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Synthesis, Characterization, ADMET, Molecular docking and Pharmacological Evaluation of Some Novel Pyrimidine derivatives

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Abstract : Novel pyrimidine derivatives were synthesized by using urea or thiourea as a starting one. The synthesized derivatives were characterized by Infra-red, ^{1}H NMR, ^{13}C NMR, Ultraviolet, Mass spectrometry. Pharmacological appraisal of synthesised derivatives was done using agar diffusion method for antimicrobial and antifungal activity. The compound showed higher inhibition zones were further tested to determine their minimum inhibitory concentrations (MIC) utilizing serial dilution technique. The results showed the compound A_5 and A_8 have promising antimicrobial activity and compound A_5 have promising antifungal activity with MIC ranging from 11 to 20 ug/ml. Molecular docking studies were performed to inquisite binding pattern of the synthesised compound against antimicrobial peptide (PDB: 2L24) using Vlife MDS 4.6 version software. The synthesised compounds were analysed for their absorption, distribution, metabolism, excretion and toxicity properties. Results revealed the synthesised compounds have no ability to penetrate blood brain barrier, good bioavailability score and inactive immunotoxicity, cytotoxicity and aryl hydrocarbon receptor toxicity.
Keywords: Pyrimidine-5-carboxylate, antimicrobial, antifungal, molecular docking, ADMET.

1. Introduction:

The modern era of antimicrobial chemotherapy dates to 1936, with the introduction of sulphanilamide into clinical practice. Penicillin became available in quantities sufficient for clinical use in 1941. Streptomycin, chloramphenicol and chlortetracycline were identified towards the end of or soon after World War II. The

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unavoidable effects of the wide spread use of antimicrobial drugs has been the dawn of antibiotic resistant pathogens, fuelling an ever-increasing demand for new drugs and contributing to the rising cost of medical care. Drugs in this class differ from other in that they are designed to inhibit/ kill the infective organism and to have no/minimal effect on the recipient. This type of therapy is generally called chemotherapy. Initially the term chemotherapeutic agent was barred to synthetic compounds, but now since many antibiotics and their analogues have been synthesized these criteria has become irrelevant; both synthetic and microbiologically produced drugs demand to be inducted combine. However, it will be more meaningful to use the term antimicrobial agent (AMA) to depute synthetic as well as naturally occurring drugs that attenuate microorganisms [1]. The reaction was synthesized by Biginelli reaction which was further condensed with hydrazine hydrate to afford final derivatives. The Biginelli reaction is a one-pot three-component organic reaction during a β-keto ester, an aryl aldehyde, and urea to induce pyrimidones under acidic condition [2]. Molecular docking tries to estimate the structure of the intermolecular complex formed between two or more integrate molecules [3]. This is carried out using a computer program in order to dock computer-generated representations of small molecules to a receptor (or to a user-defined part thereof, e.g. the active site of an enzyme), followed by evaluation of the molecules with respect to complementarity in terms of shape and properties, such as electrostatics [4]. Good complementarity of a molecule indicates that the molecule is potentially a good binder (Fig. 1). The outcome of a docking exercise normally includes some sort of affinity prediction for the molecules investigated, yielding a relative rank-ordering of the docked compounds with respect to affinity [5].

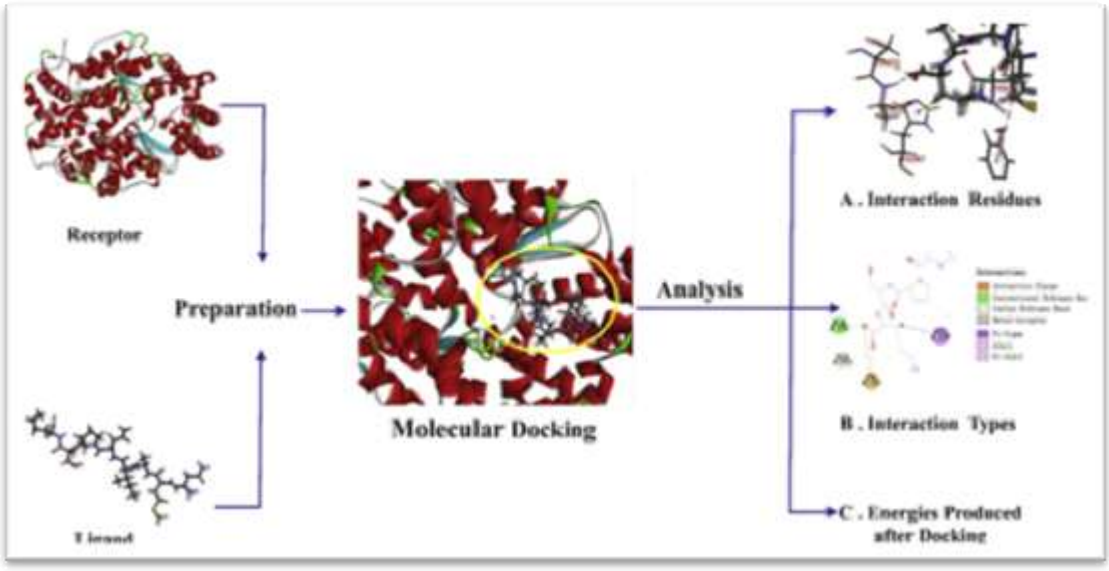
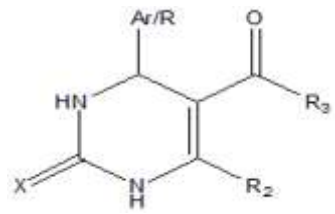


Fig. 1: General Procedure for Molecular Docking.

The prediction of Absorption, Distribution, Metabolism, Excretion and Toxicity properties shows the significant role in a drug design process because these properties are elucidating for the failure of about 60 % of all drugs in the clinical phases [4, 6].

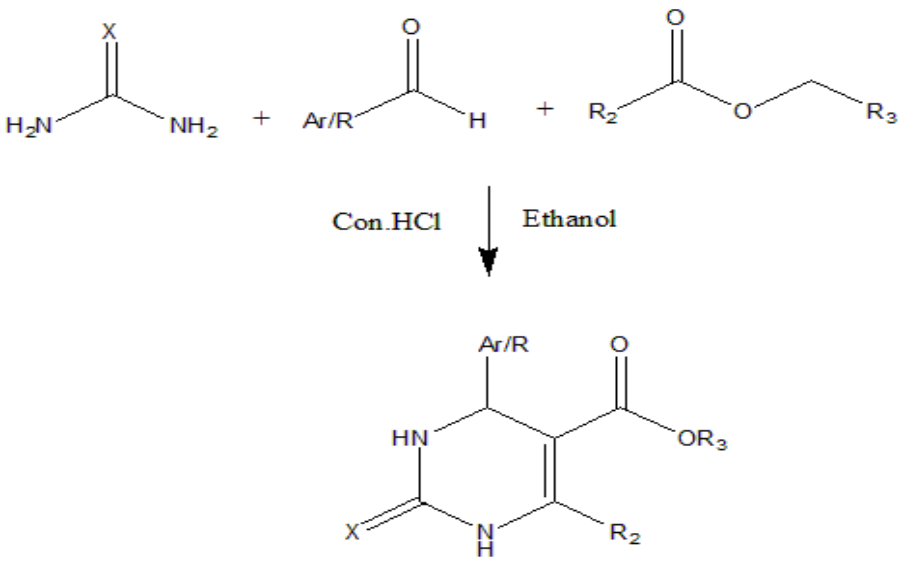
1.1. Chemistry:

Pyrimidine is an aromatic heterocyclic organic compound equal to pyridine. The six-membered heterocyclic with two nitrogen atoms in the ring, it has the nitrogen atoms at positions 1 and 3 in the ring. The anotherdiazines are pyrazine (nitrogen atoms at the 1 and 4 positions) and pyridazine (nitrogen atoms at the 1 and 2 positions) [7]. Pyrimidine, whichsoever of a class of organic compounds of the heterocyclic chain characterized by a ring structure comprised of four carbon atoms and two nitrogen atoms. The intelligible member of the family is pyrimidine itself, with molecular formula $C_4H_4N_2$ [8].



1,2,3-trisubstituted pyrimidine-5-carboxylate

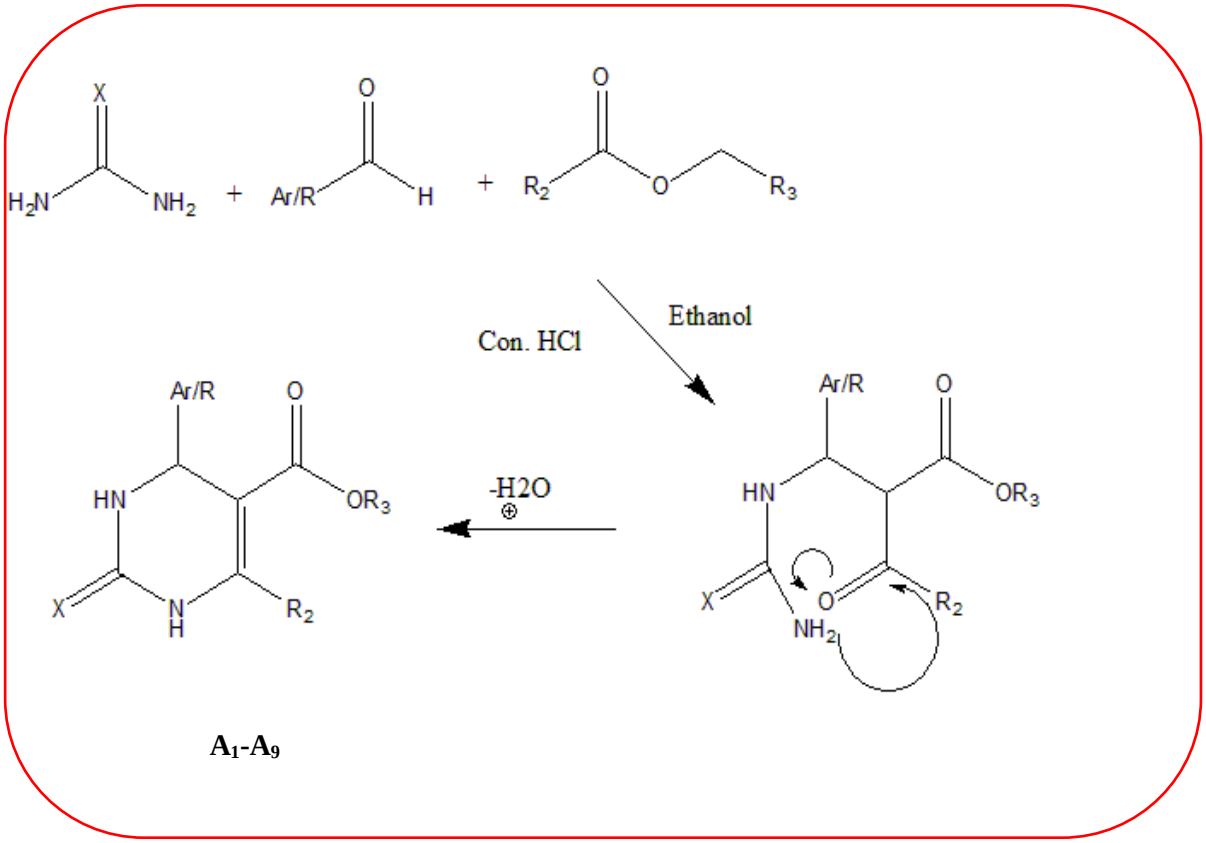
The synthesis of a series of 1,2,3-trisubstituted pyrimidine-5-carboxylate with modifications at the substituent attached at position first, second and third of the pyrimidine ring. The choice of the substitution pattern was such that a variety of group having positive contribution to the lipophilic, electronic and steric parameters were selected as depicted in Scheme-I. Reaction of urea and various ethyl acetate with various aldehydes yields pyrimidine-5-carboxylate derivatives [9].



A_1-A_9

1.2. Mechanism:

This scheme begins nucleophilic addition by the urea to the aldehyde. The ensuring condensation step is catalysed by the addition of acid, resulting in the imine nitrogen. The ester then adds to the imine bond and consequently the ring is closed by the nucleophilic attack by the amine onto carbonyl group, results into two nitrogen containing pyrimidine ring [10].



Scheme I: Synthesis of 1,2,3-trisubstituted pyrimidine-5-carboxylate (A_1-A_9).

2. Material and Methods:

Chemicals and equipments:

Urea, Thiourea, Substituted aromatic aldehydes, Ethyl acetoacetate, Ethyl cyanoacetate, Ethanol, Con. HCl, Hydrazine hydrate, Con. H_2SO_4.

Microwave Oven, TLC UV Chamber, UV Spectrometer, IR Spectrometer, NMR (^{13}C,$_1H$) Spectrometer, MASS Spectrometer.

Methods:

2.1. Synthesis of novel pyrimidine derivatives (A_1-A_9):

2.1.1. Synthesis of Ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (A_1) - A mixture of urea (0.15 mol), ethyl acetoacetate (0.1 mol) and benzaldehyde (0.1 mol) were dissolved in ethanol (25 ml) along with 3 drops of concentrated HCl and refluxed in 100 ml RBF under microwave at 595W for 6min.with continuously monitoring a reaction using TLC. The reaction mixture was then poured into 100ml ice cold water with well stirring for 15-20min., filtered and dried. The compound was recrystalised using ethanol yielding to **Ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (A_1).**

Yield: 46.25%, **UV λ max:** 376nm; log ε 0.009, **TLC:**R_f 0.65 [n-Hexane: Ethyl acetate], **M.P.:** 194-198^{0}C, **^{1}H NMR (DMSO) δppm:** δ 7.241(4H, NH), δ 1.207 (1H CH_3), δ 4.244(2H, CH_2).

2.1.2. Synthesis of Ethyl-1,2,3,4-tetrahydro-4,6-dimethyl-2-oxo-pyrimidine-5-carboxylate (A_2) - A mixture of urea (0.15 mol), ethyl acetoacetate (0.1 mol) and acetaldehyde (0.1 mol) were dissolved in ethanol (25 ml) along with 3 drops of concentrated HCl and refluxed in 100 ml RBF under microwave at 595W for 6min.with continuously monitoring a reaction using TLC. The reaction mixture was then poured into 100ml ice cold water

with well stirring for 15-20min., filtered and dried. The compound was recrystalised using ethanol yielding to **Ethyl-1,2,3,4-tetrahydro-4,6-dimethyl-2-oxo-pyrimidine-5-carboxylate (A_2).**

Yield: 40.95%, **UV λ max:** 323nm; log ε 0.103, **TLC:**R_f 0.63 [n-Hexane: Ethyl acetate], **M.P.:** 240-246^{0}C.

2.1.3. Synthesis of Ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxylate (A_3) - A mixture of urea (0.15 mol), ethyl acetoacetate (0.1 mol) and formaldehyde (0.1 mol) were dissolved in ethanol (25 ml) along with 3 drops of concentrated HCl and refluxed in 100 ml RBF under microwave at 595W for 4min.with continuously monitoring a reaction using TLC. The reaction mixture was then poured into 100ml ice cold water with well stirring for 15-20min., filtered and dried. The compound was recrystalised using ethanol yielding to **Ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxylate (A_3).**

Yield: 47.55%, **UV λ max:** 274nm; log ε 0.075, **TLC:**R_f 0.66 [n-Hexane: Ethyl acetate], **M.P.:** 234-238^{0}C, **IR (KBr cm^{-1}):** 3338.78 (γ -NH), 1627.92 (γ-C=O), 1564.27 (γ-C=C), 1136.07 (γ-C-O), **EI: M/e molecular ion peak:** 183.0, **^{13}C NMR (DMSO) δppm:** δ 40.29 (CH_2), δ 14.74 (CH_3), **^{1}H NMR (DMSO) δppm:** δ 6.534 (1H, NH), δ 3.877 (1H, CH_2, H), δ 1.334(1H, CH_3), δ 4.097 (5H, CH_2).

2.1.4. Synthesis of Methyl-4-cyano-1,2,3,6-tetrahydro-2-oxo-pyrimidine-5-carboxylate (A_4) - A mixture of urea (0.15 mol), ethyl cyanoacetate (0.1 mol) and formaldehyde (0.1 mol) were dissolved in ethanol (25 ml) along with 3 drops of concentrated HCl and refluxed in 100 ml RBF under microwave at 595W for 6min.with continuously monitoring a reaction using TLC. The reaction mixture was then poured into 100ml ice cold water with well stirring for 15-20min., filtered and dried. The compound was recrystalised using ethanol yielding to **Methyl-4-cyano-1,2,3,6-tetrahydro-2-oxo-pyrimidine-5-carboxylate (A_4).**

Yield: 47.1%**, UV λ max:** 202nm; log ε 0.014**, TLC:**R_f 0.78 [n-Hexane: Ethyl acetate]**, M.P.:** 216-218^{0}C**, IR (KBr cm^{-1}):** 3340.71 (γ -NH), 1627.92 (γ-C=O), 1564.27 (γ-C=C), 1247.94 (γ-C-N), 1136.07 (γ-C-O)**, ^{13}C NMR (DMSO) δppm**: δ 115.590 (CN), δ 164.803 (OCH_3), δ 40.561 (CH_2)**, ^{1}H NMR (DMSO) δppm:** δ 3.340 (1H, CH_3, CH_2), δ 3.851 (1H, H).

2.1.5. Synthesis of Metthyl-4-cyano-1,2,3,6-tetrahydro-2-thioxo-pyrimidine-5-carboxylate (A_5) - A mixture of thiourea (0.15 mol), ethyl cyanoacetate (0.1 mol) and formaldehyde (0.1 mol) were dissolved in ethanol (25 ml) along with 3 drops of concentrated HCl and refluxed in 100 ml RBF under microwave at 595W for 4min.with continuously monitoring a reaction using TLC. The reaction mixture was then poured into 100ml ice cold water with well stirring for 15-20min., filtered and dried. The compound was recrystalised using ethanol yielding to **Metthyl-4-cyano-1,2,3,6-tetrahydro-2-thioxo-pyrimidine-5-carboxylate (A_5).**

Yield: 44.8%, **UV λ max:** 354nm; log ε 0.095, **TLC:**R_f 0.80 [n-Hexane: Ethyl acetate], **M.P.:** 230-232^{0}C.

2.1.6. Synthesis of Ethyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-pyrimidine-5-carboxylate (A_6) - A mixture of thiourea (0.15 mol), ethyl acetoacetate (0.1 mol) and formaldehyde (0.1 mol) were dissolved in ethanol (25 ml) along with 3 drops of concentrated HCl and refluxed in 100 ml RBF under microwave at 595W for 8min.with continuously monitoring a reaction using TLC. The reaction mixture was then poured into 100ml ice cold water with well stirring for 15-20min., filtered and dried. The compound was recrystalised using ethanol yielding to **Ethyl-1,2,3,4-tetrahydro-6-methyl-2-thioxo-pyrimidine-5-carboxylate (A_6).**

Yield: 43.6%, **UV λ max:** 293nm; log ε 0.729, **TLC:**R_f 0.62 [n-Hexane: Ethyl acetate], **M.P.:** 232-234^{0}C.

2.1.7. Synthesis of 1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxylate (A_7) - A mixture of synthesised compound A_3 and hydrazine hydrate (0.1 mol) were dissolved in ethanol (20ml) along with 4 drops of concentrated H_2SO_4 and refluxed in 100 ml RBF under microwave at 595W for 16min.with continuously monitoring a reaction using TLC. The reaction mixture was then evaporated to obtain a residue which was further recrystalised from ethanol yielding to **1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxylate (A_7).**

Yield: 49.55%, **UV λ max:** 376nm; log ε 0.028, **TLC:**R_f 0.54 [n-Hexane: Ethyl acetate], **M.P.:** 184-188^{0}C.

2.1.8. Synthesis of 4-cyano-1,2,3,6-tetrahydro-2-oxo-pyrimidine-5-carboxylate (A_8) - A mixture of synthesised compound A_4 and hydrazine hydrate (0.1 mol) were dissolved in ethanol (20ml) along with 4 drops of concentrated H_2SO_4 and refluxed in 100 ml RBF under microwave at 595W for 18min.with continuously monitoring a reaction using TLC. The reaction mixture was then evaporated to obtain a residue which was further recrystalised from ethanol yielding to **4-cyano-1,2,3,6-tetrahydro-2-oxo-pyrimidine-5-carboxylate (A_8).**

Yield: 41.05%, **UV λ max:** 359nm; log ε 0.032, **TLC:**R_f 0.73 [n-Hexane: Ethyl acetate], **M.P.:** 196-198^{0}C.

2.1.9. Synthesis of 4-cyano-1,2,3,6-tetrahydro-2-thioxo-pyrimidine-5-carboxylate (A_9) - A mixture of synthesised compound A_5 and hydrazine hydrate (0.1 mol) were dissolved in ethanol (20ml) along with 4 drops of concentrated H_2SO_4 and refluxed in 100 ml RBF under microwave at 595W for 20min.with continuously monitoring a reaction using TLC. The reaction mixture was then evaporated to obtain a residue which was further recrystalised from ethanol yielding to **4-cyano-1,2,3,6-tetrahydro-2-thioxo-pyrimidine-5-carboxylate (A_9).**

Yield: 47.25%**, UV λ max:** 281nm; log ε 0.139, **TLC:**R_f 0.61 [n-Hexane: Ethyl acetate], **M.P.:** 212-216^{0}C.

Table 1: Characterization data of synthesized compounds

Comp. Code	Ar/R	R_2	R_3	X	Molecular Formula	Molecular Weight	Melting Point (^{0}C)
A_1		CH_3	OC_2H_5	O	$C_{14}H_{16}N_2O_3$	260.29	194-198
A_2	CH_3	CH_3	OC_2H_5	O	$C_9H_{14}N_2O_3$	198.22	240-246
A_3	H	CH_3	OC_2H_5	O	$C_8H_{12}N_2O_3$	184.19	236-240
A_4	H	CN	OCH_3	O	$C_7H_7N_3O_3$	181.15	216-218
A_5	H	CN	OCH_3	S	$C_7H_7N_3O_2S$	197.21	230-236
A_6	H	CH_3	OC_2H_5	S	$C_8H_9N_3O_2S$	211.24	232-234
A_7	H	CH_3	$NHNH_2$	O	$C_6H_{10}N_4O_2$	170.17	192-194
A_8	H	CN	$NHNH_2$	O	$C_6H_7N_5O_2$	181.55	190-192
A_9	H	CN	$NHNH_2$	S	$C_6H_7N_5O_5S$	197.22	212-214

2.2. Molecular Docking:

Molecular docking studies and conformational analysis were performed using the Vlife Molecular Design Suite (VLife MDS software package, version 4.6; from VLife Sciences, Pune, India).

2.2.1. Preparation of protein: The Protein Data Bank (PDB) structures (www.rcsb.org) were downloaded and energy minimization of the protein complex. All the bound water molecules, ligands and cofactors were eliminated (pre-process) from the proteins which should be taken in pdb format.

2.2.2. Structure Conformation Generation: Structures of compounds were draw exploitation the two dimensional structure draw application Vlife MDS, 2D draw and regenerate to 3D structures. All the structures were minimized and optimized with the Merck Molecular force field (MMFF) methodology taking the root mean square gradient (RMSD) and also the repetition limit to 10,000. Conformers for every structure were induced using MonteCarlo by applying the MMFF force field technique and minimum energy conformer was chosen for more study.

2.2.3. Preparation of ligands: Structures of the ligands were draw using built Vlife 2D draw taken in mol format. Converts it into 3D structure and perform a geometry decrease of the ligands. Merck Molecular Force Fields (MMFF) with default settings were used for the ligand minimization.

2.2.4. Docking methodology: The molecular docking study was performed on Vlife MDS version 4.6 software. The GRIP-based ligand docking was performed using specific cavity of the receptor. The minimum dock score of the complex were measured by PLP scoring function. Docking studies of the newly designed 1,2,3-trisubstituted pyrimidine-5-carboxylateusing the X-ray crystal structure of antimicrobial peptide (Fig. 2) for antimicrobial activity [11].

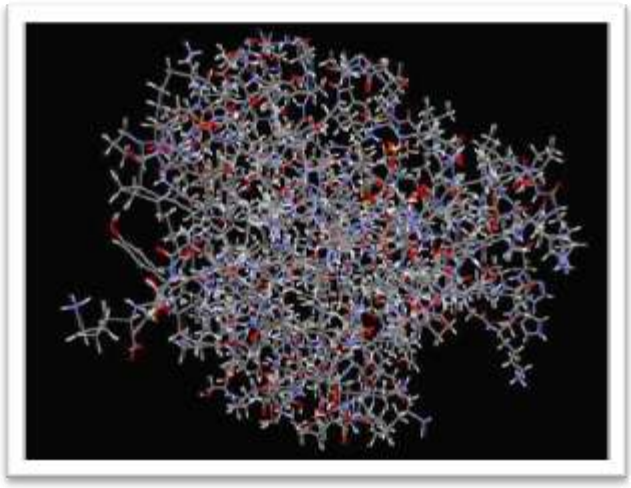


Fig. 2: X-ray crystal structure of antimicrobial peptide enzyme.

GRIP implemented in Molecular design suite (MDS) has been concerted to dock the inhibitors into catalytic site of the antimicrobial protein and to well correlate the derived binding score with inhibitory activities of compounds. In this comparative molecular docking experiments of designed compounds dock score were calculated. Derived results were evaluated in terms of docking score in to the active site of 2L24 (Fig. 3).

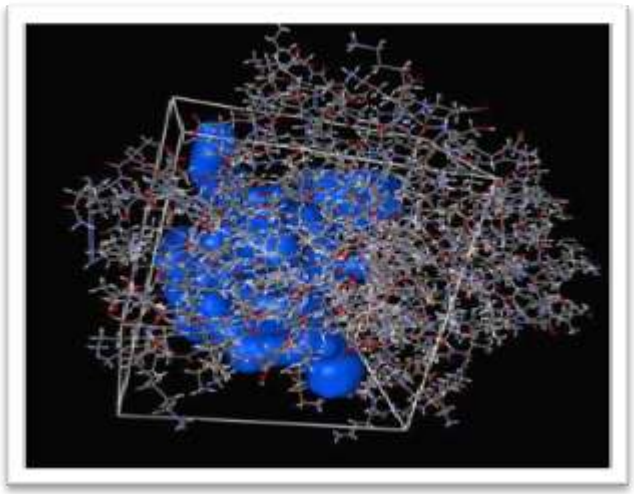


Fig. 3: The active site (Cavity) of 2L24 receptor.

Table 2: Docking score of the newly designed 1,2,3,4-disubstitutedpyrimidine-5-carboxylate (A_1-A_9) using the X-ray crystal structure of X-ray crystal structure of antimicrobial peptide enzyme for antimicrobial activity.

Sr. No.	Compound Code	Dock Score (kcal/mole)
1.	**A_1**	-25.091660
2.	**A_2**	-20.949807
3.	**A_3**	-21.850879
4.	**A_4**	-21.807010
5.	**A_5**	-24.057022
6.	**A_6**	-24.055748
7.	**A_7**	-21.852963
8.	**A_8**	-22.087326
9.	**A_9**	-26.057022

2.3. ADMET:

Today a lot of online and offline software are bewailable which assist us in predicting this experiment of the drug candidate therefore. All designed compounds were filtered by predicting their ADME properties by means of swissADME online software and toxicity by Protox-II prediction of toxicity of chemicals.

3. Results and Discussion:

3.1. Antimicrobial activity:

The synthesized compound was examineed for antimicrobial activity against gram-positive bacteria such as Staphylococcus aureus and gram-negative bacteria such as Eschershia coli, Pseudomonas aeruginosa by agar diffusion method. Dimethyl formamide was used as control solvent. Gentamicin was used as standard control. Compound A_5exhibited activity against gram-positive and gram-negative bacteria and compound A_8exhibited mild activity against gram-positive bacteria compared to that of standard (Fig. 4).

3.2. **Antifungal activity:**

The synthesized compounds were examined for antifungal activity against Candida albicans species by agar diffusion method. Dimethyl formamide was used as control solvent. Nystatin was used as standard control. Compound A_5 showed activity against Candida albicans species (Fig. 5).

The data of antimicrobial and antifungal activity were summarized in **Table 3**.

Table 3: Antimicrobial and Antifungal activity of Synthesized compounds.

Sr. No.	Compound Code	E. coli ATCC 25922	P. aeruginosa ATCC 27853	S. aureus ATCC25923	C. albicans species
1.	A_1	-	-	-	-
2.	A_2	-	-	-	-
3.	A_3	-	-	-	-
4.	A_4	-	-	-	-
5.	A_5	12mm	-	19mm	18mm
6.	A_6	-	-	-	-
7.	A_7	-	-	-	-
8.	A_8	-	-	11mm	-
9.	A_9	-	-	-	-
10.	Gentamicin	23mm	30mm	28mm	-
11.	Nystatin	-	-	-	28mm

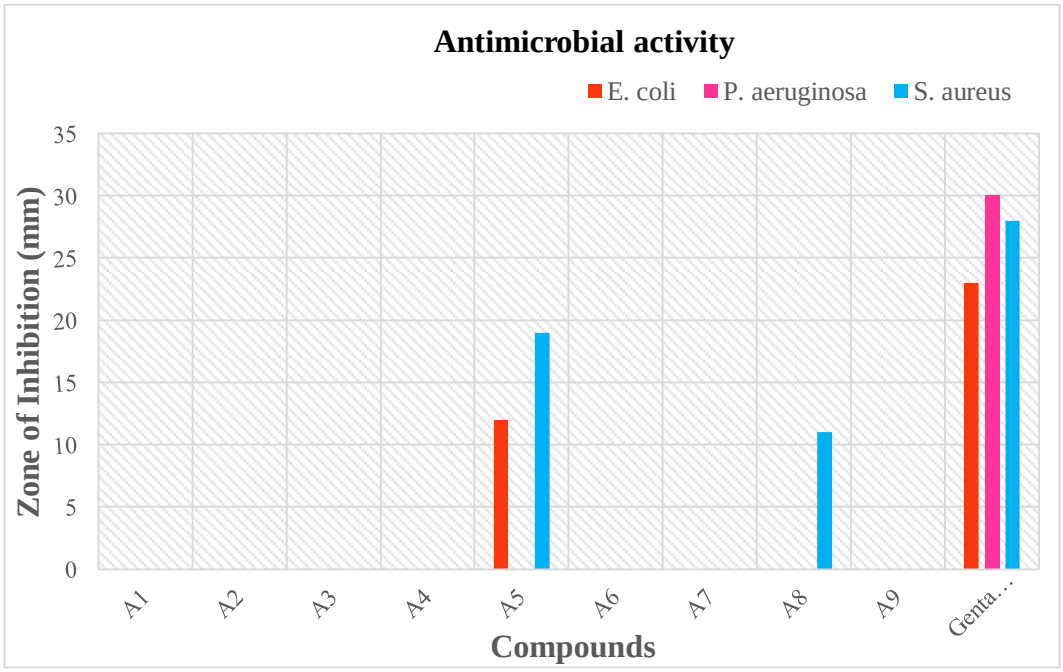


Fig. 4: Antimicrobial activity of synthesized compounds by Agar diffusion Method.

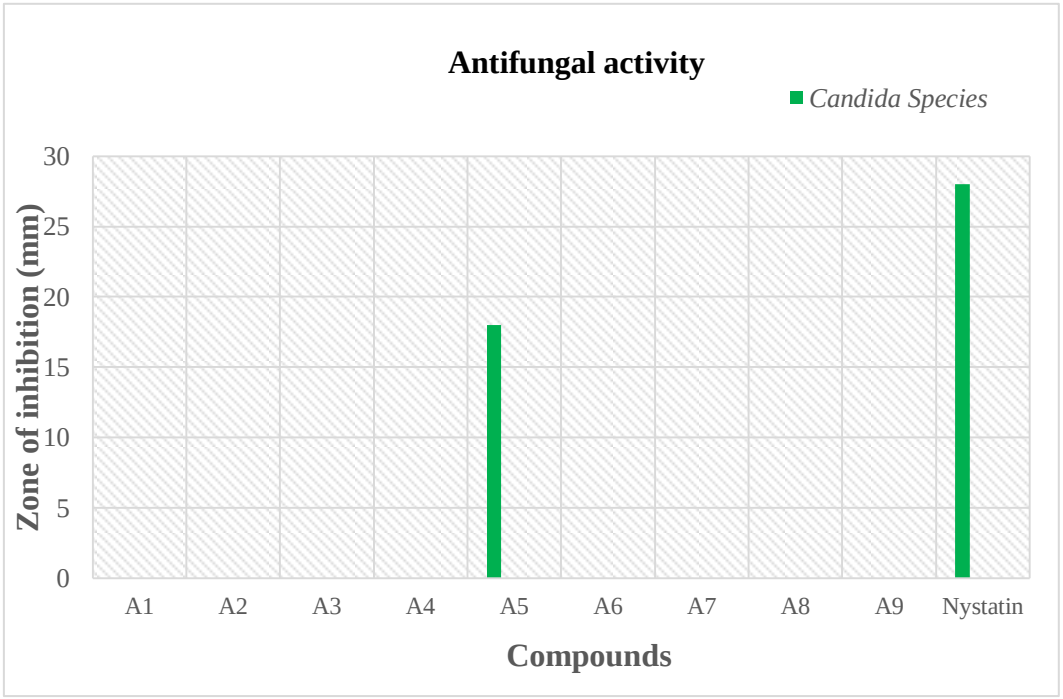


Fig. 5: Antifungal activity of synthesized compounds by Disk diffusion Method.

3.3. Molecular docking studies:

Molecular docking is key tool in drug modelling process. Docking is a novel method in which the ligand, binds on the active site of the receptor molecule. This method is regarded as one of the major innovations in drug discovery. The nine compounds were docked using Vlife MDS 4.6 version software successfully. The interactions and binding energy of the compounds are listed in **Table 2**. Good interactions were observed between residues of ligand and molecules. Molecules which show minimum dock score shows more affinity for antimicrobial action. The compounds showed binding energy between -20.94 to 26.05 kcal/mol. The results were analysed based on binding energy of the complex. The number of hydrophobic

bonds was calculated with bond length between atoms of receptor-ligand docked complex. Compound A_2 illustrate high affinity for the receptor with score -20.94 kcal/mol (Fig. 6 and 7). The compound A_2 showed six hydrophobic bonding interaction with antimicrobial peptide. Compound A_2 shows interactions with ASN11 residue of protein. The molecular docking of the compound A_2 showed good binding mode and interaction energy. Hydrophobic bond was analysed and showed that the A_2 compound possessed possible antimicrobial activity.

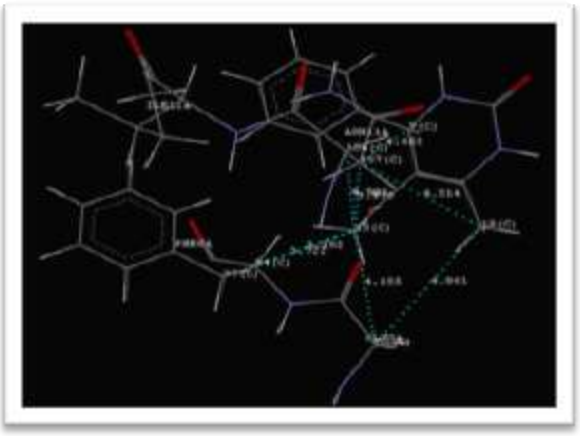


Fig. 6: The molecule A_2 shows the hydrophobic bonding.

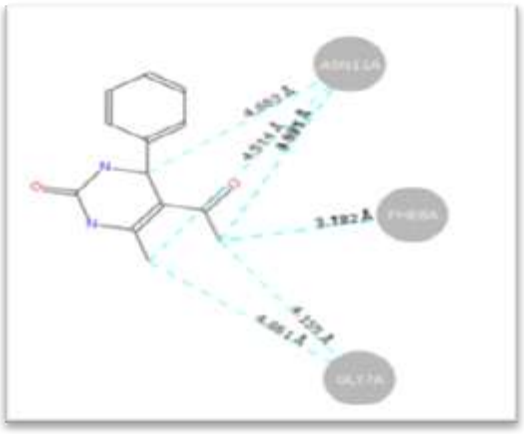


Fig. 7: 2D view of the molecule A_2 shows the hydrophobic bonding.

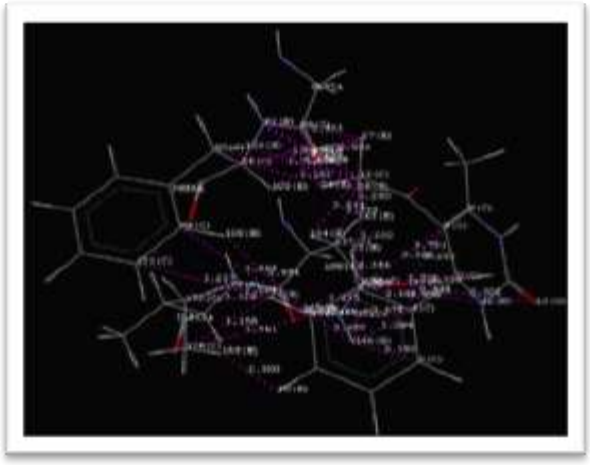


Fig. 8: The molecule A_2 shows the Vander Waals bonding.

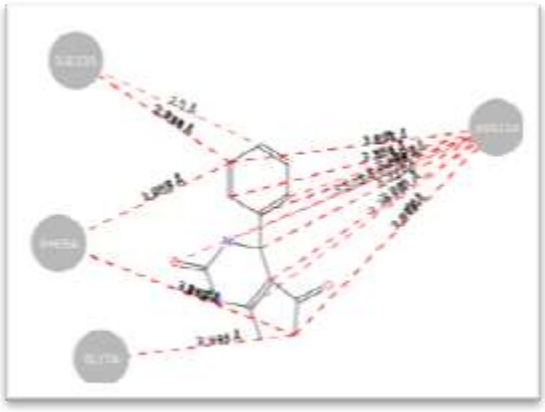


Fig. 9:2D view of the molecule A_2 shows the Vander Waals bonding.

3.4. Pharmacokinetic and Toxicity studies:

The prediction of ADMET shows the significant role in a drug design process because these properties are elucidating for the defeat of about 60 % of all drugs in the clinical phases [11]. Prediction of ADME properties was used as last screen to sort out those compounds that follow Lipinski's rule to obtain drug like pharmacokinetic properties**(Table: 4)**. Pharmacodynamics properties and toxicity profile were also studied number of the toxicity profile of designed analogues are predicted by Protox-II tool, but here we have reported significant properties like Hepatotoxicity, Carcinogenicity, Mutagenicity, Immunotoxicity and Aryl hydrocarbon receptor. From these toxicity studies it was found the ligand A_1 to A_9 shows carcinogenicity, compound A_7 and A_8 shows Mutagenicity and compound A_7 to A_9 shows hepatotoxicity**(Table: 5)**.

Table 4: ADME Predictions of Synthesised compounds.

Sr. No.	Comp. Code	GI	BBB	Bioavail-ability Score	Skin Permeation Log Kp (cm/s)	Lipophilici-ty Log P	Synthetic accessibil-ity	Molar Refrac-tivity
1.	A_1	High	No	0.55	-6.19	2.34	3.60	77.78
2.	A_2	High	No	0.55	-7.45	1.97	3.64	58.10
3.	A_3	High	No	0.55	-7.65	1.75	3.02	53.29
4.	A_4	High	No	0.55	-8.21	0.96	3.00	48.23
5.	A_5	High	No	0.55	-7.88	1.31	2.93	55.43
6.	A_6	High	No	0.55	-7.32	2.06	2.98	60.49
7.	A_7	High	No	0.55	-8.76	0.64	3.01	48.10
8.	A_8	Low	No	0.55	-9.14	0.05	3.08	47.85
9.	A_9	Low	No	0.55	-8.82	0.30	3.08	55.05

Table 5: Toxicity profiles of synthesized compounds using Protox-II -prediction of toxicity of chemicals.

Sr. No.	Comp. Code	Predicted LD_{50} (mg/kg)	Predict-ed Accura-cy	Hepatot-oxicity	Carcino-genicity	Mutage-nicity	Cytotox-icity	Immunoto-xicity
1.	A_1	2495	67.38	Inactive	Active	Inactive	Inactive	Inactive
2.	A_2	2495	68.07	Inactive	Active	Inactive	Inactive	Inactive
3.	A_3	2495	68.07	Inactive	Active	Inactive	Inactive	Inactive
4.	A_4	2495	67.38	Inactive	Active	Inactive	Inactive	Inactive
5.	A_5	746	67.38	Inactive	Active	Inactive	Inactive	Inactive
6.	A_6	746	68.07	Inactive	Active	Inactive	Inactive	Inactive
7.	A_7	750	54.26	Active	Active	Active	Inactive	Inactive
8.	A_8	750	54.26	Active	Active	Active	Inactive	Inactive
9.	A_9	746	54.26	Active	Active	Inactive	Inactive	Inactive

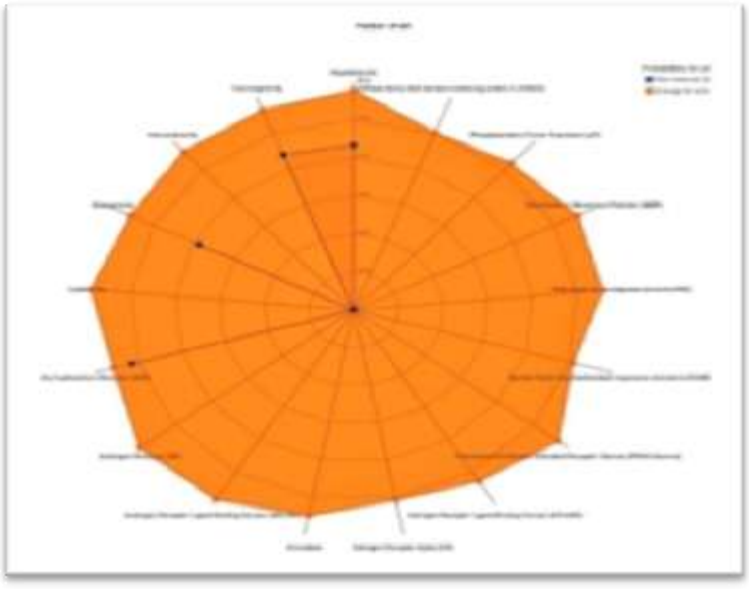


Fig.10: Radar picture of predicted toxicity of compounds.

3. Conclusion:

In this study, we report the synthesis and valuation of synthesized derivatives as antimicrobial and antifungal by using agar diffusion method, such that the antimicrobial activity, compound A_5exhibited promising activity against E.coli, compound A_8exhibited promising activity against S. aureus and the antifungal activity, compound A_5exhibited promising activity against C. albicans species. The obtained derivatives were characterized by IR, NMR (^{13}C, ^{1}H), MASS, UV spectrometry. Ligand-receptor complex displayed that more negative charge of the energy of binding the superior is affinity of the molecule to the receptor. Number of the Vander Waals interaction shows that the ligand structure is having a greater number of bulky group due to which Vander Waals interactions can be formed. Our study confirmed that the investigated compounds reveal carcinogenicity, good oral bioavailability and skin permeability and also, they have high gastrointestinal absorption.

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