Gordaliza*et al*., 2009), and antiviral (Yahyazadeh*et al.,* 2007), and antidiabetic (dipeptidylpeptidase-4 inhibitor) (Spasov *et al*., 2017). The marketed anticancer drugs of purine moiety is given in Fig 1.

CADD is referred an *in silico* screening technique which hasten the process of drug discovery through molecular docking, ADMET Prediction, and pharmacophore hypothesis or mapping (Prajapat*et al.,* 2017).

Molecular docking technique predominantly used to study the molecular interactions among the designed ligands and surface of target receptors. For interacting the ligand to protein receptor site or surface, protein structure is downloaded from the protein data bank in proper PDB format. Molecular docking is used chiefly for optimization of lead compound and it forecast proper orientation of ligand molecule on receptor site. By molecular docking we can select potent medicine from large database or library of series of compounds (Dar *et al*., 2017).

ADMET prediction data is considered as vital part of developing and discovery of new drugs. ADME-Toxicity properties can be used to predict or estimate the drug's behavior after

administering into body (Zhang *et al*., 2012). ADME-Toxicity and drug likeness properties affect pharmacodynamics and pharmacokinetic properties of the drug molecules (Kalita *et al*., 2019).

Pharmacophore mapping is used to characterize the pharmacophoric features like HBA, HBD, partial charge, acidic and basic groups etc. of dataset of compounds in which molecules are divided into test and training set. After developing pharmacophore hypothesis, the compounds are aligned into 3 sets active, inactive partial and inactive full according to their fitness score and site score. The compound which has highest fitness score is best suited for the generated or predicted hypothesis (Pathare *et al*., 2015).

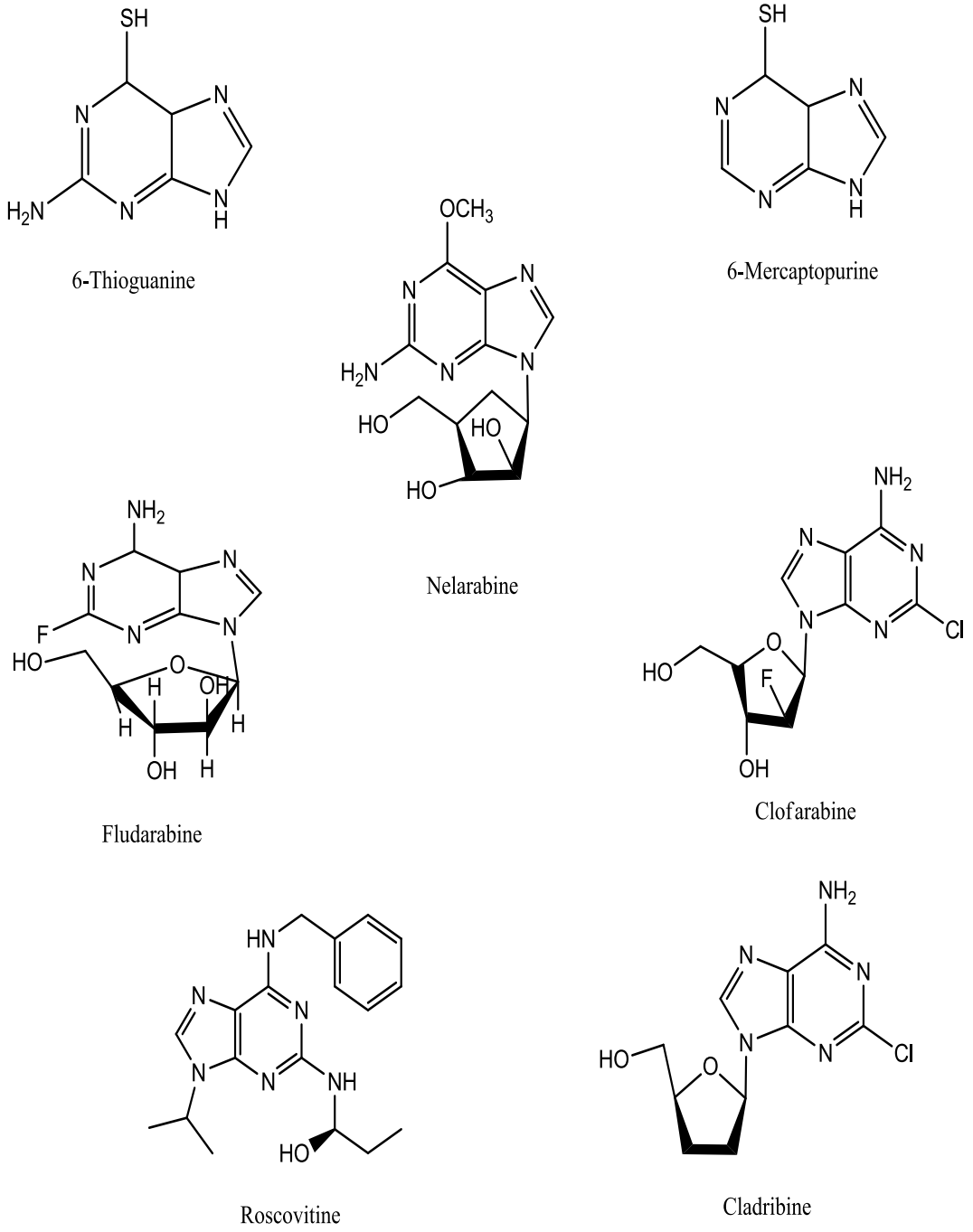

Fig 1: Marketed formulations of anticancer drug containing Purine as moiety

2. Computational Methodology:

2.1 Selection of Dataset: Total **50** compounds of purine presented in Table 1 are selected from previously published work (Kucukdumlu*et al*., 2017 and Tuncbilek*et al*., 2020) is used for the study.

Table 1 : Structures of purine derivatives from Kucukdumlu *et al*., 2017 &Tuncbilek *et al*., 2020.

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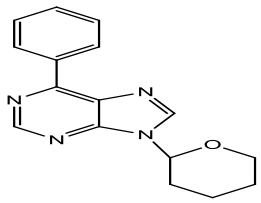
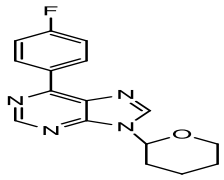
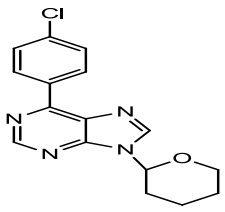
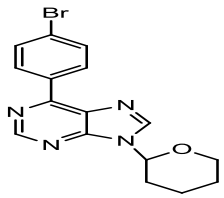
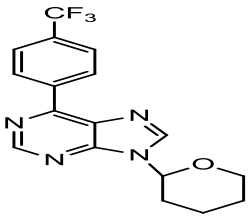
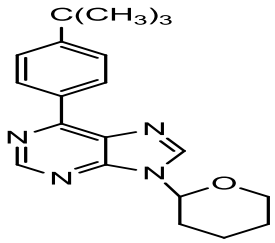
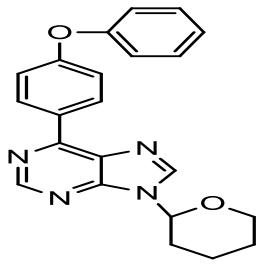
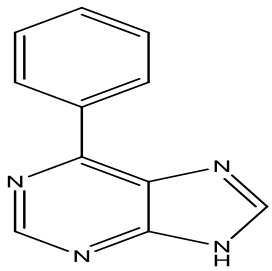
1.		2.	
3.		4.	
5.		6.	
7.		8.	

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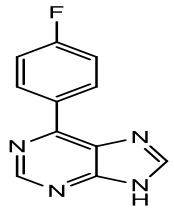
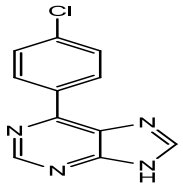
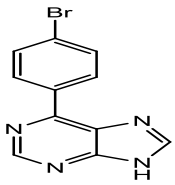
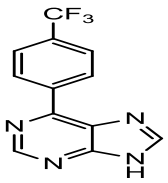
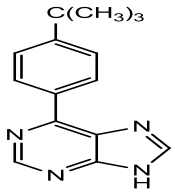
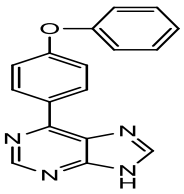
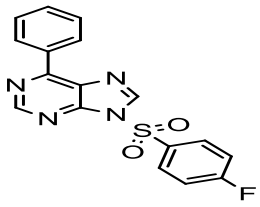
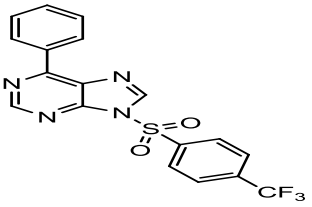
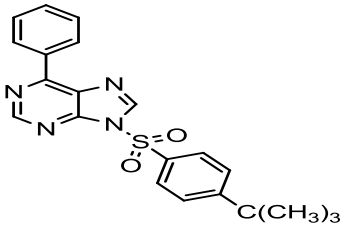
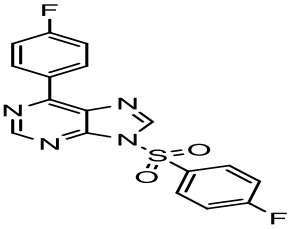
9.		10.	
11.		12.	
13.		14.	
15.		16.	
17.		18.	

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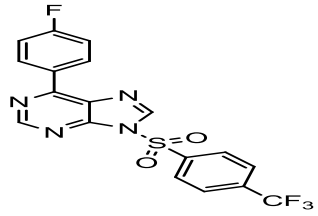
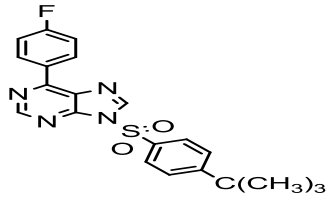
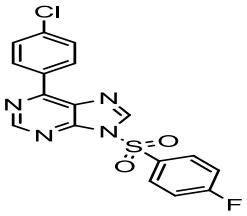
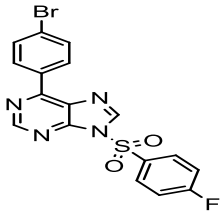
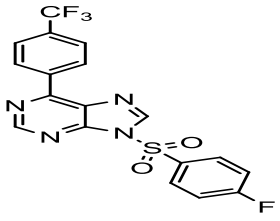
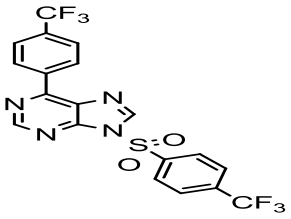
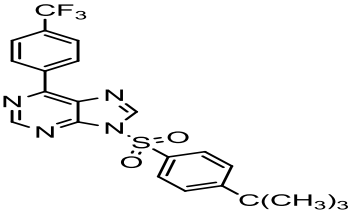
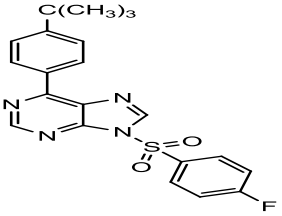
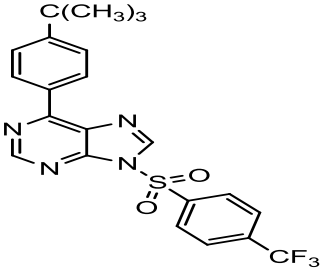
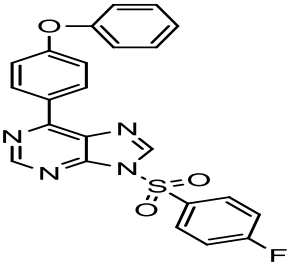
19.		20.	
21.		22.	
23.		24.	
25.		26.	
27.		28.	

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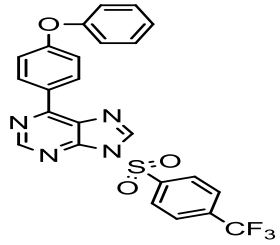
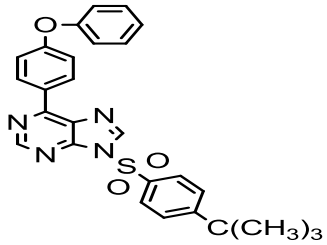
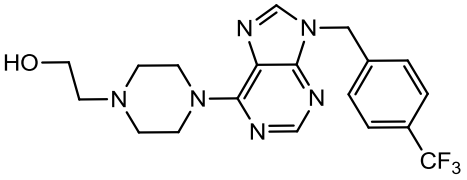
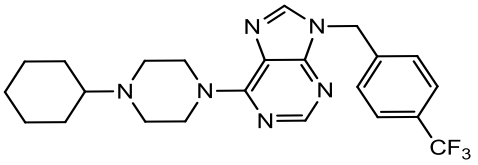
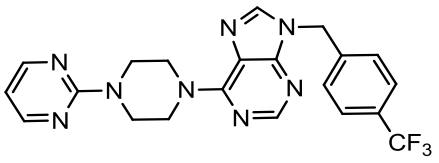
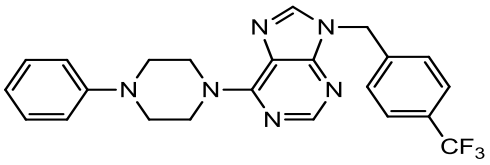
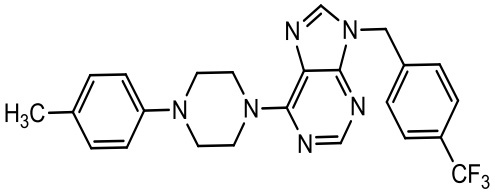
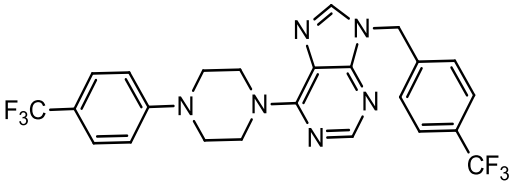
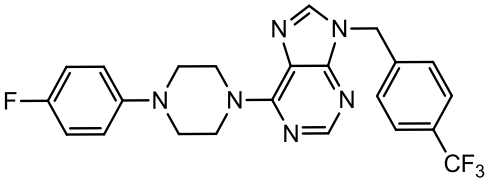
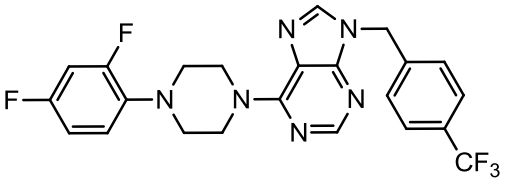
29.		30.	
31.		32.	
33.		34.	
35.		36.	
37.		38.	

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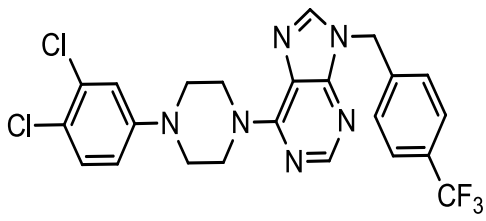
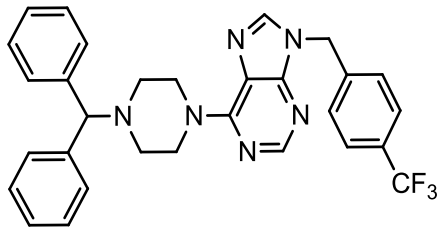
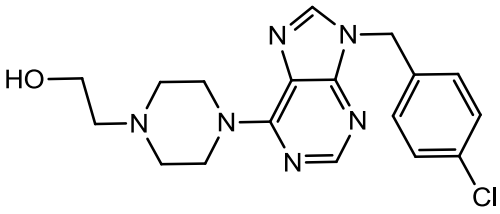
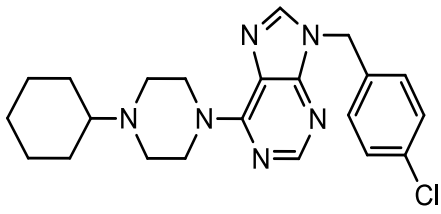
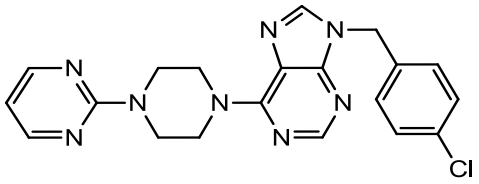
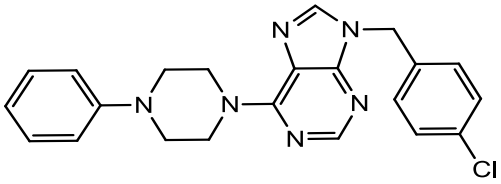
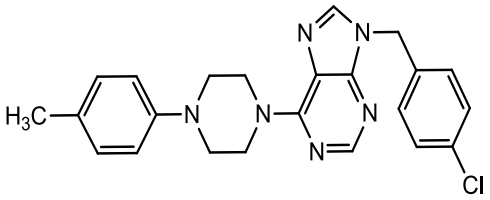
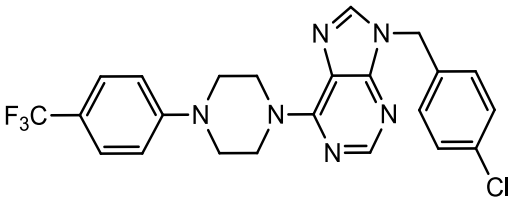
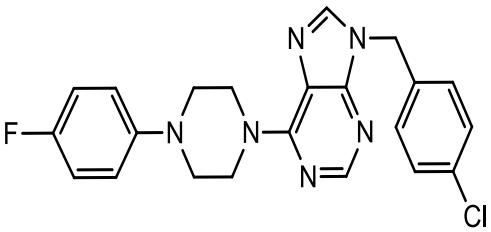
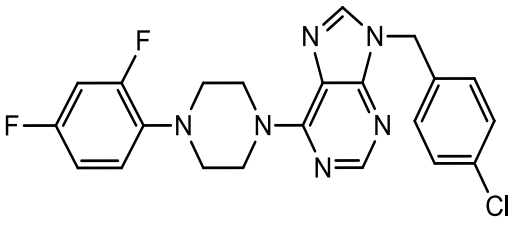
39.		40.	
41.		42.	
43.		44.	
45.		46.	
47.		48.	

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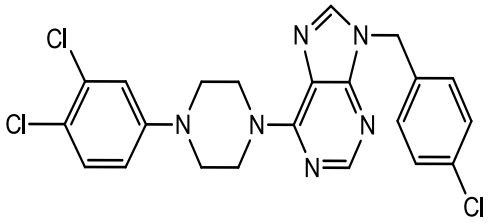
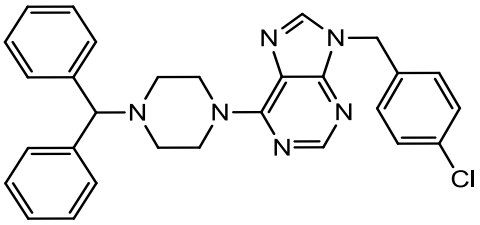
49.		50.	

2.2 Molecular docking study:

ChemDraw ultra 12.0 is used to create the sketches of library of purine anticancer derivatives **(1-50)** in MDL mol format. Molecular docking was performed using Schrodinger maestro 13.0 v suite against PDB ID: 5FGK and 3ERT.

2.2.1 Protein preparation

The PDB structure of protein (PDB ID: 5FGK and PDB ID: 3ERT) was downloaded from RSCB protein data bank in clear and high resolution. Then using 'protein preparation workflow' tool in maestro, water molecules were deleted and OPLS_2005 force field used for minimization of energy of protein (Friesner *et al.*, 2004).

2.2.2 Receptor grid generation

After protein preparation, grid was generated by clicking on 'Receptor grid generation' tool in maestro. Most active site of downloaded protein is selected by selection of atoms of site, Then 'run' the program and our receptor grid is generated which is used for docking with importing ligands (Kalirajan *et al*., 2016).

2.2.3 Ligand preparation

All the purine ligands selected from dataset were imported in MDL mol file format (MDL.mol) and using 'LigPrep tool', energy is minimized by force field OPLS_2005 (Kulkarni *et al*., 2023).

2.2.4 Ligand docking

After protein and purine ligands preparation, docking is done by clicking on 'Ligand docking' tool in Schrodinger maestro 13.1. From 'browse' option Glide grid file is selected for interacting with purine ligands and docking precision is set to extra precision, Then click on 'Run' option and docking results were saved in spreadsheet (MS Excel) by exporting from project table (Bender *et al*., 2021).

2.3 ADMET&Druglikeness prediction:

ADME/Toxicity properties and drug-likeness calculation data is considered as vital part of developing and discovery of new drugs. ADME-Tox properties can be used to predict or estimate the drug's behavior after administering into body (Zhang *et al*., 2012). In 1st step imported purine ligands is prepared by clicking 'Ligprep', after that in 2nd step by clicking on 'Qikprop' tool in maestro and then click on 'Run' option, ADMET properties are determined. All the predicted data are exported in spreadsheet from maestro project table. Those purine compounds are best suited for administering into the body which doesn't violated any criteria of Lipinski's rule of Five (Kalita *et al*., 2019).

2.4 Pharmacophore mapping:

Pharmacophore groups are the set of electronic and steric properties of a compound, these are required to examine the molecular interactions with biological target and it reduce or start a biological response. Library of 50 purine derivatives were selected for generating a pharmacophore hypothesis which is a method of ligand-based pharmacophore models. Derivatives of purines are divided into active & inactive set. Fitness score, phase hypo score, survival score, site score are taken into consideration for understanding the pharmacophore hypothesis (Bouacha*et al.,* 2022).

Ligand Preparation:

For performing Pharmacophore hypothesis purine derivatives structures are imported in maestro and ligand is prepared by clicking on 'LigPrep' and energy is minimized by force field OPLS_2005. After that IC 50 (µm) of compounds are converted into pIC 50 value and activity of each compound is added manually in the project table (Bouacha*et al.,* 2022).

Develop Pharmacophore Hypothesis:

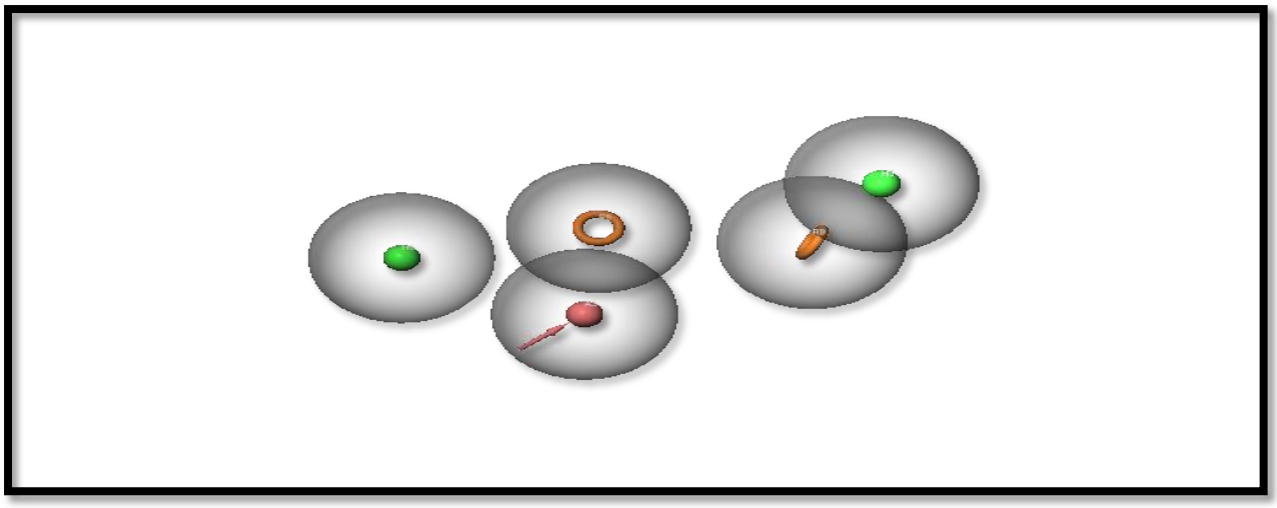


Fig 2: Pharmacophore hypothesis

After ligand preparation click on 'Develop Pharmacophore Hypothesis' tool in schrodinger maestro 13.0 v suite and choose activity property which is added by user. By defining pharma set, The compounds which has pIC50 ≥ 5.0 is considered to be active and which has pIC50 ≤ 4.5 is considered to be inactive. After that click on 'Enrichment viewer' tool in maestro then phase hypo score EF1% ,AUOC and ROC values are calculated. Five point pharmacophore hypothesis is shown in Fig 2. Results are saved into spreadsheet by exporting from the maestro project table (Bouacha*et al.,* 2022).

3. Results and Discussion

3.1 Molecular docking:

Docking against PDB ID: 5FGK: Docking score of 50 purine compounds against PDB ID: 5FGK is presented in Table 2.

Table 2: Docking score of 50 purine compounds against PDB ID: 5FGK

C. No.	Docking score	Glide energy	C. No.	Docking score	Glide energy
1	-6.109	-36.9	**26**	-5.311	-42.416

2	-5.397	-38.44	**27**	-7.299	-46.275
3	-6.965	-35.238	**28**	-6.27	-45.745
4	-6.078	-31.396	**29**	-7.638	-50.511
5	-6.909	-36.181	**30**	-7.296	-48.747
6	-6.265	-33.685	**31**	-7.539	-44.164
7	-5.928	-38.193	**32**	-6.192	-43.454
8	-8.62	-31.748	**33**	-6.279	-40.907
9	-8.621	-33.532	**34**	-6.708	-46.095
10	-8.69	-34.753	**35**	-5.368	-49.373
11	-8.703	-35.251	**36**	-5.008	-49.577
12	-7.81	-33.436	**37**	-6.679	-44.181
13	-6.723	-34.868	**38**	-6.714	-41.857
14	-7.585	-42.544	**39**	-5.827	-45.036
15	-6.924	-45.212	**40**	-6.289	-49.314
16	-6.943	-49.868	**41**	-6.914	-43.628
17	-6.956	-49.17	**42**	-5.717	-41.549
18	-6.309	-41.954	**43**	-5.226	-45.609
19	-6.5	-49.363	**44**	-6.252	-44.009
20	-7.794	-45.333	**45**	-5.723	-45.092
21	-6.343	-43.583	**46**	-5.924	-42.4
22	-6.721	-41.4	**47**	-5.641	-44.295
23	-6.406	-43.067	**48**	-5.169	-44.386
24	-7.041	-46.837	**49**	-5.404	-44.431
25	-7.788	-45.403	**50**	-6.625	-46.522
5-fluorouracil	**-6.582**	**-21.51**			
Doxorubicin	**-6.24**	**-52.454**			
Cladribine	**-6.121**	**-40.328**			

Best Docking score against PDB ID: 5FGK: Best docking results of top 4 purine compounds against PDB ID: 5FGK presented in Table 3

Table 3: Docking results of top 4 purine compounds against PDB ID:5FGK

C. No.	Docking score	Glide energy	Glide e model	Interacting residues
11	-8.703	-35.251	-49.056	ALA 100
10	-8.69	-34.753	-47.839	ALA 100, LYS 52
9	-8.621	-33.532	-46.522	ALA 100, TYR 32
8	-8.62	-31.748	-43.696	ALA 100, TYR 32

5FGK Protein: Prepared protein structure of 5FGK is given in Fig 3.

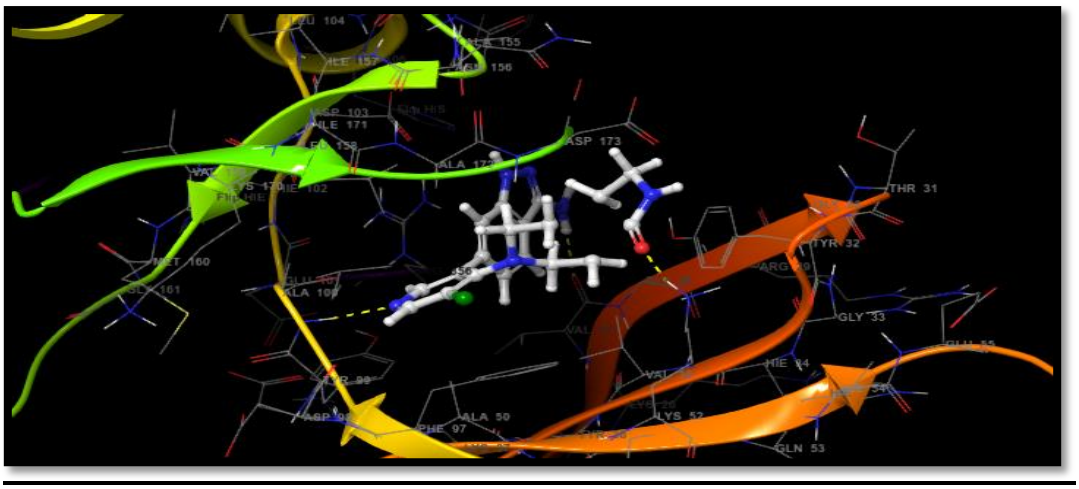


Fig 3: 5FGK Prepared protein structure

The docking study of purines was performed using Schrodinger maestro 13.0 v suite against PDB ID: 5FGK and the docking results are presented in Table 3. Total 34 compounds out of 50 have better docking score than Doxorubicin, total 25 compounds out of 50 have better docking score than 5-fluorouracil and total 35 compounds out of 50 have better docking score than cladribine. Docking studies on PDB ID: 5FGK (colorectal cancer) showed that compounds no. **11** and **10** showed very high docking score -8.703 and -8.69 Kcal/mol as compared to reference drug 5-fluorouracil (-6.582Kcal/mol), doxorubicin (-6.24Kcal/mol) and cladribine (-6.121 Kcal/mol). Top 4 compounds which have good docking score and amino acid interactions against PDB ID:5FGK are presented in Table 4. **ALA 100** is a common interacting residue in compound no. **11, 10, 9** and **8.** While **TYR 32** is a common interacting residue in compound no. **9** and **8.**

Docking against PDB ID: 3ERT:PDB ID: Docking score of 50 purine compounds against PDB ID: 3ERT is presented in Table 4.

Table 4: Docking score of 50 purine compounds against PDB ID: 3ERT

C. No.	Docking score	Glide energy	C. No.	Docking score	Glide energy
1	-7.991	-36.843	**26**	-6.285	-39.785
2	-7.357	-32.222	**27**	-7.063	-39.914
3	-6.42	-32.651	**28**	-6.362	-49.514
4	-6.345	-32.671	**29**	-7.238	-50.504
5	-6.972	-32.335	**30**	-7.262	-47.012
6	-6.923	-32.114	**31**	-8.342	-36.032
7	-6.935	-42.119	**32**	-5.805	-40.602
8	-6.613	-33.367	**33**	-5.899	-41.54
9	-7.711	-33.665	**34**	-5.438	-39.536
10	-7.941	-36.784	**35**	-7.177	-44.685
11	-8.039	-32.227	**36**	-8.364	-46.313
12	-8.528	-35.684	**37**	-7.061	-46.538
13	-8.214	-36.072	**38**	-5.925	-44.76
14	-6.459	-40.462	**39**	-8.088	-50.21
15	-7.141	-37.581	**40**	-10.262	-50.922
16	-7.877	-34.783	**41**	-7.34	-38.319
17	-7.772	-34.858	**42**	-6.462	-38.835
18	-4.969	-35.208	**43**	-5.042	-43.752

19	-3.114	-28.576	**44**	-6.476	-42.022
20	-4.515	-35.358	**45**	-6.175	-41.637
21	-4.243	-30.878	**46**	-7.925	-42.718
22	-6.9	-40.43	**47**	-7.065	-41.442
23	-7.036	-34.563	**48**	-7.28	-41.181
24	-2.105	-29.123	**49**	-8.329	-47.826
25	-6.768	-42.067	**50**	-10.368	-52.404
Tamoxifen	**-10.669**	-42.359			
Cladribine	**-7.027**	-39.329			
Doxorubicin	**-5.804**	-43.492			

Best Docking score against PDB ID: 3ERT: Best docking results of top 2 purine compounds against PDB ID: 3ERT presented in Table 5.

Table 5: Docking results of top 2 purine compounds against PDB ID: 3ERT

C. No.	Docking score	Glide energy	Glide e model	Interacting residues
12	-8.528	-35.684	-53.884	GLU 353, SER 432
13	-8.214	-36.072	-33.428	GLU 353, SER 432

3ERT Protein: Prepared protein structure of 3ERT is given in Fig 4.

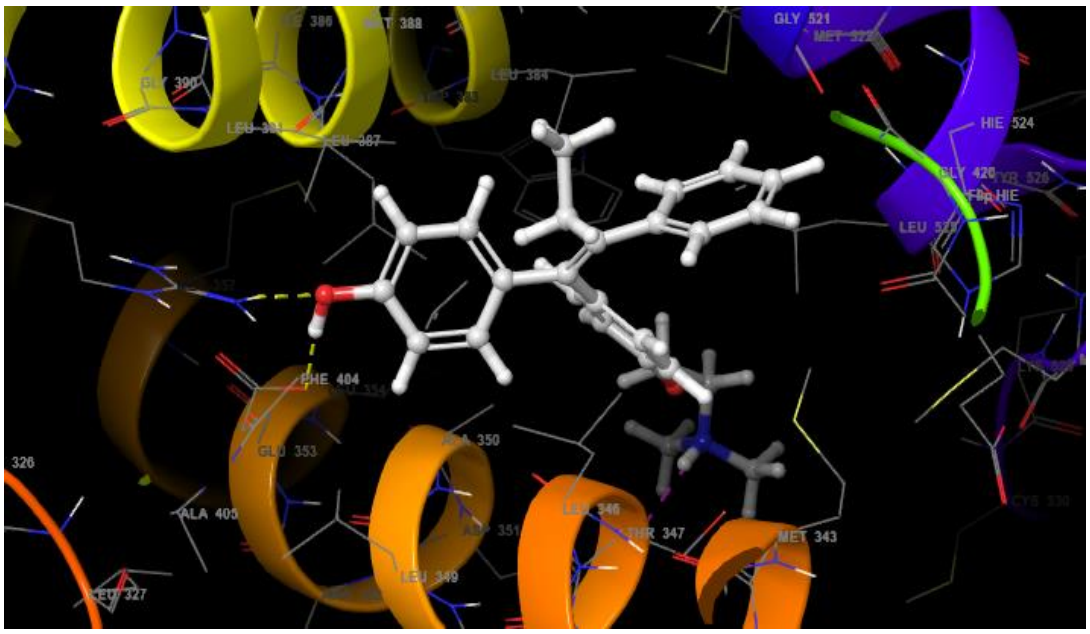
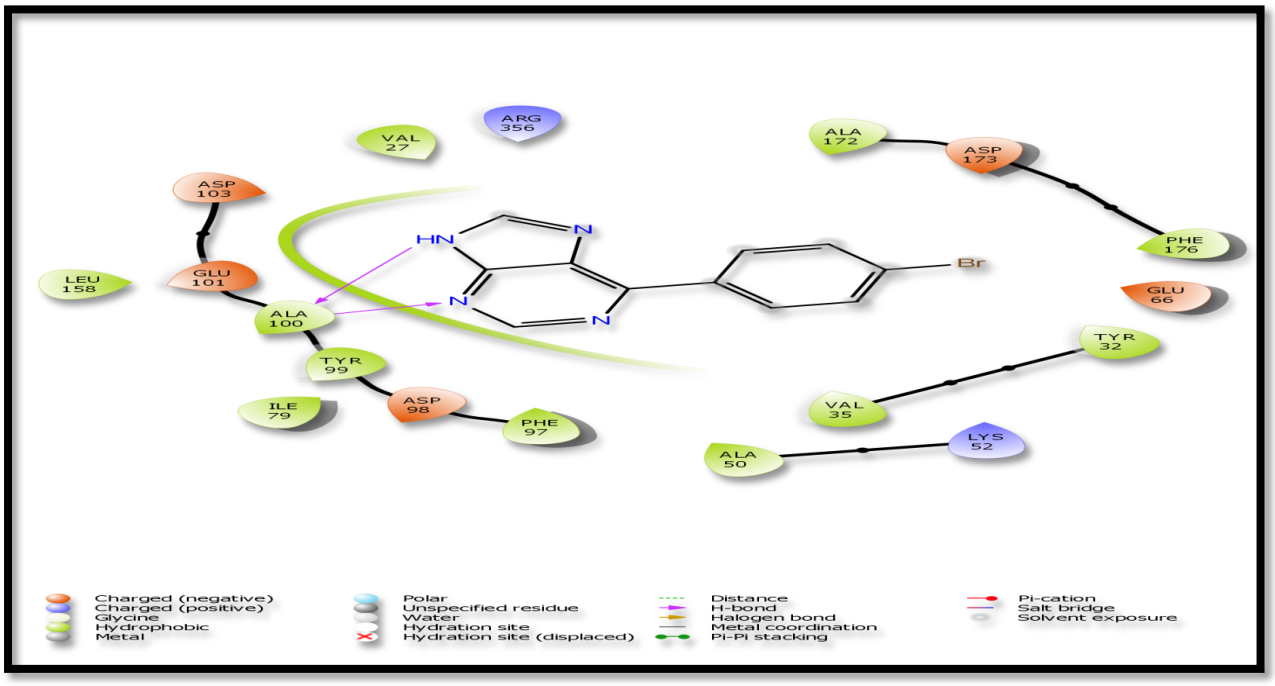


Fig 4: 3ERT Prepared protein structure

The docking study of purines against PDB ID:3ERT was performed and the docking results are presented in Table 5. Total 42 compounds out of 50 have better docking score than doxorubicin and total 25 compounds out of 50 have better docking score than cladribine. Docking studies on PDB ID: 3ERT (breast cancer) showed that compound no. **50** and **40** showed very high docking score -10.368 and -10.262 Kcal/mol as compared to reference drug Cladribine (-7.027Kcal/mol), Doxorubicin (-5.804 Kcal/mol). None of the compounds showed better activity than tamoxifen (-10.669 Kcal/mol). Top 2 compounds which have gooddocking score and amino acid interactions against PDB ID: 3ERT are presented in Table 6.**GLU 353** and **SER 432** is a common interacting residues in compound no. **12** and **13.** Ligand interaction diagram of top purine compounds against PDB ID: 5FGK and 3ERT are givenin Fig 5-10.

Docking interaction images of top 4 purine compounds against PDB ID:5FGK



2-D Ligand interaction diagram

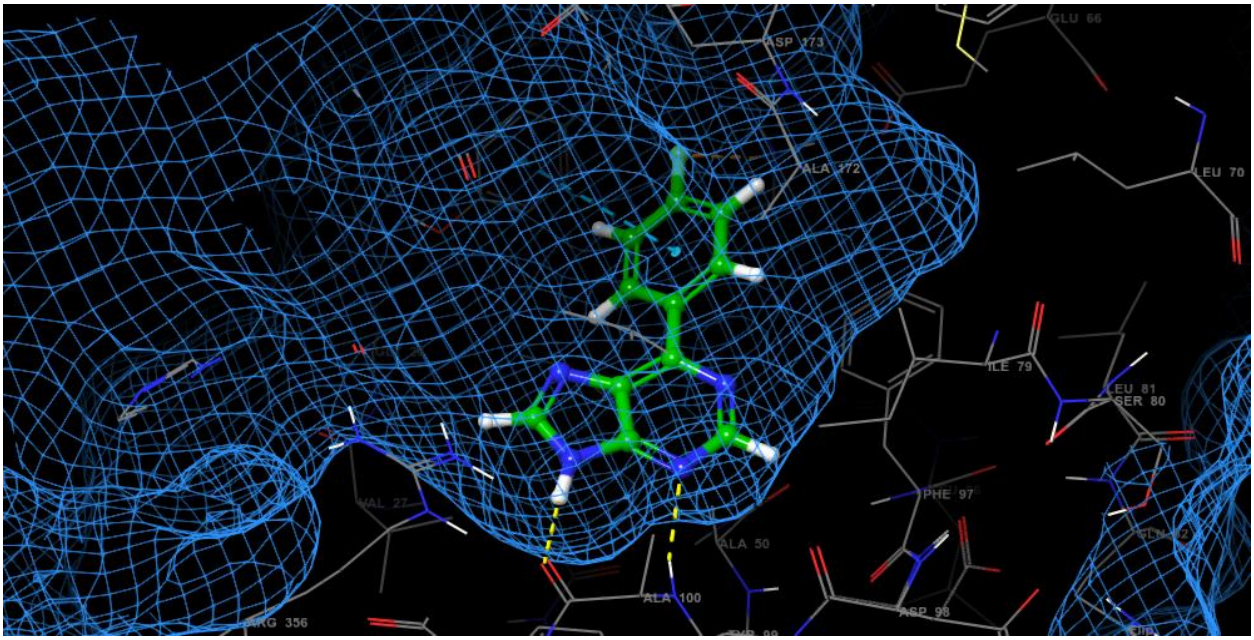
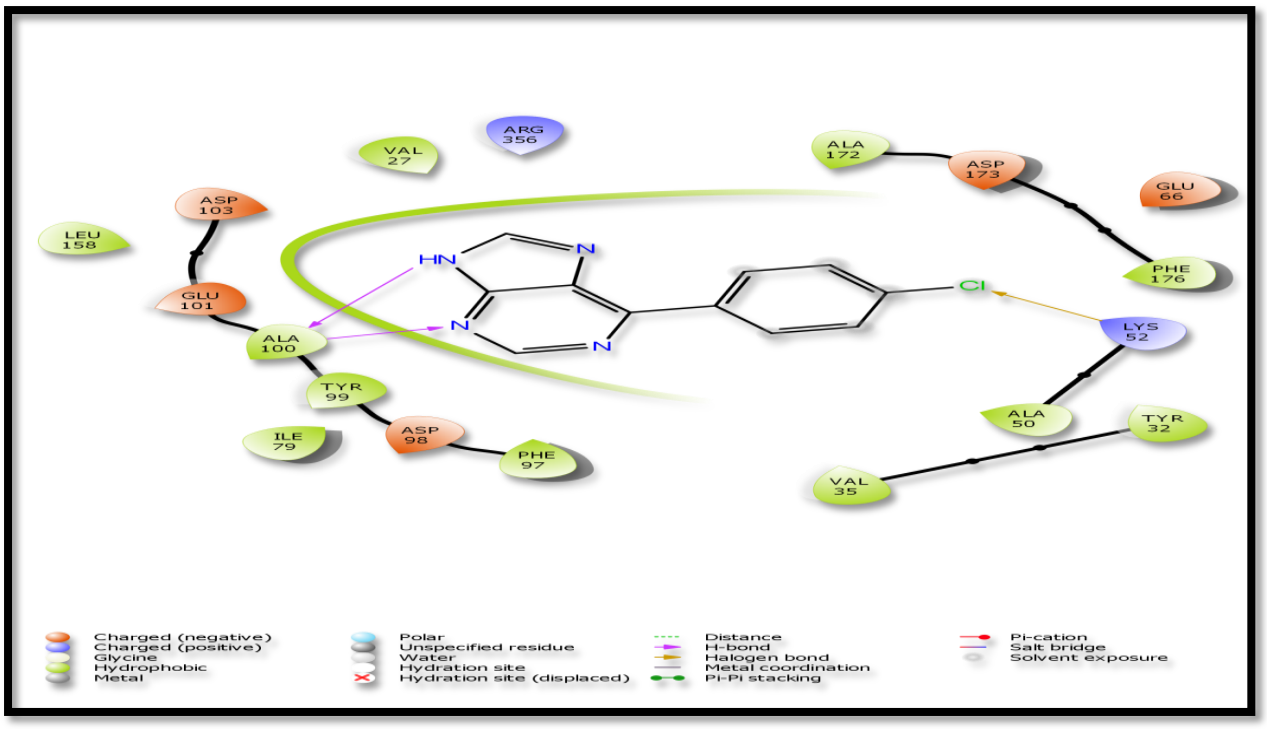


Fig 5: 3-D Ligand interaction diagram of compound 11



2-D Ligand interaction diagram

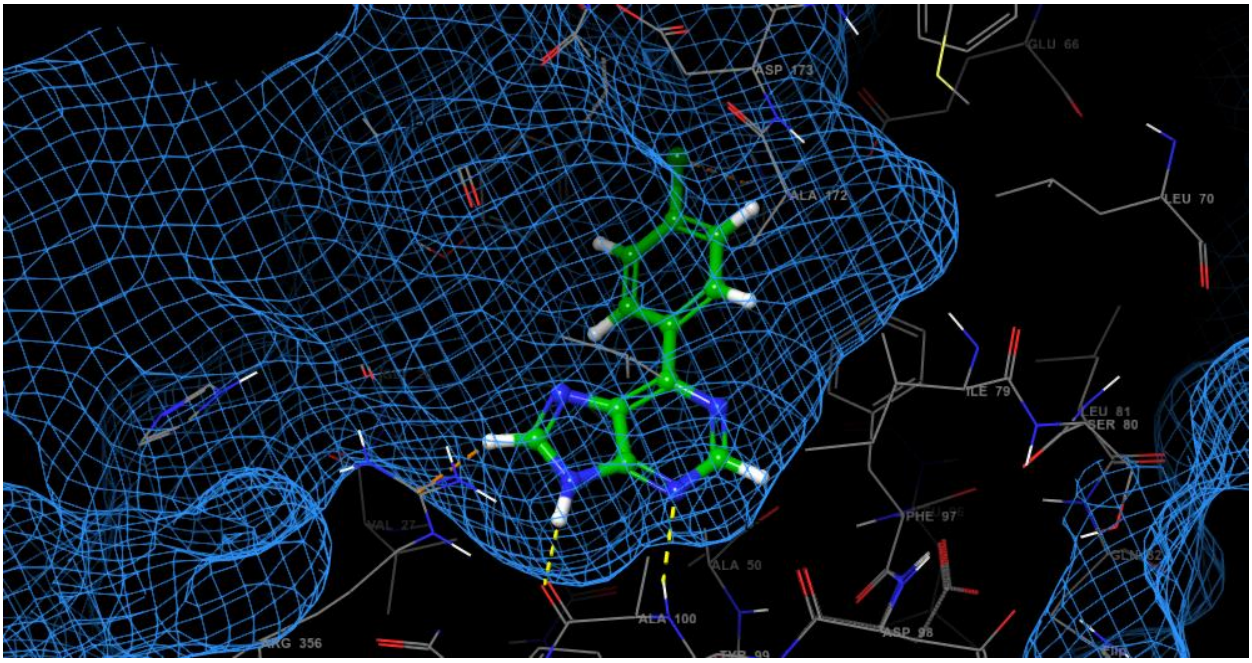
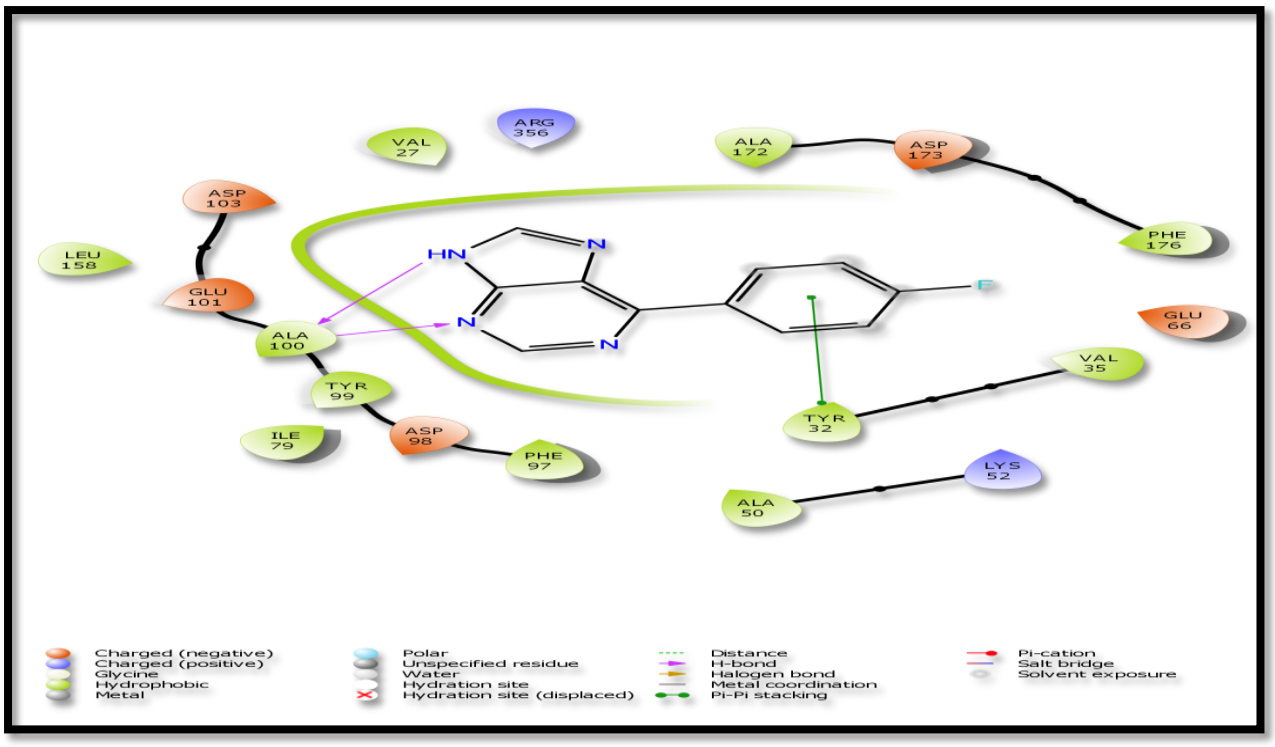


Fig 6: 3-D Ligand interaction diagram of compound 10



2-D Ligand interaction diagram

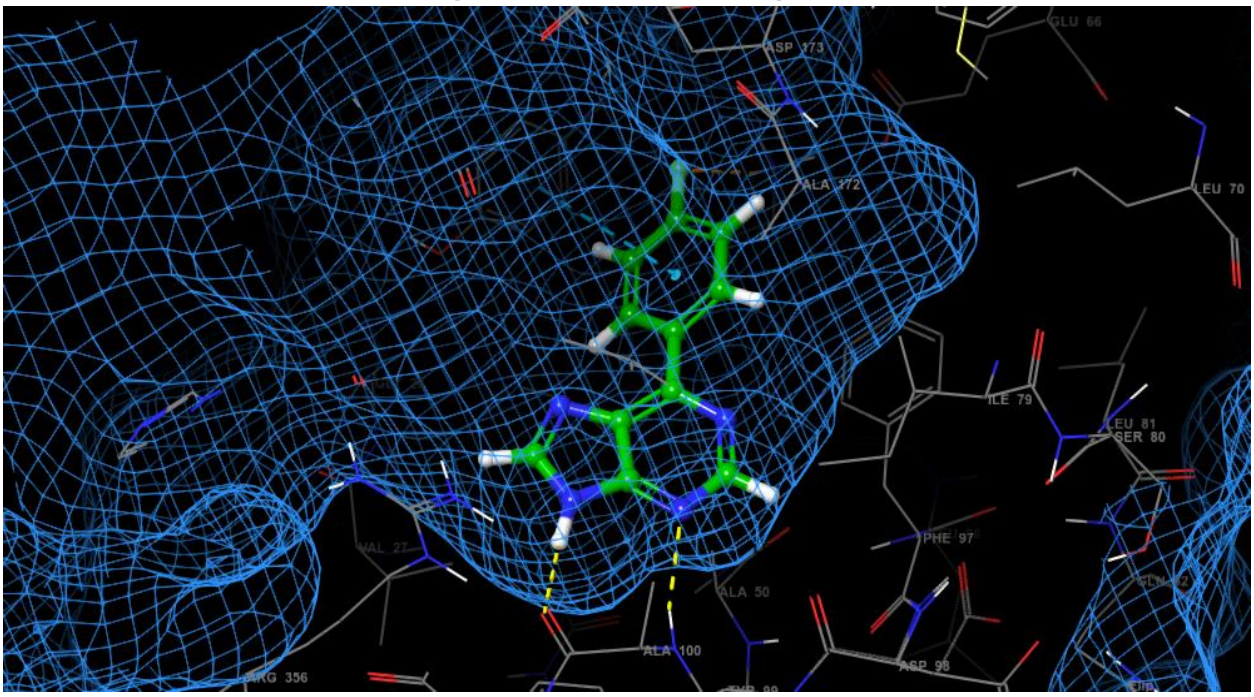
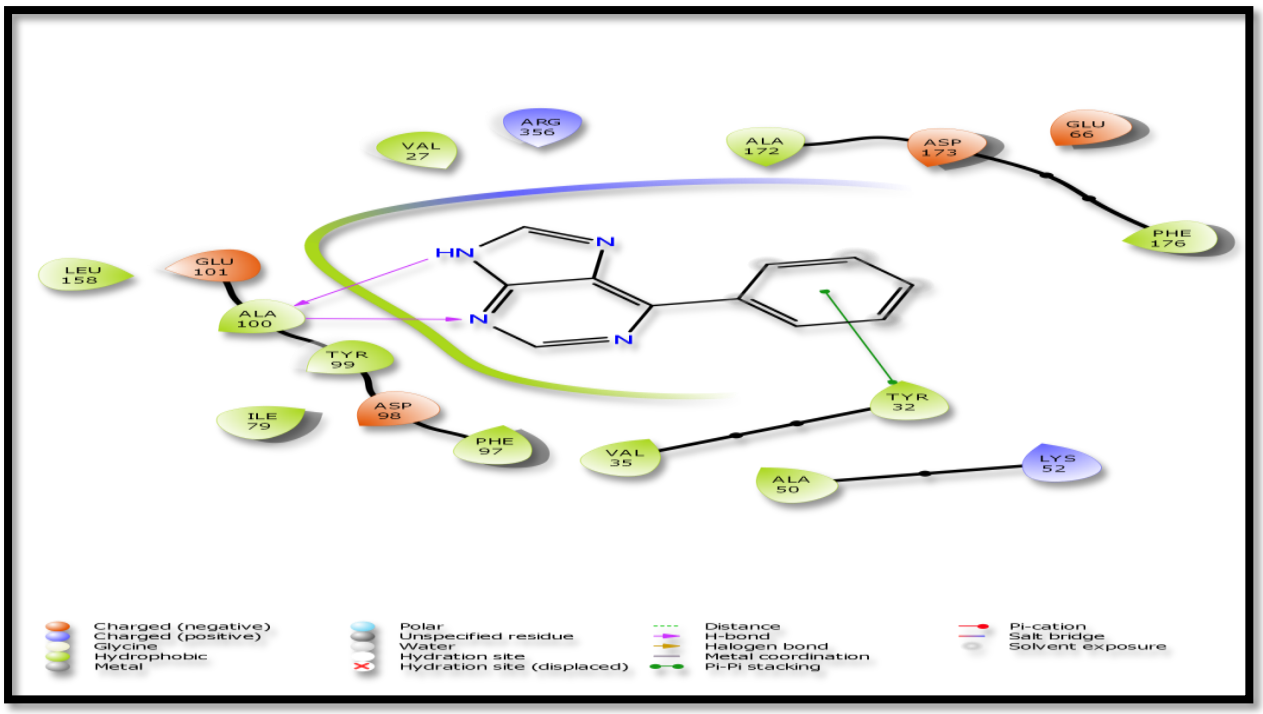


Fig 7: 3-D Ligand interaction diagram of compound 9



2-D Ligand interaction diagram

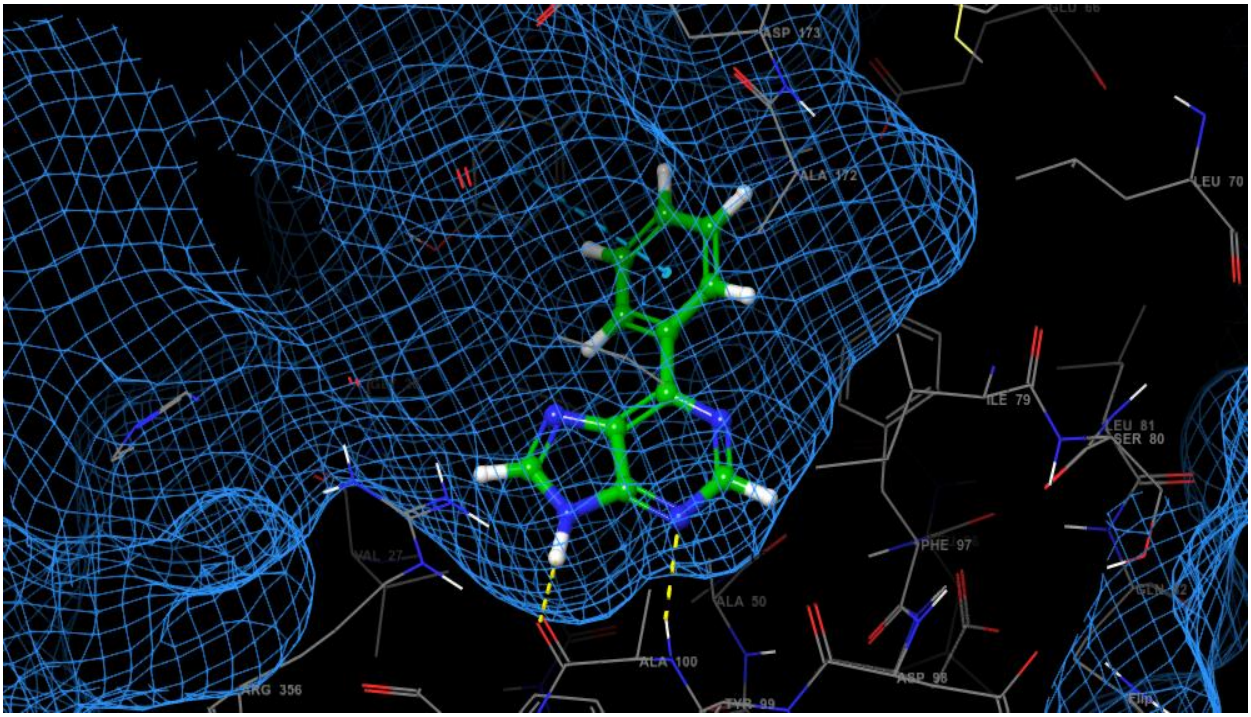
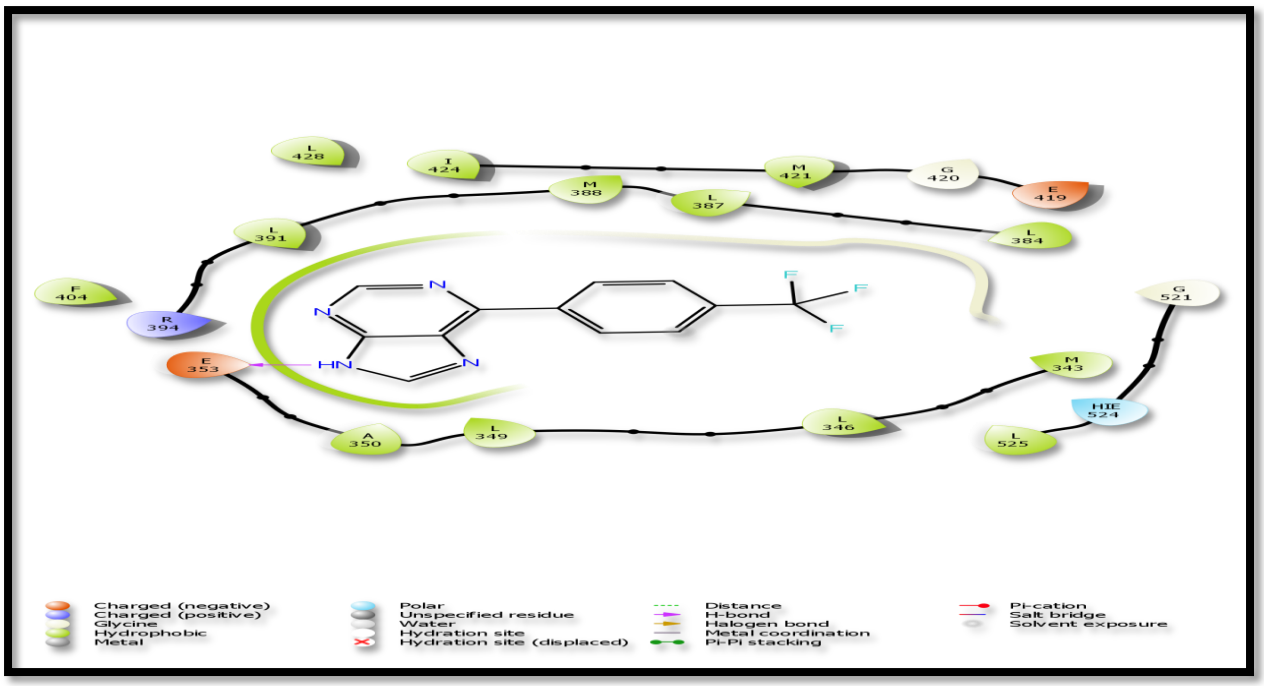


Fig 8: 3-D Ligand interaction diagram of compound 8

Docking interaction images of top 2 purine compounds against PDB ID:3ERT



2-D Ligand interaction diagram

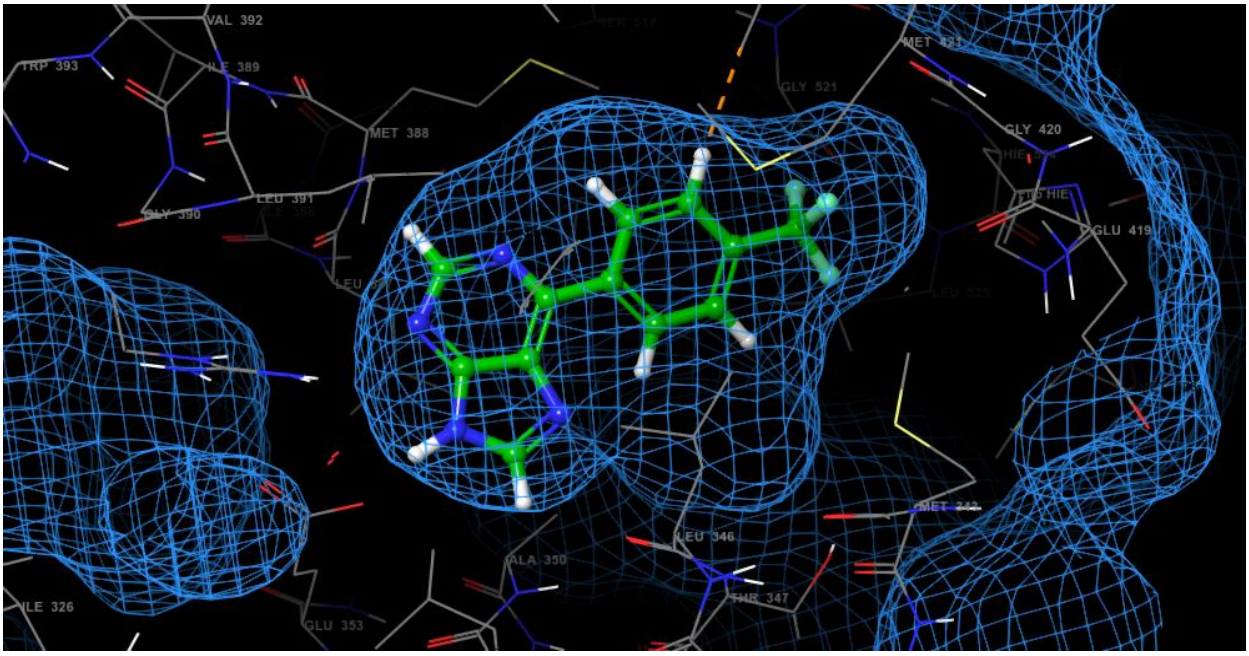
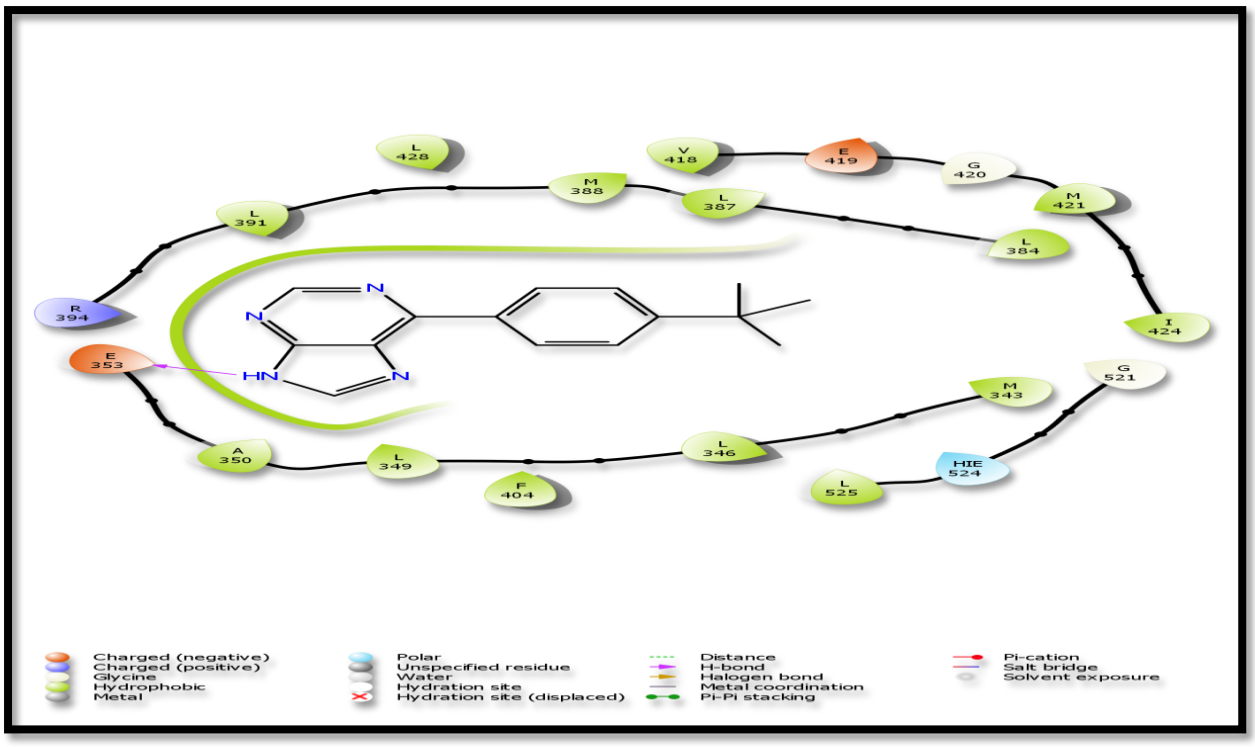


Fig 9: 3-D Ligand interaction diagram of compound 12



2-D Ligand interaction diagram

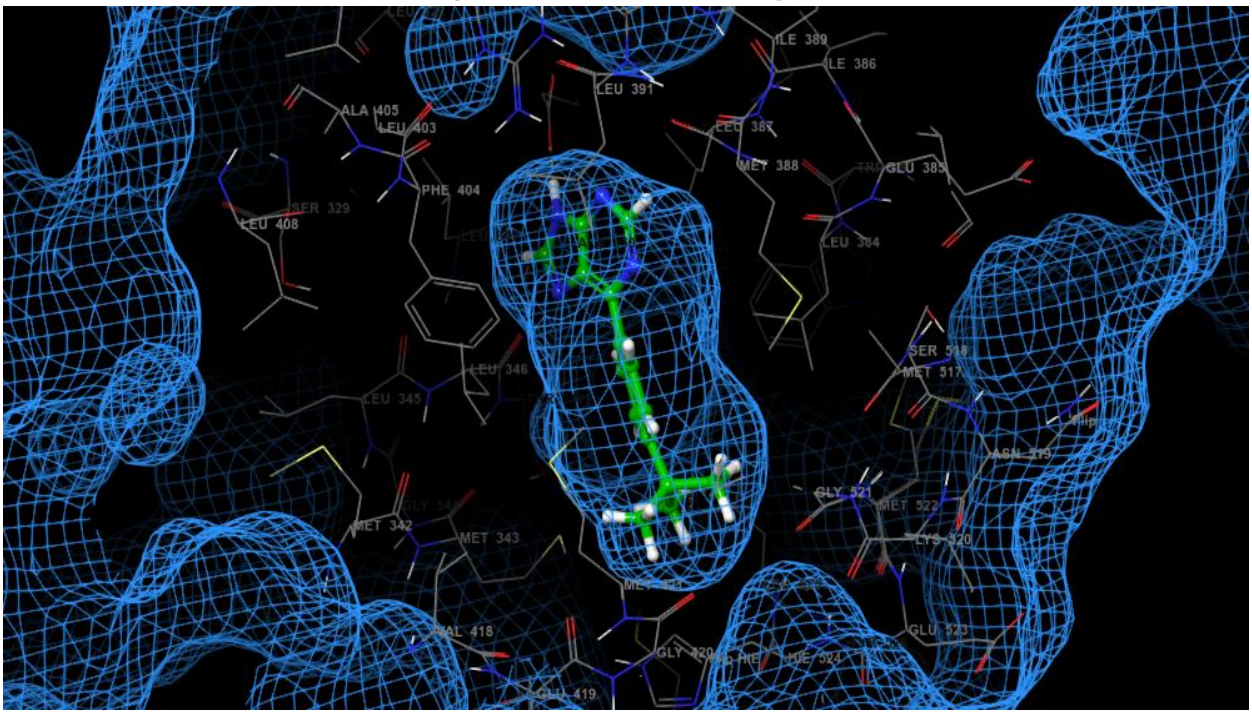


Fig 10: 3-D Ligand interaction diagram of compound 13

3.2 ADMET Prediction:

Using schrodinger maestro 13.0 v suite ADMET properties of purine derivatives are predicted byQikprop is presented in Table 6.

Table 6: ADMET properties of all the 50 purine derivatives

C.No.	MW	HBD	HBA	Log P	Dipole	Log BB	LogKhsa	Lipinski's Rule of 5	Log Kp
1	280.329	0	5.2	2.867	5.453	0.121	-0.128	0	-1.128
2	298.319	0	5.2	3.107	7.525	0.234	-0.082	0	-1.26
3	314.774	0	5.2	3.373	7.469	0.289	0	0	-1.294
4	359.225	0	5.2	3.449	7.227	0.302	0.024	0	-1.295
5	348.327	0	5.2	3.877	8.837	0.392	0.156	0	-1.36
6	336.436	0	5.2	4.151	5.078	0.037	0.448	0	-1.354
7	372.426	0	5.7	4.474	7.13	-0.045	0.41	0	-0.483
8	196.211	1	3.5	1.714	3.922	-0.342	-0.236	0	-2.152
9	214.201	1	3.5	1.946	5.859	-0.236	-0.196	0	-2.286
10	230.656	1	3.5	2.199	5.803	-0.189	-0.127	0	-2.32
11	275.107	1	3.5	2.275	5.515	-0.18	-0.105	0	-2.322
12	264.209	1	3.5	2.724	7.02	-0.098	0.005	0	-2.387
13	252.318	1	3.5	2.926	3.631	-0.455	0.271	0	-2.381
14	288.308	1	4	3.216	6.072	-0.544	0.235	0	-1.526
15	354.358	0	8	2.013	3.989	-0.541	-0.683	0	-1.689
16	404.366	0	8	2.785	3	-0.406	-0.445	0	-1.784
17	392.475	0	8	3.047	6.917	-0.778	-0.156	0	-1.794
18	372.348	0	8	2.254	4.594	-0.436	-0.636	0	-1.824
19	422.356	0	8	3.022	3.385	-0.294	-0.399	0	-1.92
20	410.465	0	8	3.29	7.746	-0.672	-0.108	0	-1.926
21	388.803	0	8	2.537	4.573	-0.38	-0.549	0	-1.842
22	433.254	0	8	2.598	4.41	-0.382	-0.529	0	-1.851
23	422.356	0	8	3.035	5.528	-0.293	-0.395	0	-1.915
24	472.364	0	8	3.808	4.464	-0.158	-0.157	0	-2.011
25	460.473	0	8	4.04	8.461	-0.551	0.126	0	-2.053
26	410.465	0	8	3.297	3.93	-0.666	-0.106	0	-1.921
27	460.473	0	8	4.062	3.16	-0.519	0.127	0	-2.003
28	446.455	0	8.5	3.567	5.478	-0.739	-0.167	0	-1.057
29	496.463	0	8.5	4.339	4.396	-0.612	0.071	0	-1.153
30	484.572	0	8.5	4.635	7.125	-0.998	0.374	0	-1.155
31	406.41	1	7.7	3.255	3.897	-0.071	0.172	0	-4.146
32	444.502	0	6	5.086	3.001	0.635	0.869	1	-3.482
33	440.43	0	6.5	4.999	3.887	0.08	0.538	0	-1.151
34	438.454	0	5	6.092	3.401	0.357	1	1	-0.542
35	452.481	0	5	6.391	3.056	0.321	1.17	1	-0.788
36	506.453	0	5	7.081	5.466	0.595	1.285	2	-0.84
37	456.445	0	5	6.755	4.457	0.503	1.183	1	-0.606
38	474.435	0	5	6.488	4.541	0.51	1.089	1	-0.777
39	507.344	0	5	7.008	4.744	0.635	1.241	2	-0.893
C.No.	**MW**	**HBD**	**HBA**	**Log P**	**Dipole**	**Log BB**	**LogKhsa**	**Lipinski's Rule of 5**	**Log Kp**
40	528.579	0	6	7.028	2.938	0.507	1.403	2	-1.832
41	372.856	1	7.7	2.771	1.436	-0.175	0.042	0	-4.102
42	410.948	0	6	4.655	2.739	0.617	0.718	0	-3.246
43	406.877	0	6.5	4.515	2.371	-0.023	0.388	0	-1.073
44	404.901	0	5	5.556	2.89	0.227	0.838	1	-0.528
45	418.928	0	5	5.884	2.746	0.214	1.014	1	-0.727
46	472.899	0	5	6.568	5.782	0.497	1.124	1	-0.764
47	422.892	0	5	5.797	4.533	0.339	0.885	1	-0.661
48	440.882	0	5	5.991	3.831	0.375	0.94	1	-0.867
49	473.791	0	5	6.495	6.073	0.521	1.084	1	-0.848

50	495.025	0	6	6.5443	2.992	0.402	1.255	1	-1.766

Compounds number **32, 34, 35, 36, 37, 38, 39, 40, 44, 45, 46, 47, 48, 49** and **50**are presented inTable 6 violated the Lipinski rule's of five and not suitable for oral administration while rest of all compounds have better ADMET properties.

3.3Pharmacophore mapping:

In pharmacophore mapping or hypothesis all the library of purine compounds are divided into active and inactive set and their pharmacophoric features are defined by alignment of compounds.

For Active set of compounds: Active compounds pharmacophore hypothesis score presented in Table 7.

Table 7: Pharmacophore hypothesis dataset of active compounds

C.No.	Pharm set	Site score	Vector score	Volume score	Fitness score
32	Active	0.93835	0.98837	0.89976	2.82649
34	Active	0.99791	0.99999	0.98392	2.98183
35	Active	0.93575	0.95528	0.90518	2.79522
36	Active	0.46076	0.98543	0.62205	2.06825
37	Active	1	1	1	3
38	Active	0.91249	0.94852	0.82745	2.68847
39	Active	0.74129	0.76960	0.71814	2.22904
44	Active	0.94650	0.99522	0.83388	2.77560
45	Active	0.95053	0.99418	0.83170	2.77642
46	Active	0.45649	0.83221	0.61392	1.90263
47	Active	0.94138	0.99521	0.83768	2.77428

Active compounds alignment:

Total 11 purine compounds out of 50 are considered to be active in nature and the pharmacophoric features of these active compounds after alignment are shown as below in Fig 11.

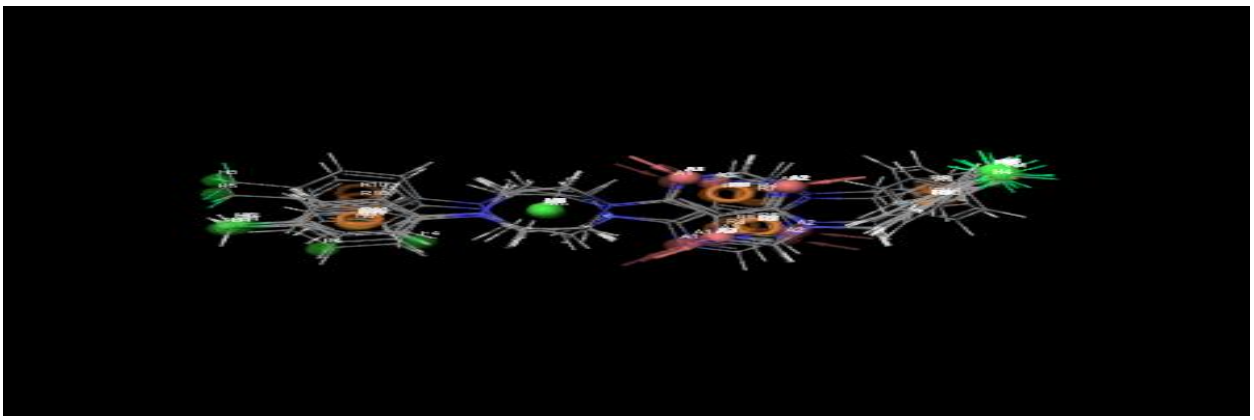


Fig 11: Active set

For inactive set of compounds: Inactive compounds pharmacophore hypothesis score presented in Table 8.

Table 8: Pharmacophore hypothesis score dataset of inactive compounds.

C.No.	Pharm set	Site score	Vector score	Volume score	Fitness score
1	Inactive	0.52207	0.86603	0.45316	1.70054
8	Inactive	0.81309	0.76257	0.38238	1.49614
9	Inactive	0.52833	0.70579	0.38997	1.48097
11	Inactive	0.51248	0.70459	0.38769	1.46767
12	Inactive	0.51366	0.70435	0.43122	1.51171
13	Inactive	0.51444	0.70826	0.42749	1.51237
15	Inactive	0.69721	0.92898	0.56499	1.97115
16	Inactive	0.75010	0.93164	0.58984	2.02153
17	Inactive	0.40535	0.93426	0.50333	1.74270
20	Inactive	0.40524	0.93395	0.50307	1.74205
22	Inactive	0.69729	0.92897	0.56410	1.97029
23	Inactive	0.41384	0.93268	0.50969	1.75327
24	Inactive	0.77376	0.94081	0.62187	2.07182
25	Inactive	0.41978	0.93420	0.50569	1.75483

C.No.	Pharm set	Site score	Vector score	Volume score	Fitness score
6	Inactive	0.40684	0.93406	0.47669	1.71688
2	Inactive	0.25141	0.82072	0.42112	1.49327
3	Inactive	0.23629	0.81638	0.41921	1.47190
4	Inactive	0.22180	0.81474	0.41749	1.45047
5	Inactive	0.20869	0.80748	0.44491	1.46109
6	Inactive	0.22061	0.81013	0.44789	1.47864
48	Inactive	0.45004	0.75094	0.60910	1.81009

Inctive compounds alignment: Total 21 compounds out of 50 are fully inactive in nature. inactive compounds alignment are shown in Fig: 12

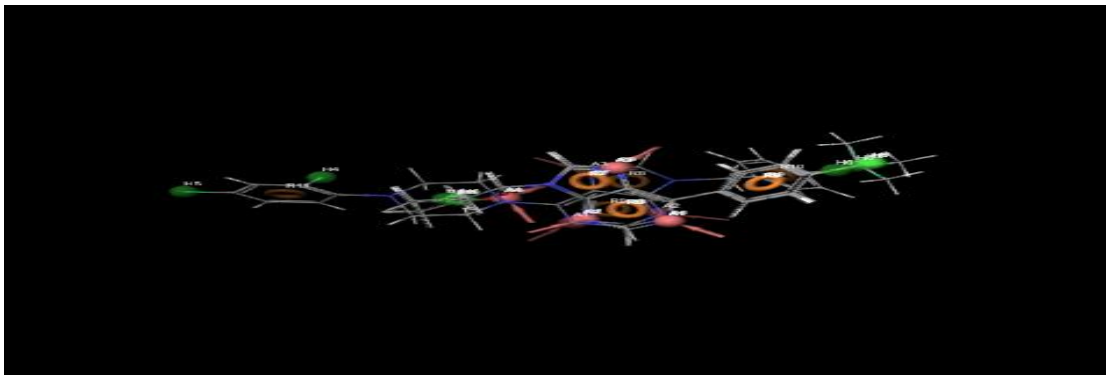


Fig 12: Inactive set

Partially inctive compounds alignment: Total 18 purine compounds out of 50 are partially inactive in nature. Partially inactive compounds alignment are shown in Fig 13.

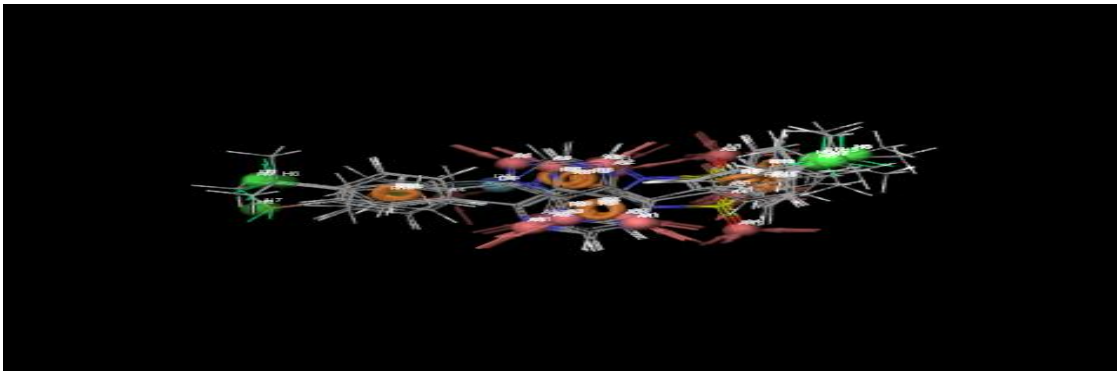


Fig 13: Partially Inactive

Enrichment: Enrichment calculation of pharmacophore hypothesis presented in Table 9.

Table 9: Enrichment calculation of pharmacophore hypothesis

Hypothesis	Phase hypo score	EF1%	BEDROC160.9	ROC	AUAC	Survival score
HRRR3	1.22	91.91	0.96	0.91	0.95	5.53439

Active purine compounds scores are presented in Table 8 and their alignment is shown in Fig 11. Total 11 compounds are active in nature from which compounds number **37** is highly active because its fitness score is **3.** Compound no.**37** interact with amino acid residue **HIS 116** against PDB ID: 5FGK and its highest value of fitness score has not any correlation with molecular docking results. Inactive purine compounds scores are presented in Table 9 and their alignment is shown in Fig 12. Total 21 compounds out of 50 are fully inactive in nature because of their lowest fitness score. Rest of the purine compounds are partially inactive in nature because of its fitness score range is between active and inactive compounds. Total 18 compounds out of 50 are partially inactive in nature and their alignment is shown in Fig 13.

4. Conclusion

All the *in silico* methodology like molecular docking, ADMET prediction and pharmacophore mapping were performed on library of 50 purine derivatives taken from literature (Kucukdumlu *et al*., 2017), (Tuncbilek *et al*., 2020) as anticancer agents. Molecular docking study was performed using PDB ID: 3ERT (for breast cancer) and PDB ID: 5FGK (for colorectal cancer). Docking studies on PDB ID: 5FGK (colorectal cancer) showed that compounds no. **11** and **10** showed very high docking score -8.703 and -8.69 Kcal/mol as compared to reference drug 5-fluorouracil (-6.582Kcal/mol), doxorubicin (-6.24Kcal/mol) and cladribine (-6.121 Kcal/mol). Docking studies on PDB ID: 3ERT (breast cancer) showed that compounds no. **50** and **40** showed very high docking score -10.368 and -10.262 Kcal/mol as compared to reference drug cladribine (-7.027Kcal/mol), doxorubicin (-5.804 Kcal/mol). The selected purines showed less activity than tamoxifen (-10.669 Kcal/mol). Compounds number **32, 34, 35, 36, 37, 38, 39, 40, 44, 45, 46, 47, 48, 49** and **50** violated the Lipinski rule's of five and not suitable for oral administration while rest of all compounds have better ADMET properties. Based on Pharmacophore hypothesis the compounds no. **37** showed very high fitness score **3** as compared to other purine compounds.

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