In Silico Modelling and ADME Studies of Pyrimidine Derivatives Act as DHFR Reductase Inhibitor

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Abstract:
Computer-aided drug design is a useful tool in advanced medicinal chemistry. The main aim of molecular docking is to achieve an optimal conformation and computationally simulate the molecular identification process to reduce the free energy of the entire system and reduce the cost and time to synthesize novel molecules. This research article aimed to examine the possibility of a link between the docking scores and the experimental bioactivities of the inhibitors. All of the docking and ADME results revealed that most of the compounds show the best docking score on PDB 2RGO and follow Lipinski's rule. This indicates that these derivatives can be used further for advanced research as a lead compound.

Keywords: Molecular docking, *In silico* modeling, ADME, Pyrimidine, Lipinski rule

1. INTRODUCTION:

Molecular docking is one of the most appropriate tools in medicinal chemistry to predict the most active compounds in the series by the interaction between a ligand and a protein (1). The process of molecular docking involves two steps first to predict the ligand conformation and second to indicate its position and orientation within these sites and to estimate the binding affinity (2). Therefore, molecular docking plays an important role in drug discovery and designing of novel drugs. Molecular docking is designed to predict the optimal binding mode of molecules and simulate their interactions using computational methods, with the ultimate goal of reducing the free energy of the system and facilitating the discovery of novel molecules with improved properties. At present day drug discovery is based on in-silico, chemical, and biological approaches. Computer-aided drug design's acceptance, use, and popularity in the drug pharmaceutical research and development process are increasing.

Molecular Docking provides an array of valuable tools simple molecular visualization and easy access to structural databases are becoming essential tools on the desktop for the medicinal chemist (3). Our current work aimed to examine the possibility of a link between the docking scores and the experimental bioactivities of the inhibitors. All of the docking tests were carried out using the default parameters to obtain reliable results.

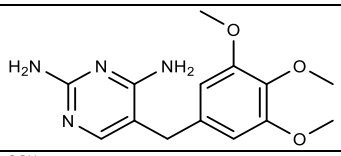
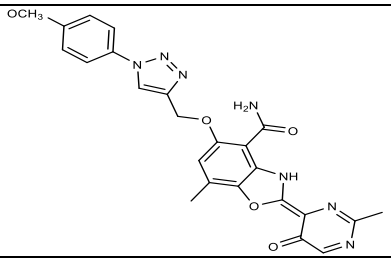
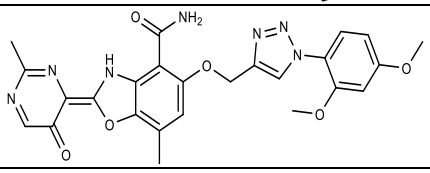
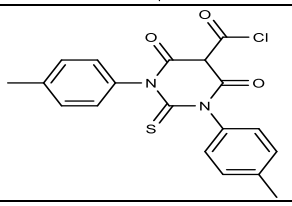
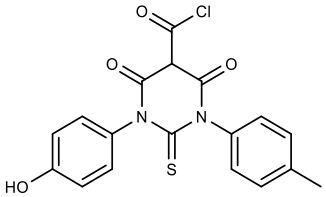
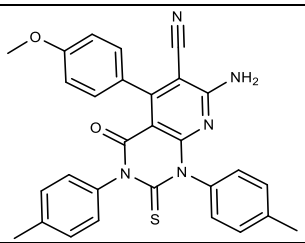
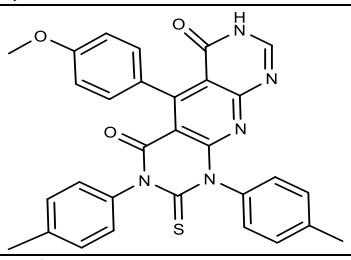
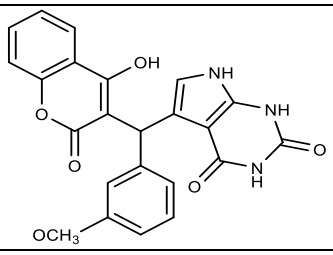
2. MATERIAL AND METHOD:

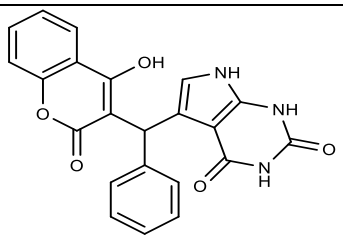
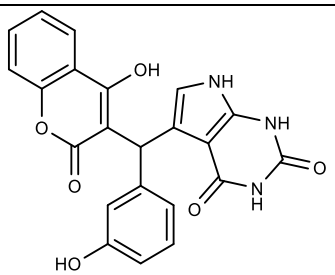
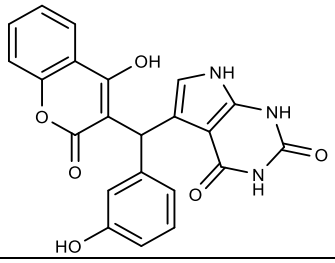
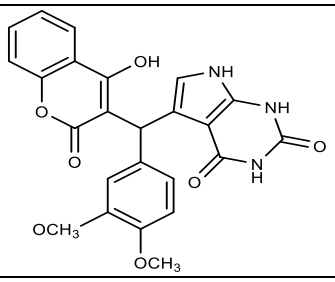
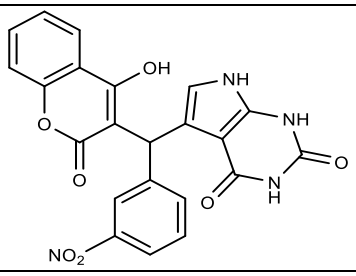
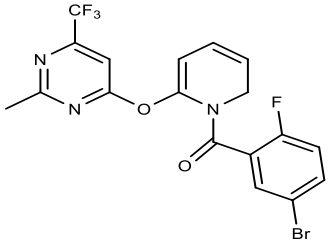
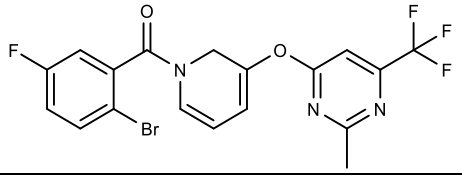
2.1 Molecular Docking Study:

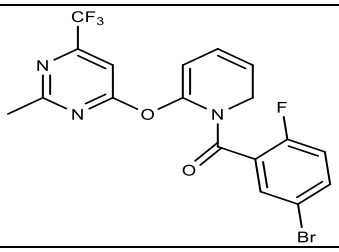
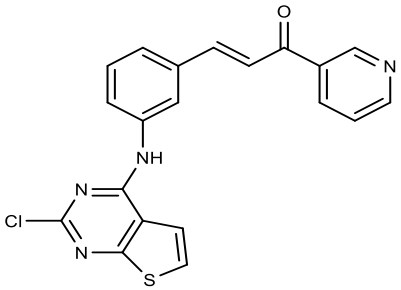
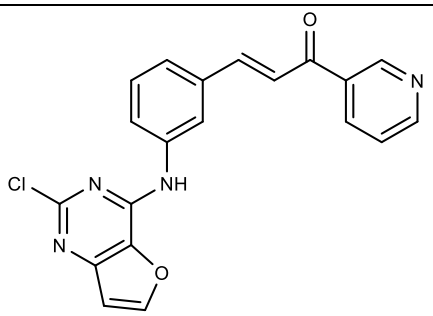
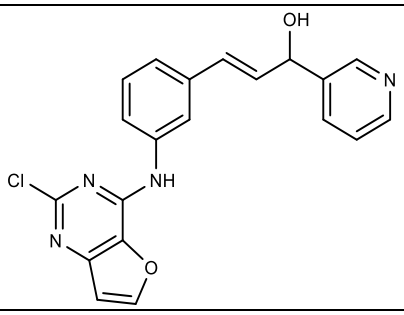
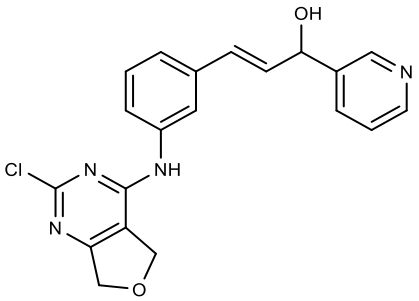
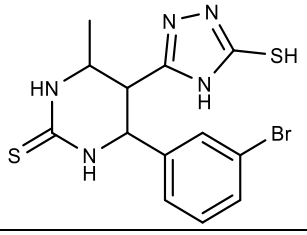
Pyrimidine containing the most active compounds having good antimicrobial potential was drawn by the chem draw 15.0 as shown in **Table 1**. The molecular docking of these compounds was done by using Schrodinger suite software 13.1. Molecular docking was performed to predict the interaction of compounds already synthesized by different researchers with the binding site of oxidoreductase the crystal structure of the protein (PDB code: 2RGO) with resolution 2.40 Å was chosen as the model for the current review (4).

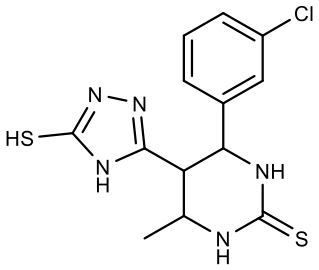
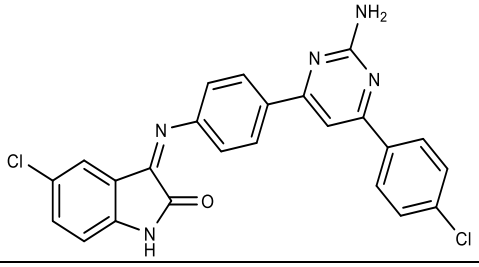
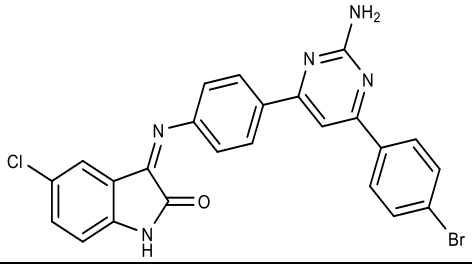
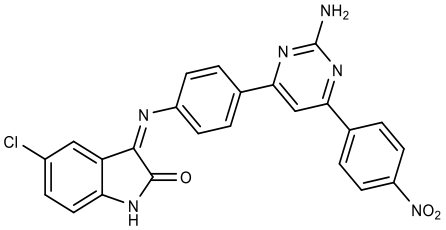
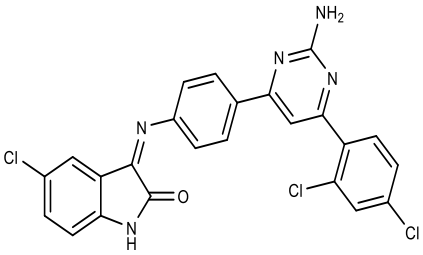
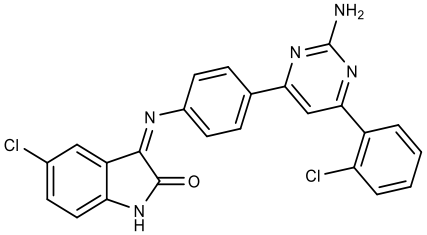
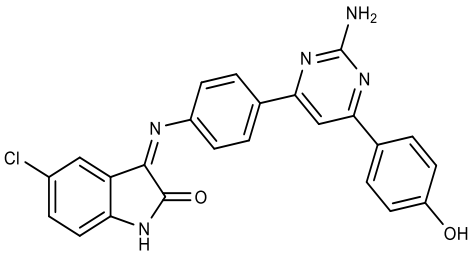
After 45 ligands with standard drug trimethoprim were run for docking, a cluster analysis was performed. According to the root mean square deviation (RMSD) tolerance of 2.0 Å conformations were clustered and were ranked by the energy of which the conformation with the best-scored pose with the lowest binding energy was selected for these ligands (5).

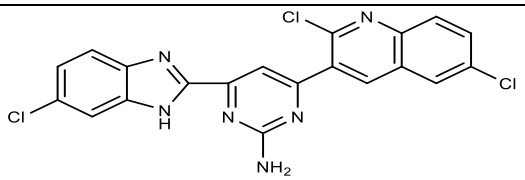
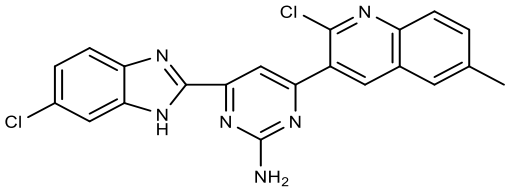
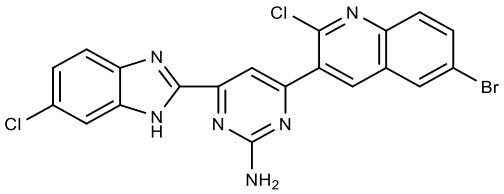
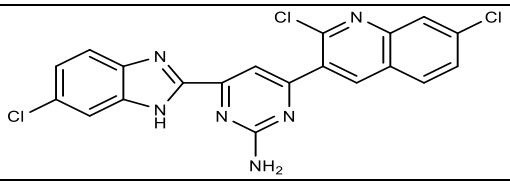
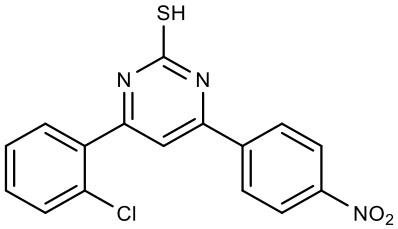
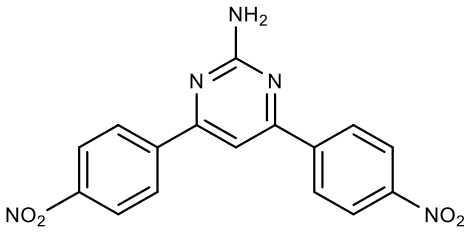
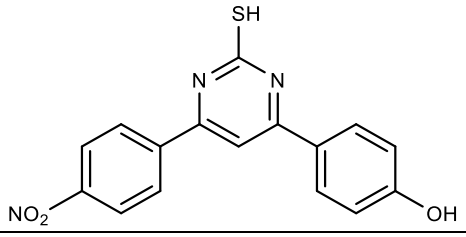
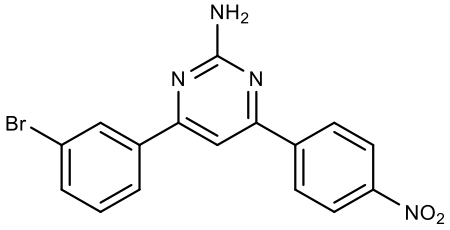
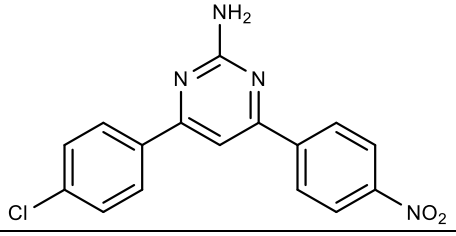
Table 1. Chemical structure and their IUPAC name containing Pyrimidine nucleus

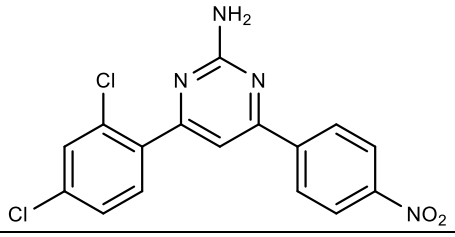
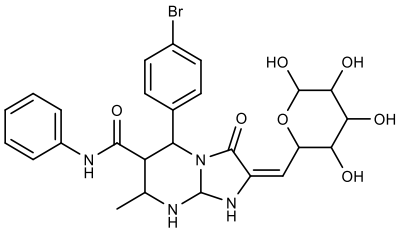
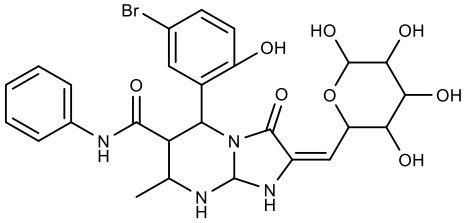
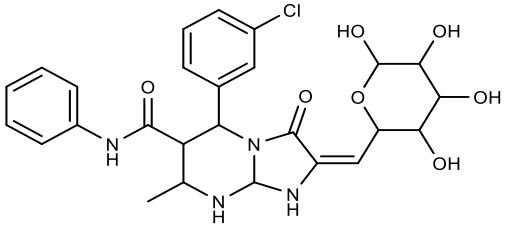
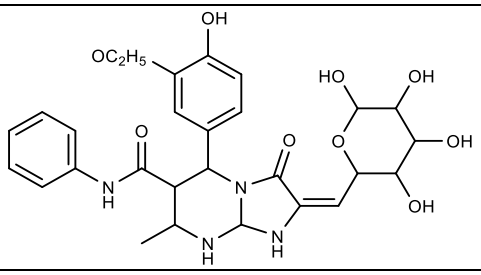
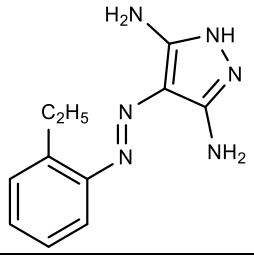
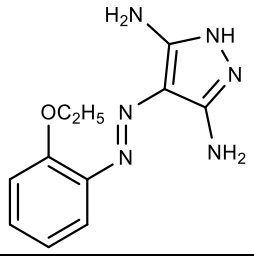
References	Compounds	Chemical Structure
	Trimethoprim	
[12}	M2	
[12}	M3	
[13]	M4	
[13]	M5	
[13]	M6	
[13]	M7	
[14]	M8	

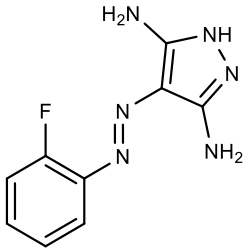
[14]	M9	
[14]	M10	
[14]	M11	
[14]	M12	
[14]	M13	
[18]	M14	
[18]	M15	

[18]	M16	
[15]	M17	
[15]	M18	
[15]	M19	
[15]	M20	
[16]	M21	

[16]	M22	
[17]	M23	
[17]	M24	
[17]	M25	
[17]	M26	
[17]	M27	
[17]	M28	

[17]	M29	
[17]	M30	
[17]	M31	
[17]	M32	
[19]	M33	
[19]	M34	
[19]	M35	
[19]	M36	
[19]	M37	

[19]	M38	
[20]	M39	
[20]	M40	
[20]	M41	
[20]	M42	
[21]	M43	
[21]	M44	

[21]	M45	

2.2 ***In silico ADME Study***

The *in silico* ADME screening and drug-likeness assessment was performed using the free web tool Qikprop Schrodinger software [6].

The early characterization of ADME properties of compounds in the drug discovery process holds significant value for selecting improved drug candidates. This importance has increased with the development and maturation of technologies impacting this process. [7-9]

Lipinski's Rule of Five is a foundational guideline for designing orally active compounds. The rule defines specific property limits, including clogP, molecular weight, and hydrogen bonding, to predict oral bioavailability. Interestingly, pharmaceutical compounds show significant variability in oral absorption and solubility. Lipinski's Rule of Five is a foundational guideline for designing orally active compounds. The rule defines specific property limits, including clogP, molecular weight, and hydrogen bonding, to predict oral bioavailability. Interestingly, pharmaceutical compounds show significant variability in oral absorption and solubility. Consequently, in pharmaceutical development, it is imperative to prioritize the enhancement of the lead compound's solubility, even at the expense of compromising the molecule's permeability[10-11].

3. Results and discussion:

The structures of ligands were optimized using the ChemDraw 15.0 software. Schrodinger 18.0 software was used to prepare the ligands and grid generation before submitting it for docking analysis with ligand-protein docking.

The outcome of the docking studies was found to be in harmony with a report for pyrimidine-containing compounds (PDB code: 2RGO). The docking score results are shown in **Table 3.** Thus, the docking analyses suggested that the pyrimidines can act as of great interest to inhibit the dihydrofolate reductase pathway. DHFR plays a crucial role in the biosynthesis of DNA, RNA, and certain amino acids because of the interaction shown in **(Fig. 1)** with the protein. It is responsible for converting dihydrofolate to tetrahydrofolate, which is used as a substrate in various one-carbon transfer reactions involved in purine and pyrimidine synthesis, including the synthesis of thymidylate. When DHFR enzymatic activity is inhibited, it depletes the tetrahydrofolate pool inside the cell, leading to the inhibition of DNA synthesis and ultimately resulting in cell death. This is why DHFR has been extensively studied, and potential drug candidates known as antifolates have been synthesized and tested.

Most of the derivatives showed good to moderate binding results when compared to Trimethoprim as a standard drug of Pyrimidine nucleus on PDB id 2RGO. Compounds having good docking scores (-10 to -7) make them more potent antimicrobial agents and these compounds may be used as leads for the development of novel antimicrobial and anticancer agents. ADME result summarized that the compounds M4, M6, M8-M12, M14-M23, M25-M37, and M42-M45 follow the Lipinski rule of five shown in **Table 2**. Lipinski's rule indicates that these derivatives can be used further for advanced research as a lead compound**.**

3.1 ***ADME study*****:**

The ADME properties of pyrimidine derivatives were determined by using the Schrodinger 13.1 Qikprop module. Ligands were prepared of all the compounds by using ligprep tool in Schrodinger software. Molecular structures are used in silico to predict ADME properties, such as molecular weight, hydrogen bonding, and lipophilicity. The Rule of Five, proposed by Lipinski, establishes a relationship between pharmacokinetic and physicochemical parameters, guiding the design of orally active drugs[22-23].

Predicting ADME parameters from molecular structure is the common goal of a wide range of in silico techniques. Lipinski et al.'s pioneering research examined active compounds when taken orally to determine the physicochemical ranges where medication is highly likely to be taken orally (i.e., the drug-likeness).

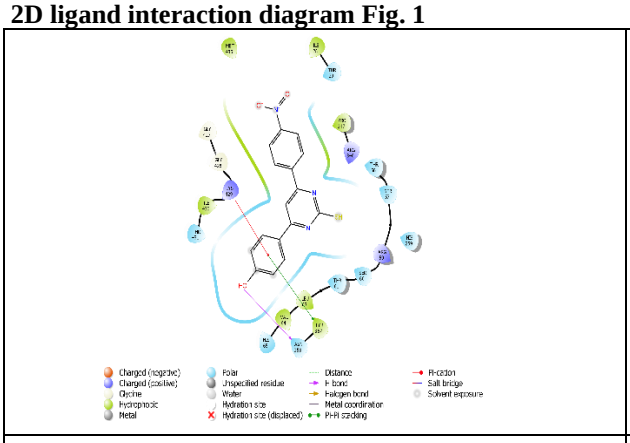
Table 3. ADME properties of the Pyrimidine derivatives

Compounds	MW	Donar HB	Accept HB	*c*logP	Human Oral Absorption	Rule of five
M2	487.474	2	9.5	3.006	1	1
M3	517.5	2	10.25	3.155	1	2
M4	386.852	0	5.5	4.1	3	0
M5	388.825	1	6.25	3.262	3	0
M6	505.593	2	6.75	5.577	1	2
M7	533.603	1	8.25	5.559	1	2
M8	431.404	4	7.5	1.978	3	0
M9	401.378	4	6.75	1.815	3	0
M10	415.404	4	6.75	2.152	3	0
M11	417.377	5	7.5	1.097	2	0
M12	461.43	4	8.25	2.098	3	0
M13	446.375	4	7.75	1.255	2	1
M14	458.209	0	5.5	4.854	1	0
M16	458.209	0	5.5	4.854	1	0
M17	392.862	1	6	4.107	3	0
M18	376.801	1	6.5	3.461	3	0
M19	376.801	1	6.5	3.461	3	0
M20	380.833	2	7.4	3.238	3	0
M21	321.414	4.8	5.25	2.213	3	0
M22	339.86	3.8	4.5	3.451	3	0
M23	460.321	3	6	4.577	1	0
M24	504.772	3	6	4.652	1	1
M25	470.874	3	7	3.409	1	0
M26	494.766	3	6	4.944	1	0
M27	460.321	3	6	4.455	1	0
M28	441.876	4	6.75	3.321	1	0
M29	441.706	3	5	4.508	1	0
M30	421.288	3	5	4.327	1	0
M31	486.157	3	5	4.583	1	0
M32	441.706	3	5	4.509	1	0
M33	343.787	0.8	3	4.406	3	0
M34	337.294	2	4.5	1.945	2	0
M35	325.341	1.8	3.75	3.194	3	0
M36	371.192	2	3.5	3.173	3	0
M37	361.187	2	3.5	3.534	3	0
M38	589.442	6	15.5	-0.214	1	3
M39	589.442	6	15.5	-0.223	1	3
M40	605.441	7	16.25	-0.844	1	3
M41	544.991	6	15.5	-0.231	1	3
M42	570.598	7	17	-1.027	1	3
M43	230.272	5	4	0.788	3	0
M44	246.271	5	4.75	0.768	3	0
M45	220.209	5	4	0.356	3	0

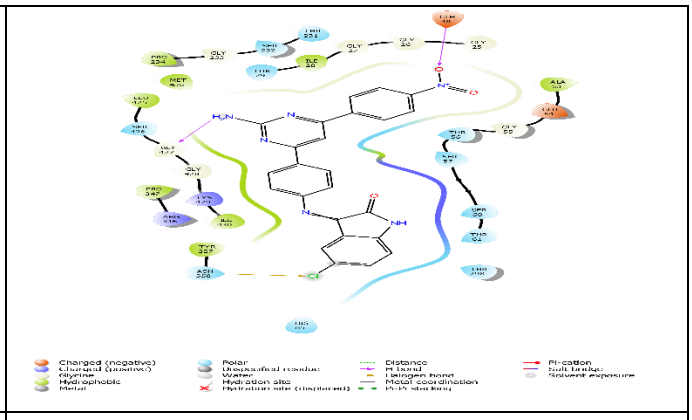
Table 2. docking score and docking energy of Pyrimidine derivatives

S.No.	Compounds	Docking score	Docking energy
1.	M 31	-10.6125	-52.442048
2.	M 35	-10.5611	-44.472317
3.	M 28	-10.4601	-43.931068
4.	M 25	-10.4091	-65.659359
5.	M 11	-10.4007	-57.745934
6.	M 30	-10.2265	-68.152263
7.	M 26	-10.1386	-66.707792
8.	M 29	-10.0978	-60.620084
9.	M 32	-10.0098	-36.228912
10.	M 23	-9.99879	-60.925892
11.	M 27	-9.91536	-60.925892
12.	M 13	-9.85825	-65.340952
13.	M 24	-9.68741	-54.105305
14.	M 15	-9.39457	-60.523937
15.	M 33	-9.14035	-45.85954
16.	M 17	-8.9671	-52.665717
17.	M 34	-8.85695	-52.198667
18.	M 10	-8.82054	-12.193819
19.	M 18	-8.82054	-36.381359
20.	M 19	-8.76604	-56.611651
21.	M 20	-8.69302	-54.638041
22.	M 36	-8.57605	-51.152995
23.	M 9	-8.57571	-52.798737
24.	M 4	-8.53163	-54.648081
25.	M 19	-8.76604	-32.075532
26.	M 37	-8.29214	-48.929696
27.	M 12	-8.25173	-46.082377
28.	M 2	-8.25173	-50.50091
29.	M 3	-8.15368	-60.456099
30.	M 8	-7.9149	-60.456099
31.	M 14	-7.89303	-37.150808
32.	M 45	-7.6942	-36.680846
33.	M 22	-7.61291	-36.680846
34.	M 16	-7.16188	-50.739229
35.	M 21	-7.15838	-60.57471
36.	M 1	-7.15838	-44.906722
37.	**Trimethoprim**	**-6.99357**	**-53.671784**
38.	M 41	-6.90556	-53.559923
39.	M 13	-6.77558	-49.727631
40.	M 21	-6.62054	-27.653115
41.	M 36	-6.60728	-53.255001
42.	M16	-6.58629	-41.971295
43.	M 32	-6.50049	-33.514457
44.	M 38	-6.17737	-34.506727
45.	M 26	-6.15292	-40.739267
46.	M 22	-5.61894	-64.320873
47.	M 4	-5.61894	-52.442048
48.	M 45	-5.6	-44.472317
49.	M 15	-5.52901	-43.931068

2D ligand interaction diagram Fig. 1



M35



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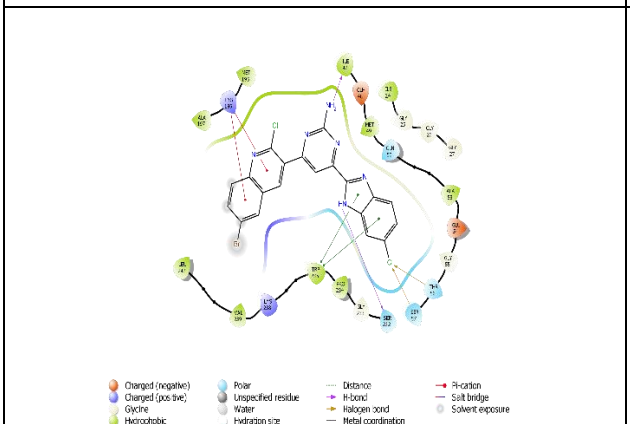
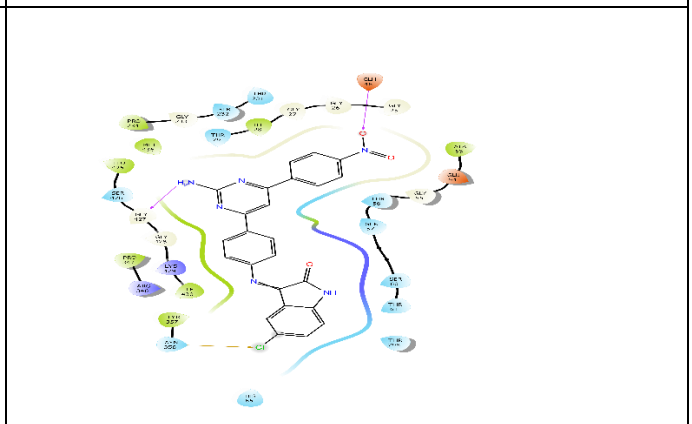


M 38



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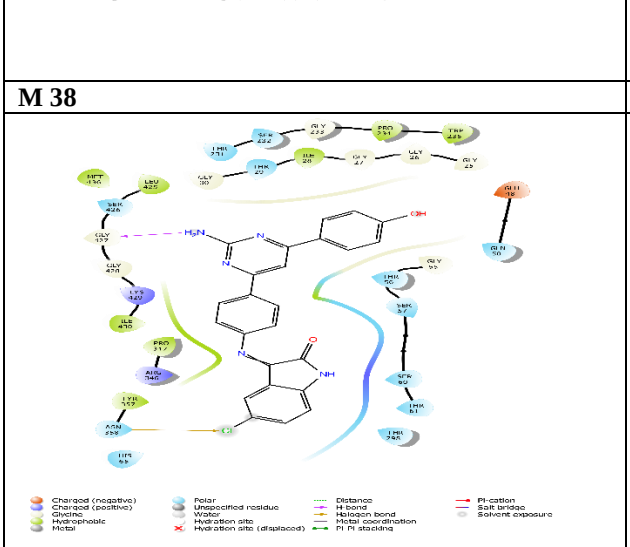
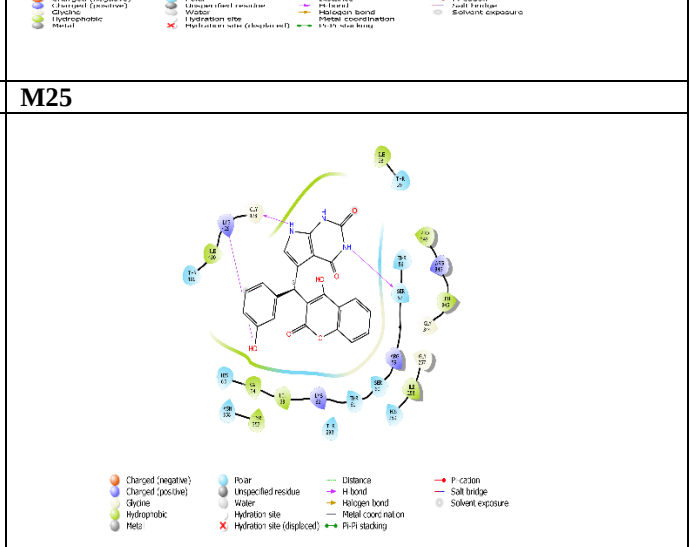
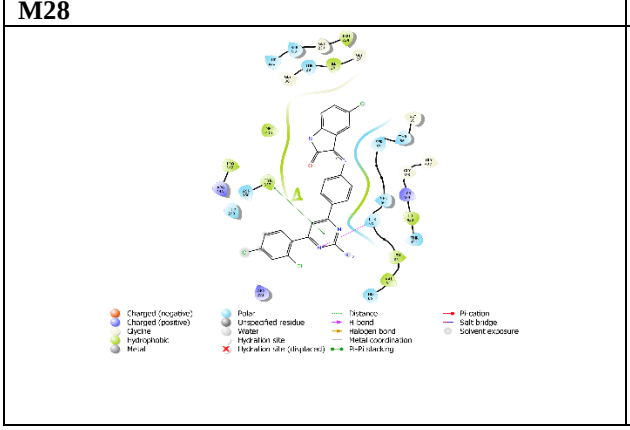
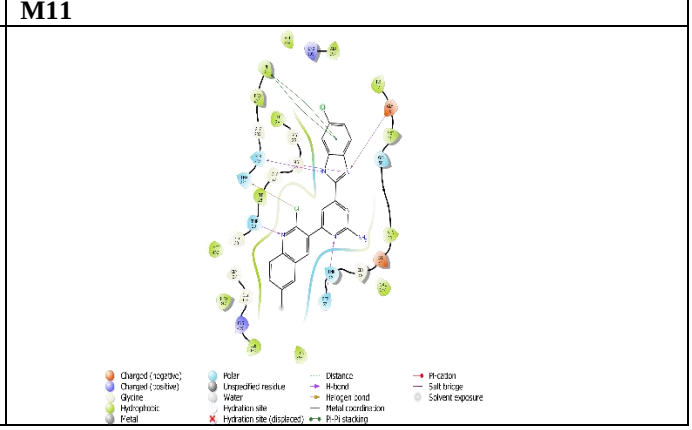


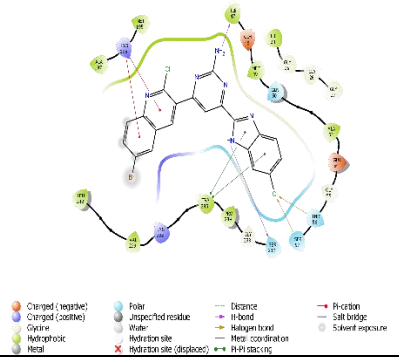
M28



M11





M29	M30
	
M31	

Conclusion: Pyrimidine derivatives designed in the study bind with the receptor 2RGO efficiently, therefore it can be concluded that these pyrimidine derivatives can be modified and synthesized for better antimicrobial potential.

Declarations

Ethical approval and consent to participate:

The authors declare no conflict of interest. This article does not involve any animal experiments or human subject experiment. All the descriptions in this manuscript are accurate and agreed by all authors in such a manner to meet the standard of the Journal**.**

Consent for publication:

We undersigned, give our consent for the publication of identifiable details, which included text, tables and figures to be published in the journal and article.

Availability of data and material:

we have presented all our main data in the form of tables and figures.

Competing interests:

The authors declare that they have no competing interests

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Authors' contributions:

Authors MK and AK perform docking and ADME studies of active compounds. Author MK read and approved the final manuscript.

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Conflict of interest:

The authors list no conflicts of interest. The paper's writing and content are entirely the authors' responsibility.

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Abbreviation list:
DHFR: Dihydrofolate reductase
ADME: Absorption, distribution, metabolism, excretion
PDB: Protein data bank
DNA: Deoxyribonucleic acid
RNA: Ribonucleic acid