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Research Article

Design, Docking and ADME-T Prediction of Novel Pyrimidine-Based Antimicrobials via the Biginelli Reaction

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ABSTRACT

Pyrimidines are a crucial group of heterocycles in pharmaceutical research due to their antiviral, anticancer, antibacterial, and antioxidant properties. The heterocyclic compound 1,2,3,4-tetrahydropyrimidine (THPM) exhibits various therapeutic applications and is recognized as a significant pharmacologically active component. Our study assessed the antimicrobial efficacy of the designed compounds against various microorganisms, including Gram-positive and Gram-negative bacteria, as well as pathogenic fungi. These compounds were synthesized using either microwave or conventional methods, or through a multi-component reaction like the Biginelli reaction. The SDF file was transformed into a PDB file using UCSF Chimera 1.18 software for molecular docking, Avagadro for energy optimization, and Autodock vina. Physicochemical characteristics and ADME-T predictions were conducted using the pkCSM web server, revealing that the most potent compound demonstrated effective binding modes with microbial targets and promising pharmacokinetic safety profiles. The research provides valuable insights into the potential use of these compounds as antibacterial and antifungal agents.

INTRODUCTION

Heterocycles are important building blocks in the rational design of novel biologically active molecules in medicinal and pharmaceutical chemistry due to their structural and chemical diversity and the fact that they are utilized throughout many biochemical processes [1,2]. One of the great benefits of heterocyclic chemistry is the fact that there are numerous ways to manipulate such structure in order to change the type and number of heteroatoms, the size of the ring or the incorporation of functional group as

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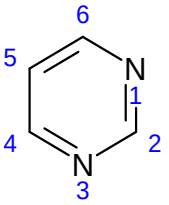
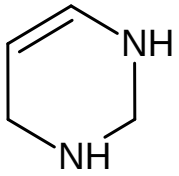
substituents or as part of the ring itself. Pyrimidine is core structural element that play an important role in nature and has wide range of application in medicinal chemistry [3]. Pyrimidine, being an integral part of DNA and RNA, imparts diverse pharmacological properties such as effective bactericide and fungicide. Fused pyrimidine derivative has attracted the attention of numerous researchers over many years, due to their important biological activities. Preclinical data from the literature survey over many years, due to their important biological activities [4]. Preclinical data from the literature survey indicated that the heterocycles in association with the pyrimidine have shown good antimicrobial [5], antioxidant[6],anxiolytic[7],antitubercular[8],anti cancer[9] and antimalarial[10] activities. 1,2,3,4-tetrahydropyrimidine derivatives have recently attracted the attention of the medicinal community due to their varied bioactivities such as antimicrobial, anti-inflammatory, etc. Pyrimidine is a aromatic, heterocyclic, organic compound similar to pyridine. It has nitrogen atoms at position 1 and 3 in the ring. Six atoms in the shape of a ring this ring is known as a pyrimidine ring. Four hydrogen atoms are attached to the outside of the pyrimidine ring to stabilize it electrically. Different pyrimidines are formed by placing different atoms at various position around the pyrimidine ring.



Pyrimidine



1,2,3,4-tetrahydropyrimidine

(Figure-1: Pyrimidine and 1,2,3,4–tetrahydropyrimidine)

Table-1: Physicochemical properties of pyrimidine and 1,2,3,4-tetrahydropyrimidine

Physicochemical Properties		
	Pyrimidine	**Tetrahydro pyrimidine**
Molecular formula	$C_4H_4N_2$	$C_4H_8N_2$
Molecular weight	80.088 g/mol	84.12 g/mol
IUPAC Name	1,3-Diazine, m-Diazine	1,2,3,4-tetrahydropyrimidine
Density	1.016 g/cm^3	0.916±0.06 g/mol^3
Solubility	Alcohol, water	Ethanol, Methanol, Iso-propyl alcohol, etc.
Melting point	20-22 °C	141-144°C
Boiling point	123-124 °C	88-89°C
Appearance	Liquid or Crystalline Solid	Liquid or Crystalline Solid

Pyrimidine derivatives have great therapeutic potential, and they play an important role in the treatment of numerous diseases due to the wide range of their biological activities. Its antibacterial, anticancer, anti-inflammatory, analgesic, antifungal, and anticonvulsant properties are remarkable. Pyrimidine derivatives' exceptional pharmacological efficacy has led to a great deal of research on the pyrimidine nucleus's antibacterial properties.

2. MATERIAL AND METHODS

Design of 1,2,3,4-tetrahydropyrimidine derivatives: The design of 1,2,3,4-tetrahydropyrimidine in the present investigation, a thorough literature review, and database searches were carried out. Twenty-four ligands were virtually designed from the designed molecules, 24 ligands were virtually designed followed by in silico analysis.

In silico screening

2.1) Molecular Docking Simulation

Step 1: Preparation of ligand: For ligand preparation, the structure of 24 ligands in the ACD/ChemSketch software [11] was designed to save the SDF file. UCSF Chimera 1.18 software[12], Avagadro (an advanced molecule editor and visualizer designed for cross-platform use in computational chemistry) for energy optimization, and Autodock vina were used to convert this SDF file into a PDB file[13].

Step2: Preparation of receptor: Using Gram-Positive bacteria, the crystal structure of staph gyrase B 24KDa in complex with Kibelomycin (PDB ID= 4URM)[14,15], Structure of urate oxidase from Bacillus substilis 168 (PDB ID = 6A4M)[16], Gram-Negative Bacteria Crystal structure of E. coli Topoisomerase IV co-complexed with inhibitor (PDB ID=2FV5)[17] and for fungal activity crystal structure of GlcNac inducible Gene2, G1G2 (DUF1479) from candida albicans (PDB ID = 6AKZ)[18]. which was retrieved from the PDB (https://www.rcsb.org/) . For the preparation of protein DS Visualizer program was used to remove the pre-associated ligand, water molecules, and any non-standard protein molecules in order to generate a protein in PDB.

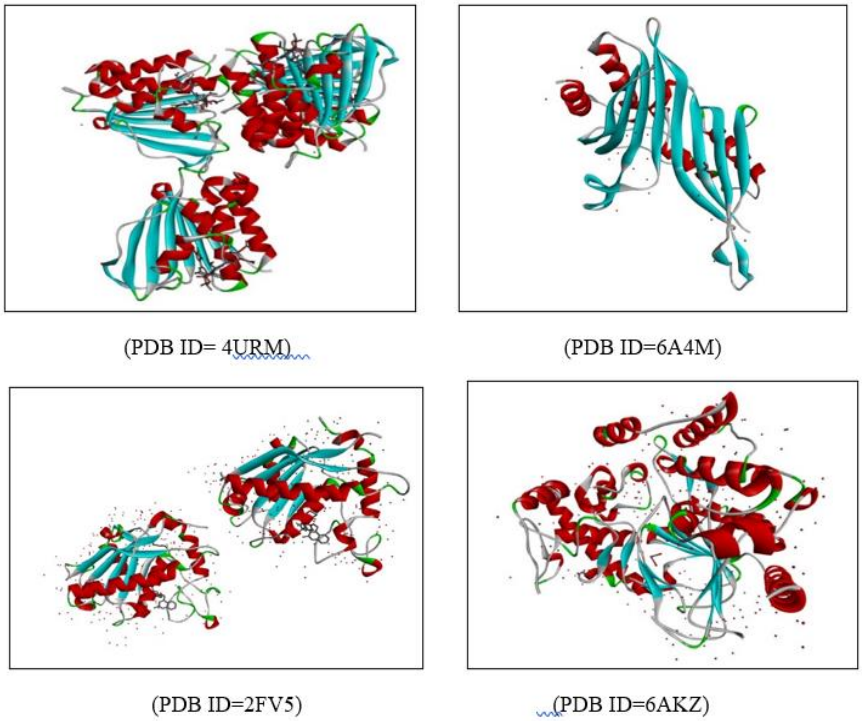


Figure-2: 3D structure of proteins retrieved from PDB

Step 3: Receptor- ligand docking interaction: All of the docking experiment used PyRx, myPresto Portal and Chimera 1.18. In order to generate a population of possible ligand rotation and confirmation inside the binding site, computational docking is implemented. The grid centre and docking dimensions were established in order to bind the ligand with the protein molecule. When preparing the grid box, great care was taken to make sure the 3D grid box was centred around the receptors active ligand binding site, covering the active site.

Step 4: Visualization: Discovery Studio Visualizer (DS-Visualizer) was used for 2D and 3D molecular interaction and visualization [19].

2.2) Drug likeness Evaluation: Different parameter of physicochemical properties was calculated in order to verify the drug-likeness rules by using pk CSM online servers [20].

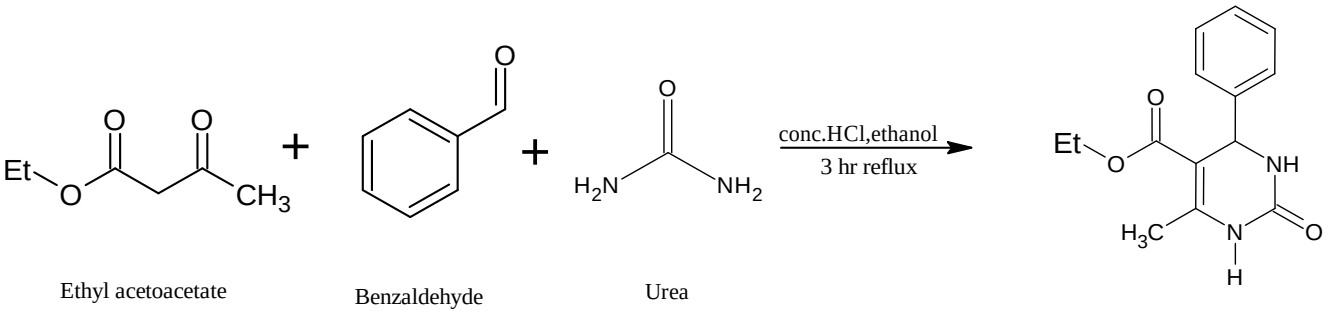
2.3) ADMET analysis: The absorption, distribution, metabolism, excretion, and toxicity

parameters were calculated by using online server pk CSM and Swiss ADME [21].

3. Experimental

3.1) Biginelli reaction

The biginelli reaction is a multiple component chemical reaction that creates 3,4 - dihydropyrimidine 3(1H) ones (1,2,3,4-tetrahydropyrimidine) from ethyl acetoacetate, an aryl aldehyde (such as benzaldehyde) and urea. It is named for Italian chemist Pietro Biginelli[22].



Ethyl acetoacetate Benzaldehyde Urea 1,2,3,4- tetrahydropyrimidine

Figure-3: The scheme of the 1,2,3,4-tetrahydropyrimidine

3.2) General procedure for the preparation of pyrimidine derivatives by multicomponent Biginelli synthesis: -

Urea, ethyl-acetoacetate and sub-aromatic aldehyde (0.1 mol) will be mixed (equimolar amount) in ethanol (25ml). A catalytic amount of conc. HCl (1ml) will be added to the mixture. The reaction mixture will be refluxed on a water bath for 3 hours. The reaction mixture will be cooled. kept in refrigerator overnight. The solid separated out was filtered off. The filtrate will be further refluxed on a water bath for 1.5 hours. A solid will be separated out on cooling & filtered and recrystallize from ethanol [23].

Design of molecules: Design of 24 molecules using the scheme. Then, 24 designed molecules were drawn using ChemSketch software. From the designed molecule's structure, we must draw the smiles of each structure and calculate online physical parameters such as molecular formula, molecular weight, composition, molar refractivity, and density of each structure using chemsketch.

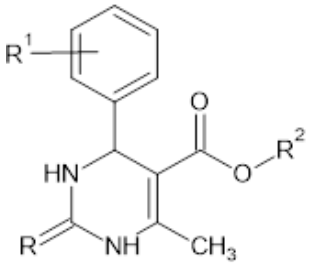


Figure-4: General Structure

Table-2: Substitution of R, R^1 and R^2 by different functional group

Sr. No	O/S(R)	Sub-Aromatic aldehyde (R^1)	Ester(R^2)
1	Urea	2-Chlorobenzaldehyde	Ethyl acetoacetate
2	Thiourea	4-Hydroxubenzaldehyde	Methyl acetoacetate
3		2-Nitrobenzaldehyde	
4		3-Nitrobenzaldehyde	
5		4-Nitrobenzaldehyde	
6		Benzaldehyde	

3.3) Molecular docking: The synthesised compound and standard norfloxacin, miconazole were picked for molecular docking experiment. The protein data bank website

(https://www.rcsb.org/) was used to get the crystal structures of the protein.

4. Results and Discussion

4.1) Molecular Docking

The Auto Dock Vina program was used to perform molecular docking of design 24 molecules; 1,2,3,4-tetrahydropyrimidine derivatives for antimicrobial activity. the crystal structure of staph gyrase B 24KDa in complex with Kibelomycin (PDB ID= 4URM), Structure of urate oxidase from Bacillus substyles 168 (PDB ID = 6A4M), Gram-Negative Bacteria Crystal structure of E. coli Topoisomerase IV co-complexed with inhibitor (PDB ID= 3FV5) formed the target structure for antibacterial activity. Crystal structure of GlcNac inducible Gene2, G1G2 (DUF1479) from candida albicans (PDB ID=6AKZ) was the target for antifungal activity.

Table-3: Molecular Docking Score of 24 Designed Compound

Sr. No	Ligand	Docking Score (Kcal/mol)			
		Gram-positive bacteria		Gram-negative bacteria	Yeasts
		S. aureus (4URM)	Bacillus subtilis (6A4M)	Escherichia coli (3FV5)	Candida albicans (6AKZ)
*	Norfloxacin	-7.2	-7.8	-6.2	-
*	Miconazole	-	-	-	-7.6
1	ethyl 4-(2-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-5.3	-6.7	-5.9	-6
2	ethyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.1	-6.9	-5.5	-6
3	ethyl 6-methyl-4-(2-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-5.9	-6.6	-5.7	-6.3
4(D1)	ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.6	-7.3	-5.8	-6.8
5(D2)	ethyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.7	-8	-5.7	-6.8
6	ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.3	-6.5	-5	-6.3
7	ethyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.8	-6.7	-5.8	-6.9
8	ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.3	-6.7	-6.3	-6.8
9(D3)	ethyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-7	-6.7	-6	-7.2
10(D4)	ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-8.5	-7.2	-7.1	-7.7

11	ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-7.4	-7.6	-5.4	-7.2
12(D5)	ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-7.9	-6.4	-6	-6.8
13	methyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.8	-6.8	-5.9	-6.7
14	methyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.4	-6.8	-5.7	-6.8
15	methyl 6-methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-5.9	-6.7	-6	-7.2
16(D6)	methyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-7.4	-7.7	-6.3	-7.3
17	methyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.3	-6.7	-6.5	-6.9
18	methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.4	-6.7	-6.5	-6.9
19	methyl 4-(2-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.1	-6.7	-5.7	-6.1
20	methyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6	-6	-5.6	-6.5
21	methyl 6-methyl-4-(2-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.3	-6.3	-5.9	-6.6
22	methyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.7	-6.7	-5.1	-6.2
23	methyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6.6	-6.6	-6	-6.2
24	methyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate	-6	-5.6	-5.3	-6

The design Compound 4,5,9,10,12 and16 shown good binding affinity towards receptor 4URM,6A4M,3FV5 and 6AKZ showed antibacterial and antifungal activities compared with the standard drug Norfloxacin and Miconazole. Design Compound 4,5,9,10,12 and 16 are D1, D2, D3, D4, D5 and D6 respectively. As shows in table-3, we found that compound D4 and D5 were predicted to be the strongest binders to the S. aureus target (PDB ID-4URM) binder that forms the complexes, with the stability confirmed by the negative score of -8.5 Kcal/mol and -7.9 Kcal/mol respectively. Notably, the score value of compound C and D greater than standard drug norfloxacin -7.2 Kcal/mol. Compound D2 and D6 were predicted to be strong binders to the B. subtilis (PDB ID- 6A4M) binder that form the complexes, with the stability confirmed by the

negative score of -8 Kcal/mol and -7.7 Kcal/mol respectively. the score value of compound D2 and D6 greater than standard drug norfloxacin -7.8 Kcal/mol.

Compound D4 and D6 were predicted to be strong binders to the E. coli (PDB ID- 3FV5) binder that form the complexes, with the stability confirmed by the negative score of -7.1 Kcal/mol and -6.3 Kcal/mol respectively. the score value of compound D4 and D6 greater than standard drug norfloxacin -6.2 Kcal/mol.

Compound D4 and D6 were predicted to be strong binders to the C. albicans (PDB ID- 6AKZ) binder that form the complexes, with the stability confirmed by the negative score of -7.7 Kcal/mol and -7.3 Kcal/mol respectively. the score value of compound D4 and D6 greater than standard drug Miconazole -7.6 Kcal/mol.

4.2) 2D and 3D Interaction of compound with receptor:

2D Binding Interaction of Standard Compound and Design Compound

2D Binding Interaction of Standard Compound with receptor.

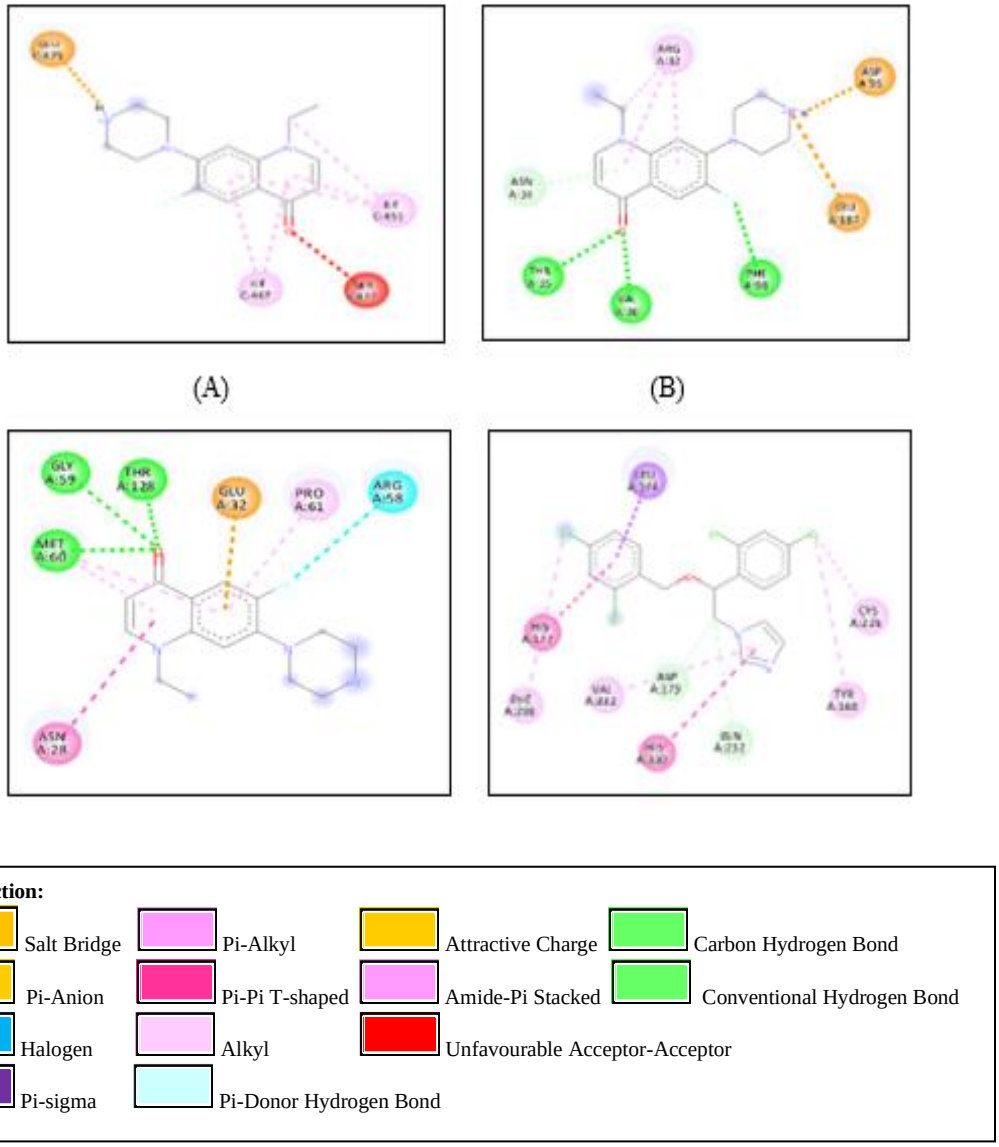
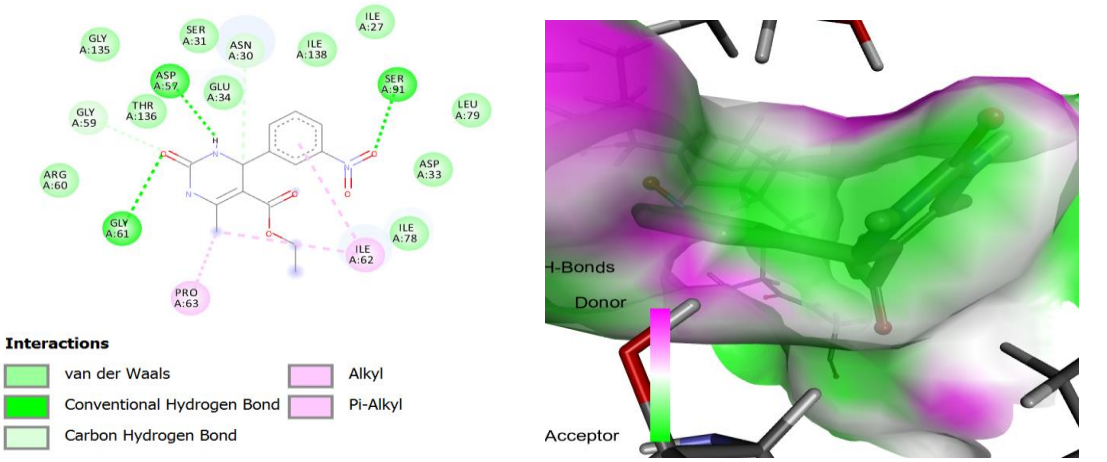
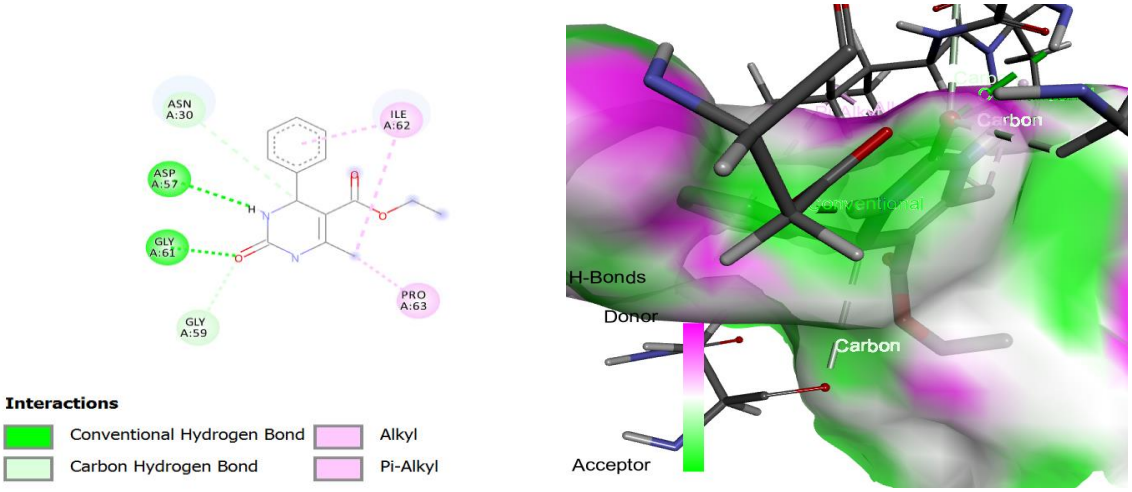


Figure-5: The 2D Binding interaction of STD-Norfloxacin with S. aureus (PDB ID:4URM) [A], B. subtilis (PDB ID-6A4M) [B], E. coli (PDB ID-3FV5) [C] and STD-Miconazole with C. albicans (PDB ID-6AKZ) [D]

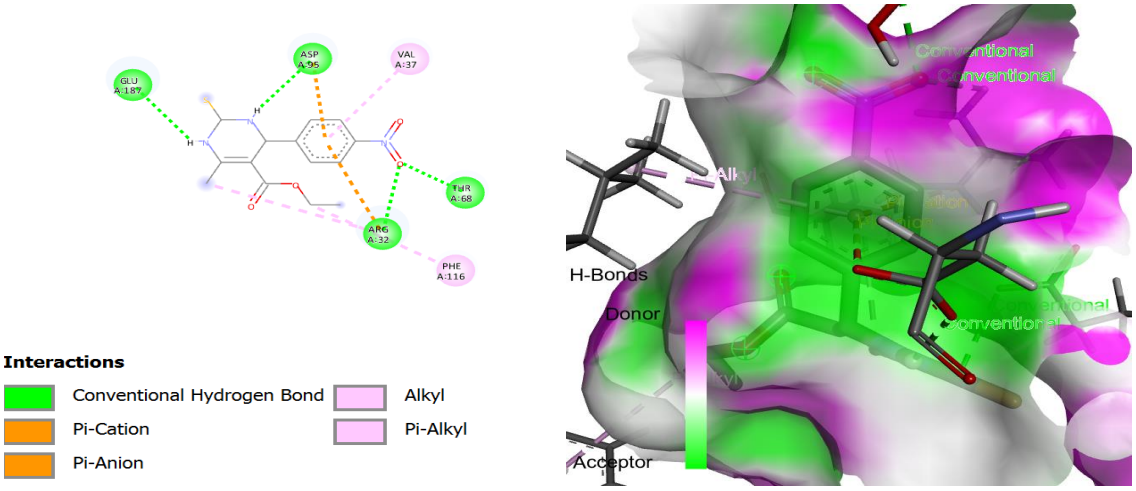
2D and 3D Binding Interaction of Design Compound with receptors:



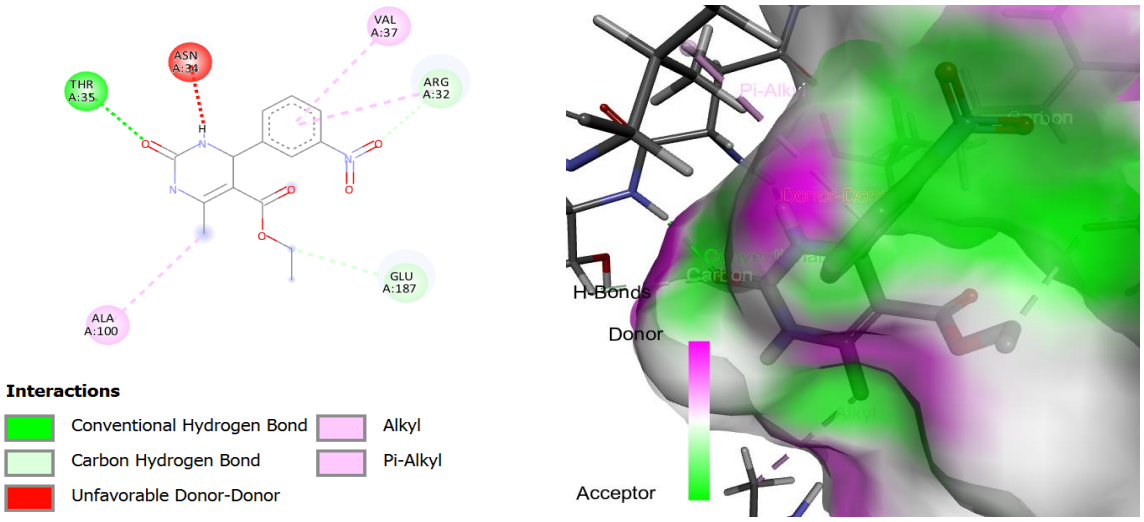
(A)2D and 3D Binding interaction between Compound D4 with S. aureus.



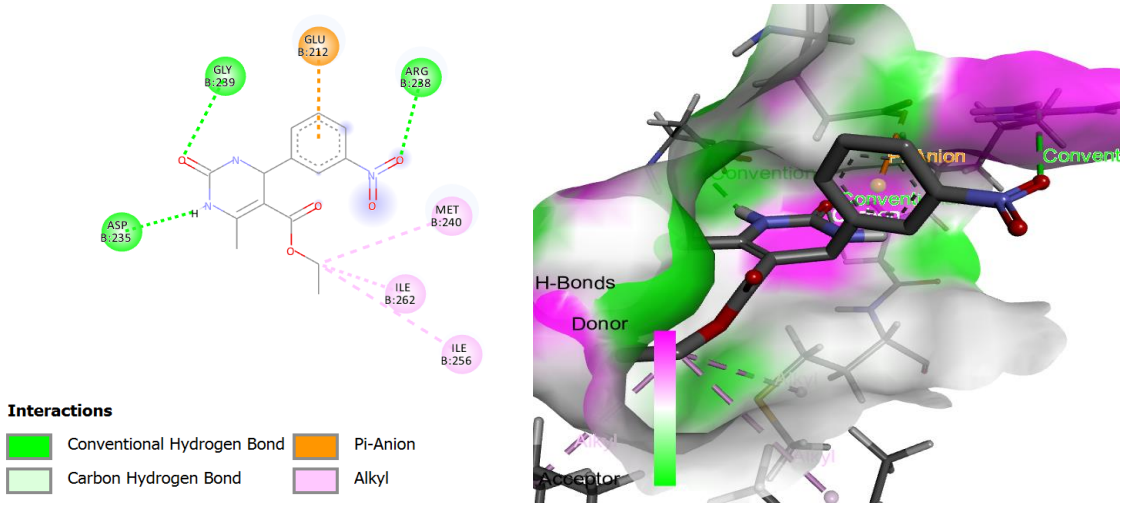
(B)2D and 3D Binding interaction between Compound D6 with S. aureus.



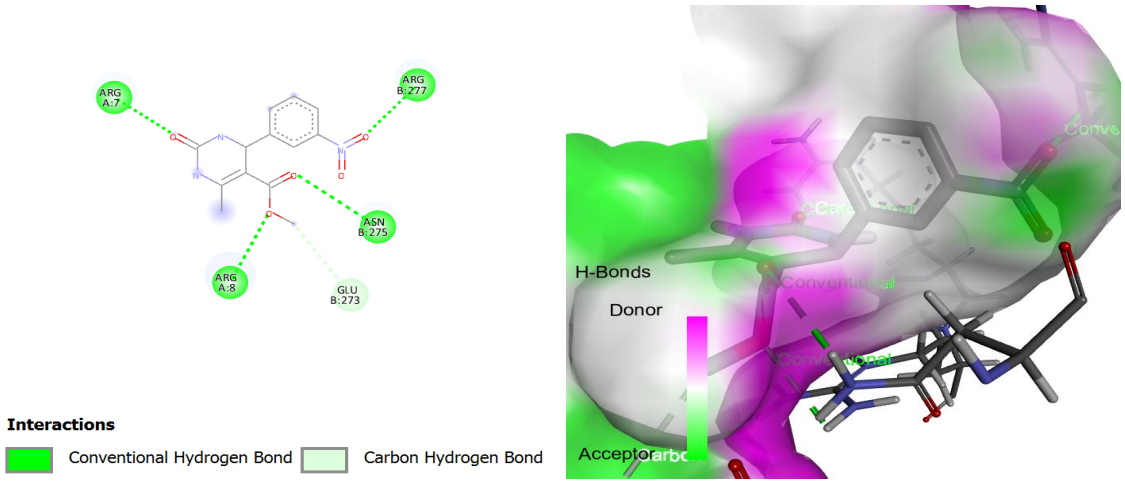
(C)2D and 3D Binding interaction between Compound D2 with B. Subtilis.



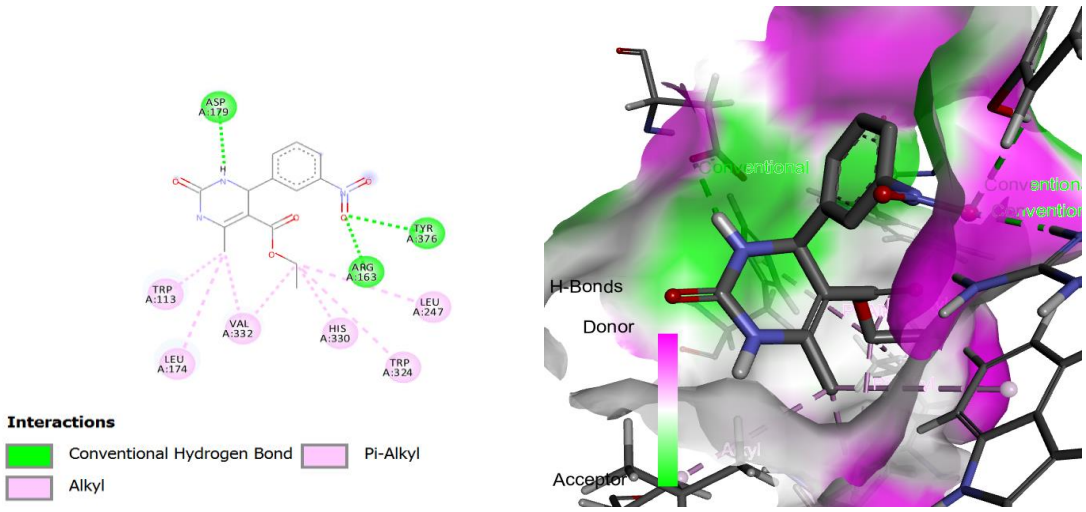
(D)2D and 3D Binding interaction between Compound D4 with B.Subtilis.



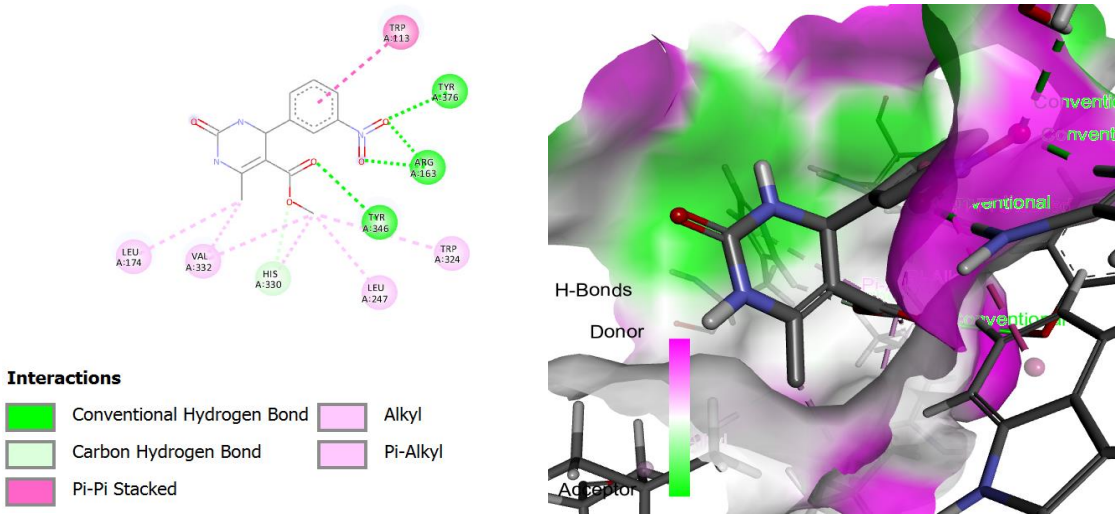
(E)2D and 3D Binding interaction between Compound D4 with E.coli.



(F)2D and 3D Binding interaction between Compound D6 with E.coli.



(G)2D and 3D Binding interaction between Compound D4 with C.albicans.



(H)2D and 3D Binding interaction between Compound D6 with C.albicans.

(Figure-6: The 2D and 3D Binding interaction between [A]Compound D4 and [B]Compound D6 with S. aureus (PDB ID-4URM); [C]Compound D2 and [D]Compound D4 with Bacillus subtilis (PDB ID-6A4M);[E]Compound D4 and [F]Compound D6 with Escherichia coli (PDB ID-3FV5) and [G]Compound D4 and [H]Compound D6 with Candida albicans (PDB ID-6AKZ))

4.3) Drug-Likeness Evaluation: Different parameter of physicochemical properties was calculated in order to verify the drug-likeness rules by using pkCSM online servers. All the results are presented in Table-4:

Table-4: Physicochemical properties and drug-likeness predictions of compounds

Compound	**Physicochemical properties**						**Medicinal Chemistry Drug-Likeness Rules**		
	TPSA (A^0)	**n-ROT**	**MW (g/mol)**	**M Log P**	**n-HA**	**n-HD**	**Lipinski**	**Veber**	**Egan**
	(0-140)	(0-11)	(100-500)	(0-5)	(0-12)	(0-7)			

D1	132.043	4	321.35	1.95	5	2	Yes	Yes	Yes
D2	132.043	4	321.35	1.95	5	2	Yes	Yes	Yes
D3	125.845	4	305.29	1.78	5	2	Yes	Yes	Yes
D4	125.845	4	305.29	1.78	5	2	Yes	Yes	Yes
D5	111.192	4	305.29	1.87	3	2	Yes	Yes	Yes
D6	119.48	3	291.26	1.39	5	2	Yes	Yes	Yes

As shown in Table-4, it is apparent that in all compounds, namely the number of hydrogen bond donors was < 5 (n-HD: (0~7)), and the number of hydrogen bond acceptors was < 10 (n-HA: (0~10)). In addition, the molecular weight values of these compounds ranged from 100 to 500 g/mol, and the M Log P values were <5. Also, n-ROTB values were <11, which denotes the flexibility of these compounds. On the other hand, all TPSA values obtained were less than 140 A. According to these results, it can be concluded that all compounds satisfy all the criteria of drug-likeness without any violation of Lipinski, Veber, and Egan rules. Clearly, not all compounds pose problems with oral bioavailability and pharmacokinetic parameters.

4.4) ADME-T study: The absorption, distribution, metabolism, excretion, and toxicity parameters were calculated by using online server pkCSM. (Caco-2: colon adenocarcinoma, HIA: human intestinal absorption, CNS: central nervous system permeability: blood–brain barrier permeability, Renal OCT2 substrate: organic cation transporter 2, hERG: human ether-ago-go-related gene.) All the results are presented in Table-5.

Table-5: ADMET/pharmacokinetic properties of compounds

ADME	Parameters	Design compound					
		D1	D2	D3	D4	D5	D6
Absorption	Caco2 (10^{-6} cm/s)	1.126	1.126	-0.093	-0.093	1.87	1.39
	HIA (%)	78.592	78.592	80.441	80.323	93.517	78.69
Distribution	CNS (log PS)	-2.51	-2.55	-2.595	-2.6	-2.449	-2.623
	BBB (log BB)	-0.328	-0.387	-0.31	-0.339	-0.144	-0.752
Metabolism	CYP1A2 inhibitor	No	No	No	No	No	No
	CYP2C19 Inhibitor	No	No	No	No	No	No
	CYP2D6 substrate	No	No	No	No	No	No
	CYP3A4 substrate	Yes	Yes	Yes	Yes	No	Yes
Excretion	Renal OCT2 substrate	No	No	No	No	No	No
	Total Clearance (log mL/min/kg)	0.057	-0.067	0.502	0.543	0.573	0.462
Toxicity	hERG I and II inhibitors	No	No	No	No	No	No
	Hepatotoxicity	Yes	Yes	Yes	Yes	No	No

As shown in table-5, All compounds had Caco-2 values greater than −5.15 (>−5.15 cm/s). This means that these compounds exhibit good permeability. In addition, it is evident that all compounds had HIA values greater than 30%, indicating that the orally administered drug candidates are absorbed from the gastrointestinal system into the bloodstream of the human body. All three compounds could penetrate the CNS, as confirmed by log PS values, which were in the range of −3 < log PS < −2. Additionally, the log BB values of compounds distributed in the brain. A P450 CYP inhibitor test was performed to determine whether the drug blocked or decreased

the activity of one or more isoforms of the CYP450 enzyme. Data from this table indicate that all compounds are not inhibitors of the CYP1A2 and CYP2C19. In addition, these compounds E is CYP3A4 substrates. Further analysis of the table showed that none of the compounds were likely to be anOCT2 substrate. Moreover, it can be clearly seen that these compounds have a low excretion clearance (<5mL/min/kg). Additionally, the selected compounds were neither hERG I nor hERG II inhibitors. However, all of them some compounds posed a hepatotoxicity risk.

DISCUSSION: In the present study, 24 designed compounds were selected for docking against the selected proteins, that is, (4URM) (6A4M), (3FV5), and (6AKZ). Among these compounds, only six showed the best binding affinity. From these studies, it was inferred that the designed compound has the highest binding affinity when compared to other standards such as Norfloxacin and Miconazole. The six compound i.e. D1, D2, D3, D4, D5, and D6 satisfied Lipinski's rule of five with zero violations and the octanol/water partition coefficient (miLogp), which is a useful parameter for predicting drug transport properties such as absorption, bioavailability, permeability, and penetration. In addition to the topological molecular polar surface area (TPSA), the number of hydrogen atoms, molecular weight (MW), number of hydrogen donors, and number of hydrogen acceptors. All the six-lead compound followed the 'rule-of-5' and it is found that all the compound has rotatable bond in the range of 3-5 has satisfied all the parameters with clogP, solubility, molecular weight, drug likeness and drug score. Our investigation revealed that the selected compound exhibited significant binding affinity with the selected protein. This in silico approach can be further investigated to generate more effective and potential drugs using ligand-based drug design approaches. These results demonstrate that all the designed compounds can be used as potential drugs with antibacterial and antifungal activities.

5) CONCLUSION: This study provides valuable insights into its prospective use as an antimicrobial and antifungal agent. Molecular docking showed that compounds D1, D2, D3, D4, D5, and D6 had high affinity for the binding modes, leading to the formation of different interaction types. Additionally, in silico ADME and toxicity prediction were performed on these compounds, and most of them complied with the Lipinski, Veber, and Egan rules with good drug-likeness, some oral bioavailability properties, and good pharmacokinetic profiles. Finally, we identifies a new 1,2,3,4-terahydropyrimidine derivative that may aid in the design and development of novel antibacterial agents.

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