A Novel Synthesis of Mannich bases and it's Docking Activity

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Abstract:

A series of new 1-(Amino/Fluro methyl - 3 Alkyl subbed - 4-arylidiene) Amino - 1,2,4-triazole was prepared according to literature method. Structure of newly synthesised compounds was established on the basis of spectral data .In IR spectra C=N stretching was observed at 1726Cm^{-1} and NH Stretching was observed at 1584Cm^{-1}, Whereas in NMR spectra these Chiral carbons appeared as doublet .Hence these compounds were screened for Docking studies, ADMET and Cytotoxicity test From the results we came to know that Compounds containing Fluorine substituent at para position showed significant action against *B.Substilis* and *A.aerogenes.*

Keywords: NMR spectra, *B.Substilis*, Cytotoxicity test, ADMET

Introduction:

The final results of the Mannich response are Mannich bases, which are beta-amino ketones bearing compounds[1-2]. A nucleophilic expansion response including the buildup of a compound with dynamic hydrogen(s) with an amine (essential or optional) and formaldehyde is known as the Mannich reaction[3]. Mannich bases are additionally fundamental pharmacophores or bioactive leads that can be utilized to integrate an assortment of high-esteem remedial specialists with an amino alkyl chain. Cocaine, fluoxetine, atropine, ethacrynic corrosive, trihexyphenidyl, procyclidine, ranitidine, and biperiden are instances of clinically significant Mannich bases of amino alkyl chains[4-6]. Mannich bases are notable for their significance in the progression of manufactured drug science. As per research, Mannich bases are exceptionally receptive and can be promptly changed over to different mixtures, like amino alcohols, which are physiologically active[7]. Mannich bases are notable for their mitigating properties [8, 9], anticancer [10, 11], antifilarial [8], antibacterial [12, 13], antifungal [13, 14], anticonvulsant [15], anthelmintic [16], antitubercular [17, 18], pain relieving [19], against HIV [17], antimalarial [20], antipsychotic [21], antiviral [22] exercises, etc. Notwithstanding organic tasks, Mannich bases are likewise utilized in cleanser added substances [23], saps, polymers, and surface dynamic specialists [24], among different applications. To defeat the restrictions, prodrugs of Mannich bases containing different dynamic mixtures have been created[25]. The enantio particular carbon-carbon security development is catalyzed (ligand sped up and metal intervened) utilizing Mannich bases (optically unadulterated chiral) of 2-naphthol. Mannich bases and their subordinates are

bioactive particle amalgamation intermediates. The Mannich response is normally used to make nitrogen-containing compounds[26-28]. Mannich bases have acquired fame because of their utilization in antibacterial action[28-29], just as in agrochemicals like plant development controllers.

Experimental Section :

All synthetics, reagents and solvents were of economically high virtue grade bought from Avra Synthesis Pvt. Ltd. also, Merck Pvt. Ltd. India. 1H NMR and 13C NMR spectra were recorded in CDCl3 on Bruker Avance 300 MHz spectrometer and the compound movements are accounted for as δ values in parts per million (ppm) comparative with TMS , with coupling consistent (J) values in Hertz (Hz). In 1H NMR, the truncation of parting alludes as s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublet and bs=broad singlet.

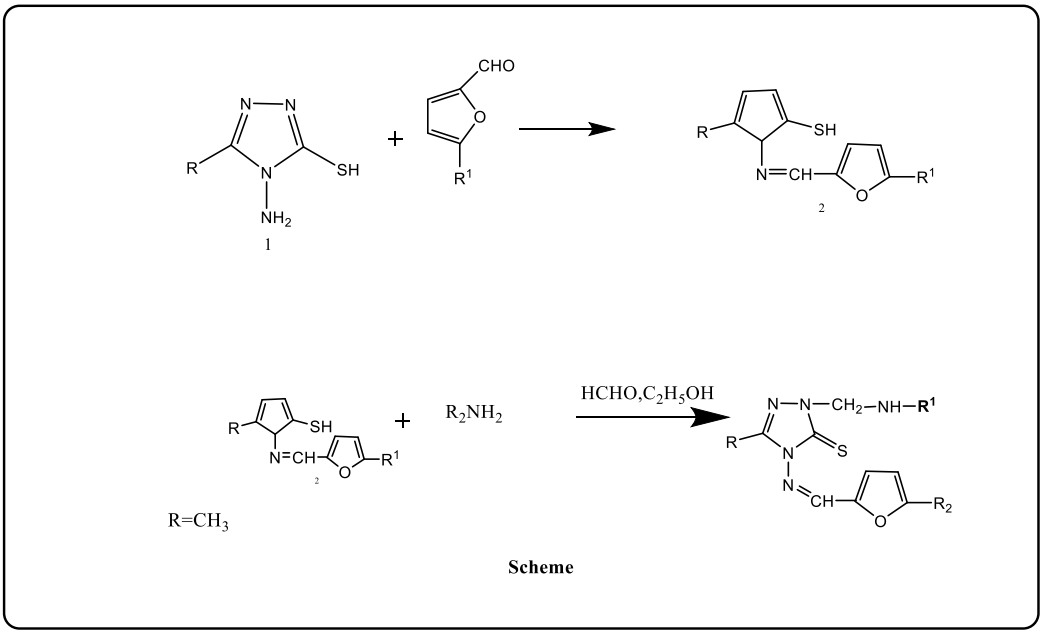


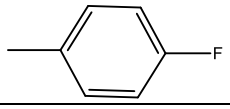
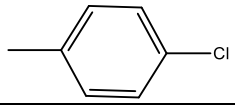
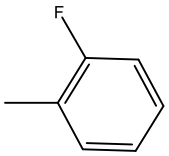
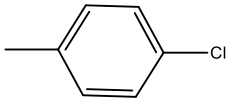
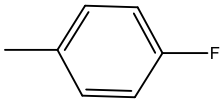
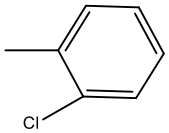
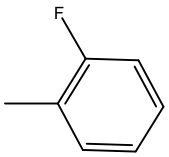
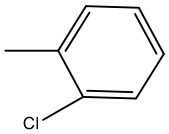
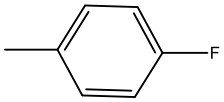
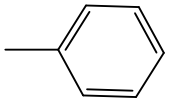
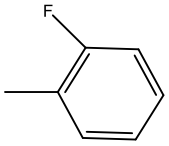
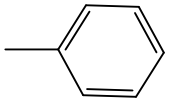
Figure 1: Scheme for synthesis

Materials and Methods

Mannich bases were prepared by the reaction of Schiff bases ,aromatic aldehyde and suitable amines in ethanol medium .primary or secondary amines were used for the preparation of Mannich bases .Schiff bases were prepared by treating triazole with aromatic aldehydes in the presence of catalytic amount of sulphuric acid in ethanol medium.

The melting points of the newly synthesised compounds were determined by capillary method and are uncorrected .NMR spectra of the samples were recorded on a 90MHzNMR spectrometer.TMS was used as internal standard .Mass spectra were recorded on a Jeol JMS –D-300 mass spectrometer operating at 70ev.

Table 1: Characterisation data of 1-(Amino/Fluro methyl -3 Alkyl substituted -4-arylidiene) Amino -1,2,4-triazole

Compound Number	R^1	R_2	Color and Crystal Form	Melting point
1R			Yellow Crystals	125^0C
2R			Yellow Crystals	140^0c
3R			Yellow Flakes	170^0C
4R			Yellow Flakes	172^0C
5R			Yellow Micro Needles	108^0C
6R			Orange Crystals	106^0C

Spectral Properties of Synthesised Compounds

Compound 1R

Yield =76%

H^1 NMR :12.02(s,Ar-OH,2H), 7.51(dd, 7.3Hz, ,2H), 7.65(dd, ,2H), 7.57(dd,,2H), 7.16 (s,2H), 6.86(dd,2H), 3.84(t, 4H), 2.50(s ,6H), 2.40–2.33(m,2H).

Mass spectral values (m/z)(%): 441(M^++1)

IR (KBr, cm^{-1}):1726(νC= N), 1587(ν NH), 1552(νC = C), 1022(νCN–C).

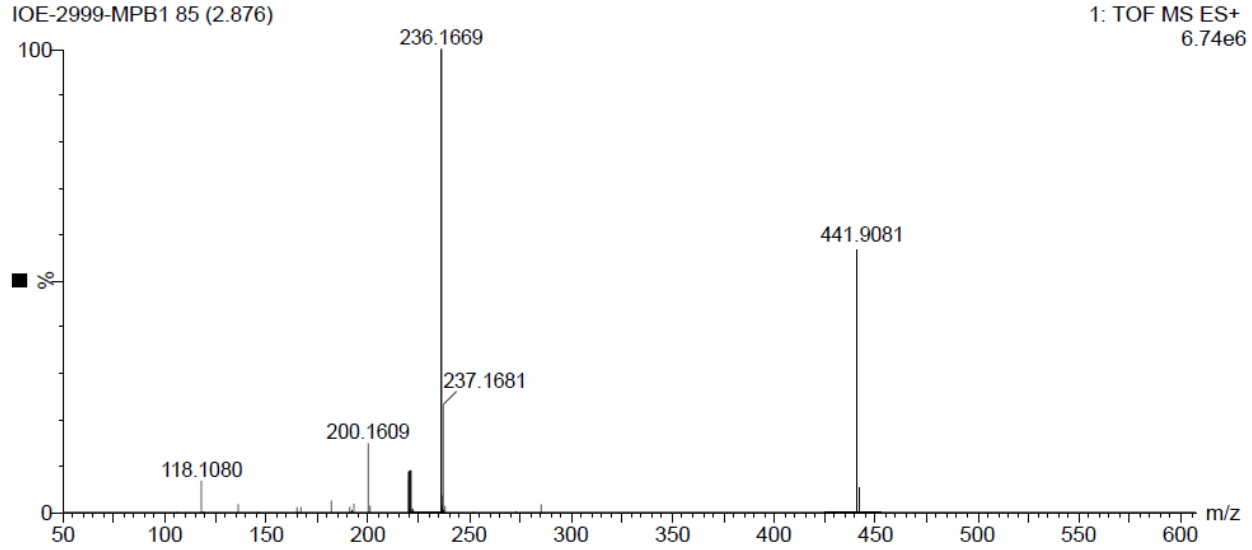


Figure 2: mass spectra of compound 1R

Compound 2R

Yield =77%

H[1] NMR : 12.12(s,Ar-OH,2H), 7.49(dd, 7.3Hz, ,2H), 7.65(dd, ,2H), 7.58(dd,,2H), 7.26 (s,2H), 6.87(dd, 2H), 3.85(t, 4H), 2.49(s ,6H), 2.19–2.22(m, 2H).

Mass spectral values (m/z)(%): 471(M^++1)

IR (KBr, cm^{-1}): 1716(νC= N), 1584(ν NH), 1551(νC = C), 1021(νCN–C).

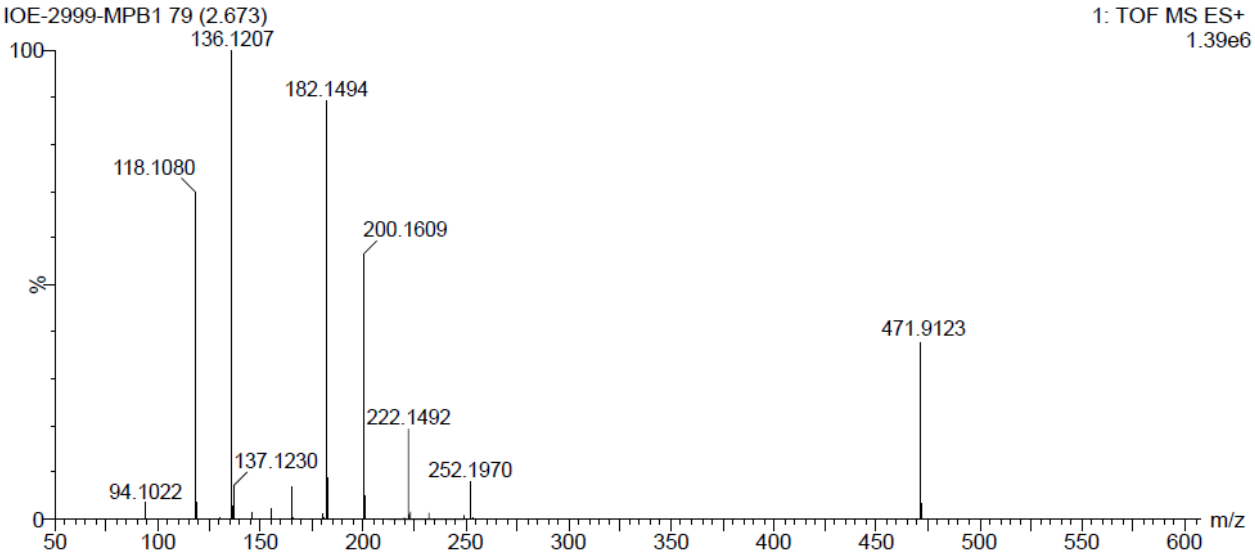


Figure 3: mass spectra of compound 2R

Compound 3R

Yield =74%

H[1] NMR : 12.19(s,Ar-OH,2H), 7.39(dd, 7.3Hz, ,2H), 7.67(dd, ,2H), 7.59(dd,,2H), 7.28(s,2H), 6.85(dd, 2H), 3.84(t, 4H), 2.48(s ,6H), 2.15–2.17(m, 2H).

Mass spectral values (m/z)(%):476(M^++1)
IR (KBr, cm^{-1}): 1716(νC= N), 1584(ν NH), 1551(νC = C), 1021(νCN–C).

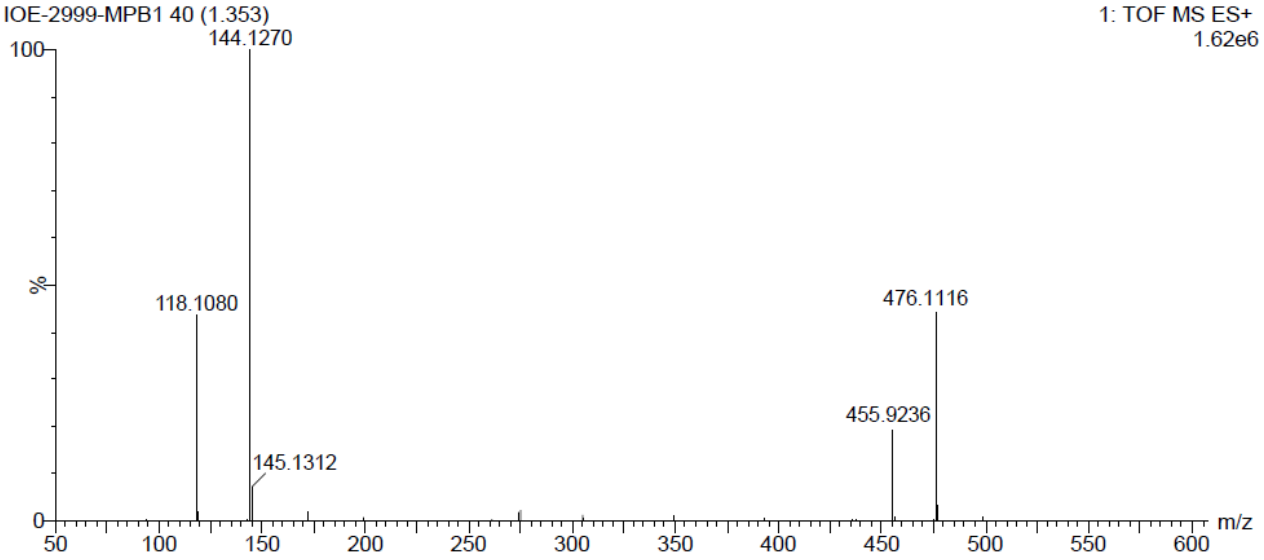


Figure 4: mass spectra of compound 3R

Compound 4R

Yield :70%
H^1NMR : 12.0(s,Ar-OH,2H),7.32(dd,7.3 Hz,2H),7.57(dd, 2H), 7.46(dd,2H),7.28(s,2H),6.85(dd,2H),3.84(t,4H),2.48(s,6H), 2.15-2.16(m,2H).
Mass spectral values (m/z)(%) : 437(M^++1)
IR(KBr,Cm^{-1}): 1708(νC= N),1540(ν NH),1549(νC = C),1019(νCN–C).

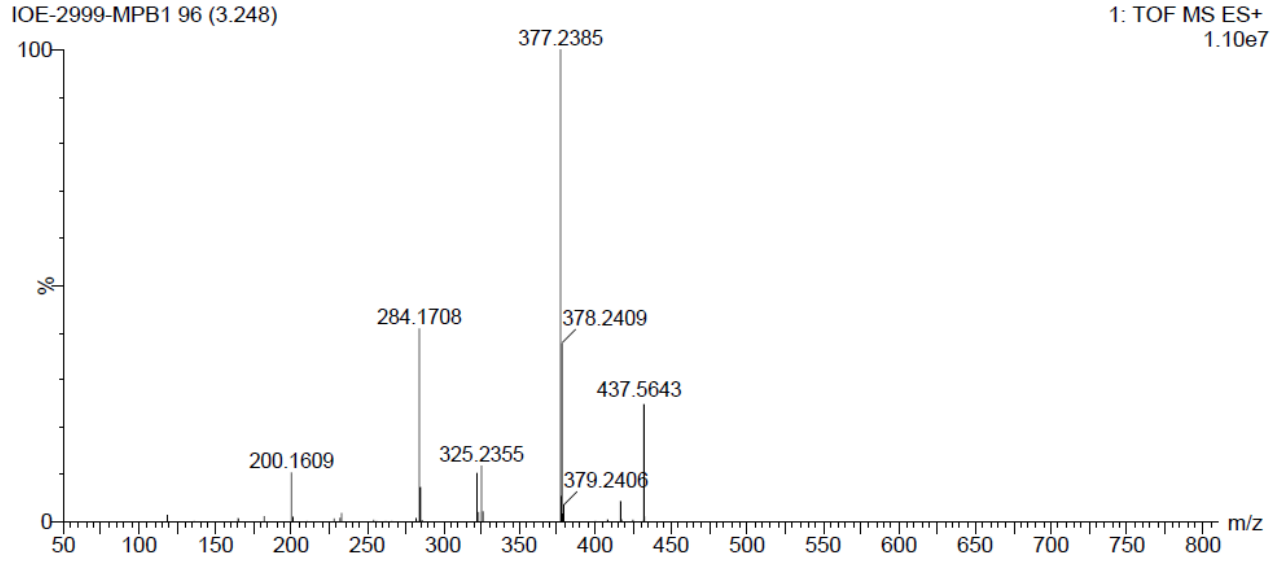


Figure 5: mass spectra of compound 4R

Compound 5 R

Yield:60%

H^1 NMR : 12.11(s,Ar-OH,2H), 7.31(dd, 7.3Hz, ,2H), 7.57(dd, ,2H), 7.51(dd,,2H), 7.22(s,2H), 6.75(dd, 2H), 3.56(t, 4H), 2.43(s ,6H), 2.09–2.12(m, 2H).

Mass spectral values (m/z)(%):407(M^++1)

IR(KBr,Cm^{-1}): 1702(νC= N),1520(ν NH),1542(νC = C),1012(νCN–C).

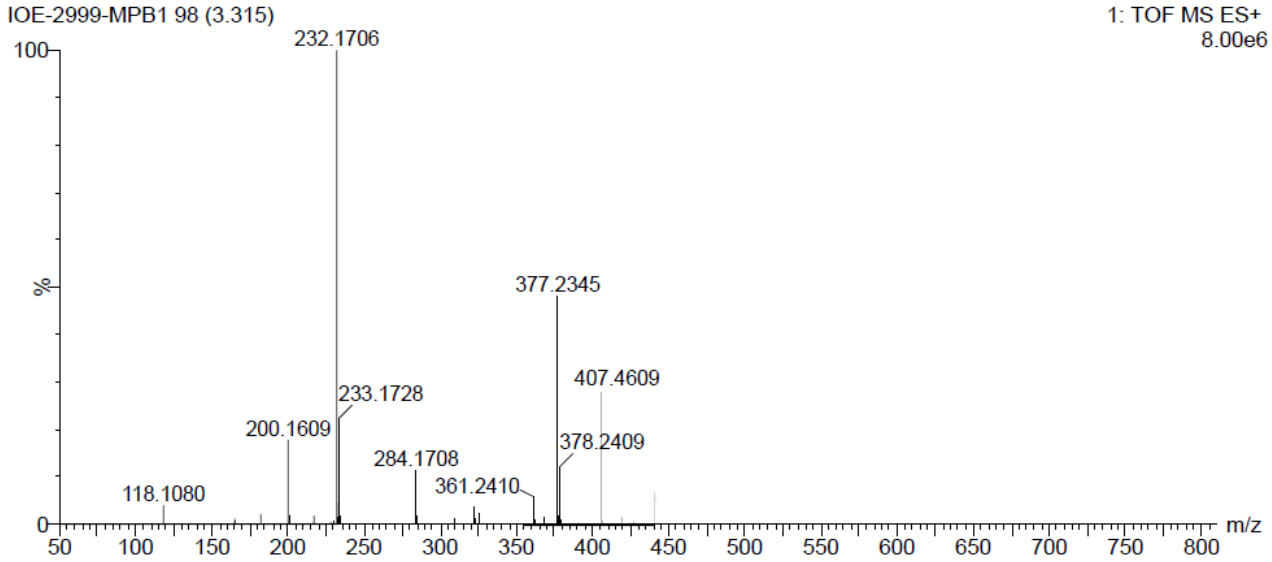


Figure 6: mass spectra of compound 5R

Compound 6R

Yield : 75%

H^1 NMR : 12.06 (s,Ar-OH,2H), 7.21(dd, 7.3Hz, ,2H), 7.36(dd, ,2H), 7.44(dd,,2H), 7.18(s,2H), 6.65(dd, 2H), 3.43(t, 4H), 2.21(s ,6H), 2.02–2.08(m, 2H).

Mass spectral values (m/z)(%) : 437(M^++1)

IR(KBr,Cm^{-1}): 1699(νC= N),1502(ν NH),1534(νC = C),1011(νCN–C).

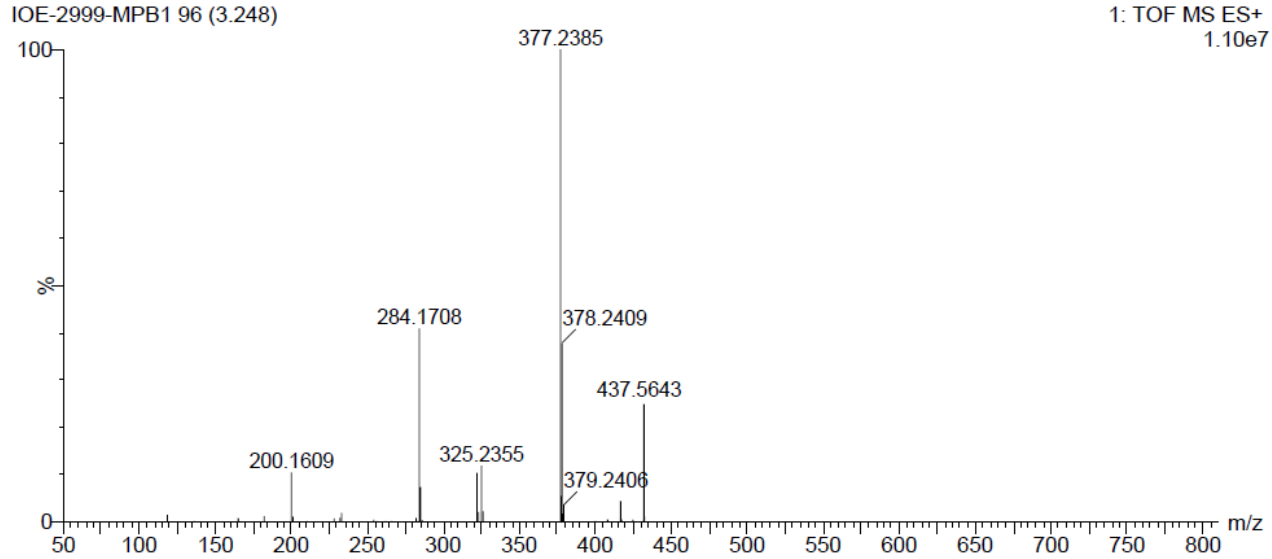


Figure 7: mass spectra of compound 6R

Biological activities

All recently pre-arranged mixtures were evaluated for antibacterial activity against B.Subtilis and A.aerogenes by utilizing plate dispersion method [30].The circles of every fixation were put in three-fold on supplement agar medium cultivated with new bacterial societies separately.The broodingwascompleted at 37^0c for 24 hrs.

Table 2: Minimum Inhibitory concentration of compounds

Compound Number	Minimum Inhibitory concentration Mg/disk (diameter of Zone of inhibition in mm)	
	B.s	A.nor
1R	5(10.2)	5(9.7)
2R	<5(7.4)	5(8.2)
3R	5(11.4)	10(10.2)
4R	10(9.2)	<5(7.1)
5R	<5(7.8)	5(9.1)
6R	5(9.1)	5(8.6)

Screening impact showed that Compound Containing Fluorine at para position showed more dynamic than other comparative mixtures tried against B.Substilis and A.aerogenes.

Docking studies

Materials and Methods

Ligand Preparation

The ligands 1R-6R were drawn using ChemBioDraw Ultra 12.0. Using the 3D editor, the structures were minimised using the MMFF94 forcefield. The ligands were saved as SDF files and converted to Autodock PDBQT files using OpenBabel GUI. Polar Hydrogens were added while converting to PDBQT. The ligand files were visualised and checked for errors using Discovery Studio.

ADME and Toxicology Calculations

To predict the Absorption, Distribution, Metabolism and Excretion properties of the ligands, SwissADME1 web tool was used. The Toxicology studies were taken from pkCSM webserver[31].

Protein Preparation

The proteins were downloaded from the RCSB PDB website (www.rcsb.org). The PDB files were visualised using Discovery Studio, and then loaded into the PyRx software, which

automatically converted the PDB files to PDBQT files, with all polar Hydrogens and Kollmann Charges added. The substrates/known inhibitors of the proteinswere downloaded from PubChem database.(https://pubchem.ncbi.nlm.nih.gov)

Molecular Docking

The Autodock Vina[32] module in PyRx was used for molecular docking of all proteins, one by one, against its own substrate/inhibitor and the six ligands. The docking was performed at the active sites of each of the proteins, with an exhaustiveness of 16. All the computational studies and visualisations were done using Discovery Studio.

Table 3: Protein Structures

PDB ID	Name of Organism	Name of Protein	Function	Known Inhibitor/ Substrate	References
2kau	Klebsiella aerogenes	Urease	Hydrolysis of Urea into Carbamic acid and ammonia	Hydroxylurea(HU), Acetohydroxamic acid(AHA)	[33],[34], [35],[36], [37]
4s0r	Bacillus subtilis	Glutamine Synthase	Amination of Glutamic acid to Glutamine	Glutamine(GLN)	[38],[39], [40]
1h4p	Saccharomyces cereviceae	Beta 1,3-glucan Synthase	Cell Expansion, Cell wall Synthesis	Caspofungin(CAS)	[41],[42], [43]
5v5z	Candida albicans	Lanosterol-14-alpha-Demethylase	Ergosterol biosynthesis	Fluconazole(FLU)	[44],[45], [46]
3o96	Homo sapiens	Alpha Serine/threonine kinase	Phosphorylation of OH of Serine/Threonine	GSK-690693(GSK)	[47],[48], [49], [50]
5tet	Homo sapiens	ATP-Citrate Synthase	Cleavage of Citrate into Oxaloacetate Acetyl-CoA	Bempedoic Acid(BPA)	[51],[52], [53], [54],[55]

Table 4 : ADME studies

Molecule	1R	2R	3R	4R	5R	6R
#Rotatable bonds	6	6	6	6	6	6
#H-bond acceptors	4	4	4	4	4	4
#H-bond donors	1	1	1	1	1	1
TPSA	92.37	92.37	92.37	92.37	92.37	92.37
Molecular Mass	441.91	441.91	441.91	441.91	407.46	407.46
MLOGP	3.63	3.63	3.63	3.63	3.15	3.15

PAINS #alerts	0	0	0	0	0	0
ESOL Log S	-6.1	-6.1	-6.1	-6.1	-5.51	-5.51
ESOL Solubility (mg/ml)	0.000348	0.000348	0.000348	0.000348	0.00125	0.00125
Lipinski #violations	0	0	0	0	0	0
GI absorption	High	High	High	High	High	High
BBB permeant	No	No	No	No	No	No
Pgp substrate	No	No	No	No	No	No
CYP1A2 inhibitor	No	No	No	No	Yes	Yes
CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
CYP2D6 inhibitor	No	No	No	No	No	No
CYP3A4 inhibitor	Yes	No	Yes	Yes	Yes	Yes
log Kp (cm/s)	-5.19	-5.19	-5.19	-5.19	-5.43	-5.43

Toxicity Prediction

Table 5 Compound 1R

Model Name	**Predicted Value**	**Unit**
AMES toxicity	**No**	Categorical (Yes/No)
Max. tolerated dose (human)	**-0.227**	Numeric (log mg/kg/day)
hERG I inhibitor	**No**	Categorical (Yes/No)
hERG II inhibitor	**Yes**	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	**2.818**	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	**1.325**	Numeric (log mg/kg_bw/day)
Hepatotoxicity	**Yes**	Categorical (Yes/No)
Skin Sensitisation	**No**	Categorical (Yes/No)
T.Pyriformis toxicity	**0.355**	Numeric (log ug/L)

Table 6:Compound:2R

Model Name	**Predicted Value**	**Unit**
AMES toxicity	**No**	Categorical (Yes/No)

Max. tolerated dose (human)	**-0.15**	Numeric (log mg/kg/day)
hERG I inhibitor	**No**	Categorical (Yes/No)
hERG II inhibitor	**Yes**	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	**2.888**	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	**1.313**	Numeric (log mg/kg_bw/day)
Hepatotoxicity	**Yes**	Categorical (Yes/No)
Skin Sensitisation	**No**	Categorical (Yes/No)
T.pyriformis toxicity	**0.343**	Numeric (log ug/L)

Table 7:Compound 3R

Model Name	**Predicted Value**	**Unit**
Model Name	Predicted Value	Unit
AMES toxicity	Yes	Categorical (Yes/No)
Max. tolerated dose (human)	0.032	Numeric (log mg/kg/day)
hERG I inhibitor	No	Categorical (Yes/No)
hERG II inhibitor	Yes	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	2.75	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	1.349	Numeric (log mg/kg_bw/day)
Hepatotoxicity	Yes	Categorical (Yes/No)
Skin Sensitisation	No	Categorical (Yes/No)
T.pyriformis toxicity	0.378	Numeric (log ug/L)

Table 8: Compound:4R

Model Name	**Predicted Value**	**Unit**
AMES toxicity	**Yes**	Categorical (Yes/No)
Max. tolerated dose (human)	**0.181**	Numeric (log mg/kg/day)
hERG I inhibitor	**No**	Categorical (Yes/No)
hERG II inhibitor	**Yes**	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	**2.643**	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	**0.813**	Numeric (log mg/kg_bw/day)
Hepatotoxicity	**Yes**	Categorical (Yes/No)
Skin Sensitisation	**No**	Categorical (Yes/No)
T.pyriformis toxicity	**0.397**	Numeric (log ug/L)
Minnow toxicity	**-0.48**	Numeric (log mM)

Table 9: Compound: 5R

Model Name	**Predicted Value**	**Unit**
AMES toxicity	**Yes**	Categorical (Yes/No)

Max. tolerated dose (human)	**0.058**	Numeric (log mg/kg/day)
hERG I inhibitor	**No**	Categorical (Yes/No)
hERG II inhibitor	**Yes**	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	**2.684**	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	**1.509**	Numeric (log mg/kg_bw/day)
Hepatotoxicity	**Yes**	Categorical (Yes/No)
Skin Sensitisation	**No**	Categorical (Yes/No)
T.pyriformis toxicity	**0.378**	Numeric (log ug/L)
Minnow toxicity	**-0.401**	Numeric (log mM)

Table 9: Compound:6R

Model Name	**Predicted Value**	**Unit**
AMES toxicity	**Yes**	Categorical (Yes/No)
Max. tolerated dose (human)	**0.22**	Numeric (log mg/kg/day)
hERG I inhibitor	**No**	Categorical (Yes/No)
hERG II inhibitor	**Yes**	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	**2.59**	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	**0.97**	Numeric (log mg/kg_bw/day)
Hepatotoxicity	**Yes**	Categorical (Yes/No)
Skin Sensitisation	**No**	Categorical (Yes/No)
T.pyriformis toxicity	**0.4**	Numeric (log ug/L)
Minnow toxicity	**-0.51**	Numeric (log mM)

Table 10: Docking Results

	Binding Affinity(kcal/mol)				
Ligand	**2kau**	**4s0r**	**1h4p**	**5v5z**	**3o96**
1R	-7.3	-7.2	-9.5	-10	-10.7
2R	-6.7	-7.6	-9.6	-10.1	-10.4
3R	-6.8	-7.6	-9.1	-9.9	-10.6
4R	-7.5	-7	-9.7	-9.3	-10.2
5R	-7.4	-7.9	-9.7	-10.2	-10.3
6R	-7.2	-7.5	-9.7	-8.9	-10.3
HU	-4.7	-	-	-	-
AHA	-4.2	-	-	-	-
GLN	-	-5.7	-	-	-
CAS	-	-	-8	-	-
FLU	-	-	-	-7.6	-
GSK	-	-	-	-	-10
BPA	-	-	-	-	-

Visualisations of 2D diagrams, binding pocket and hydrophobic pocket of Compounds

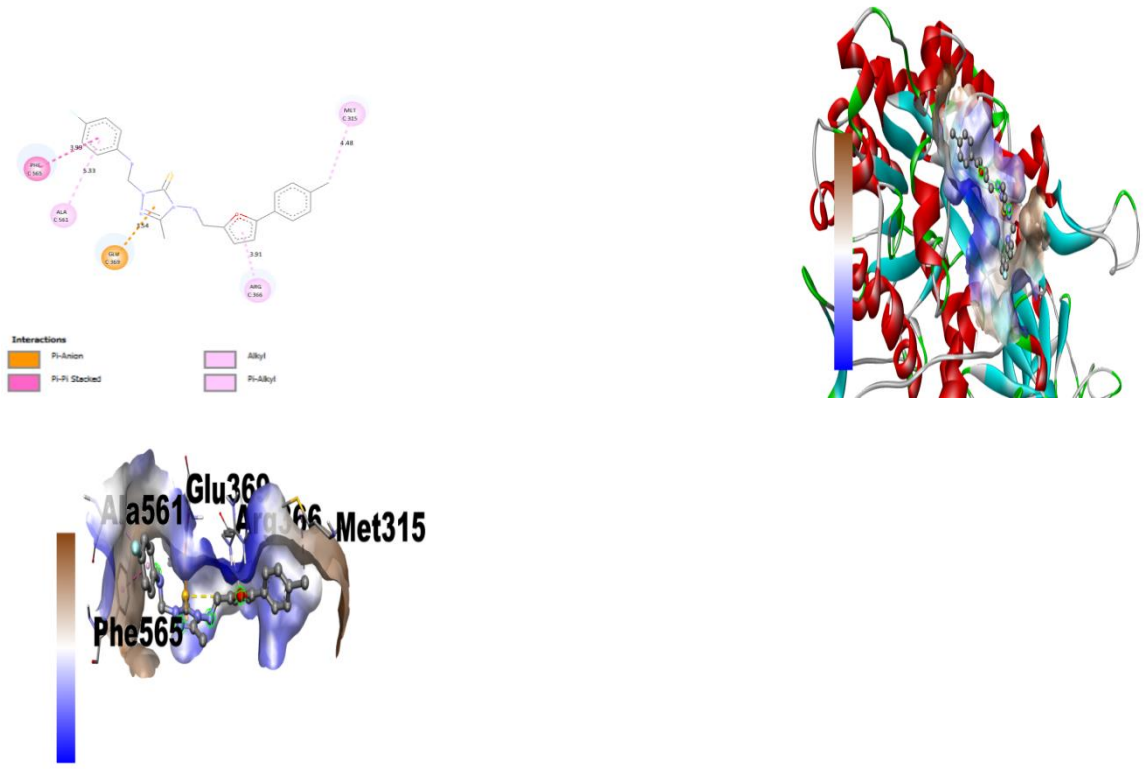


Figure 8: 2D diagrams, binding pocket and hydrophobic pocket of CompoundsCompound 1R

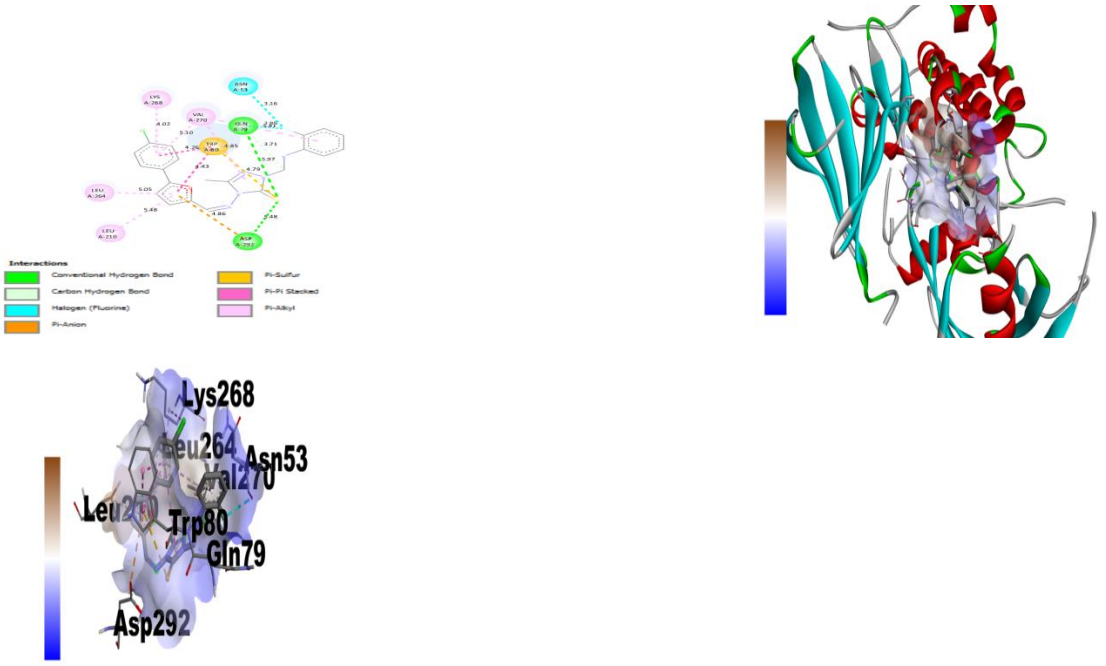


Figure 9: 2D diagrams, binding pocket and hydrophobic pocket of Compound 2R

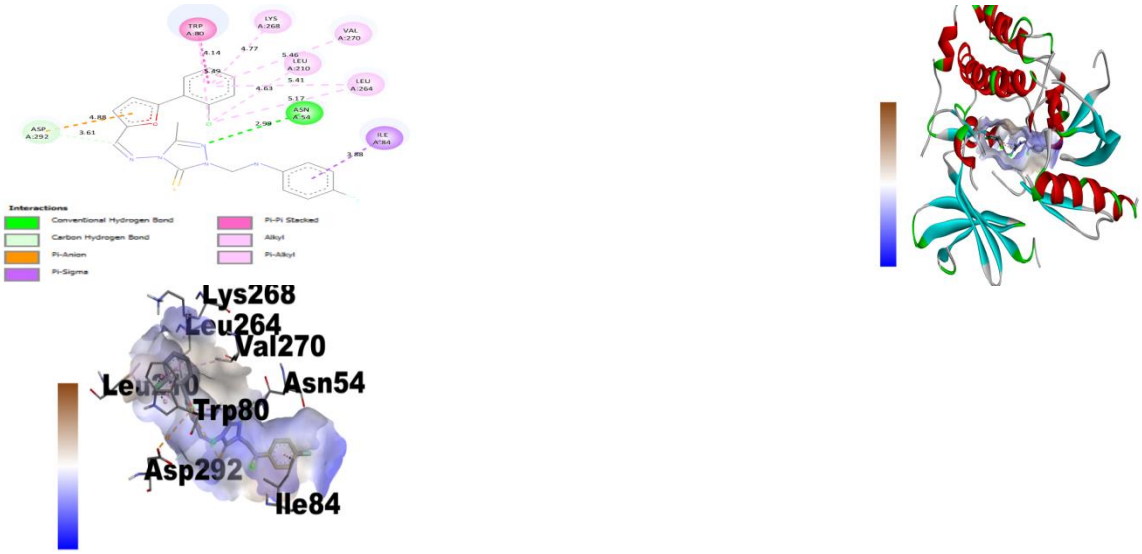


Figure 10: 2D diagrams, binding pocket and hydrophobic pocket of Compound 3R

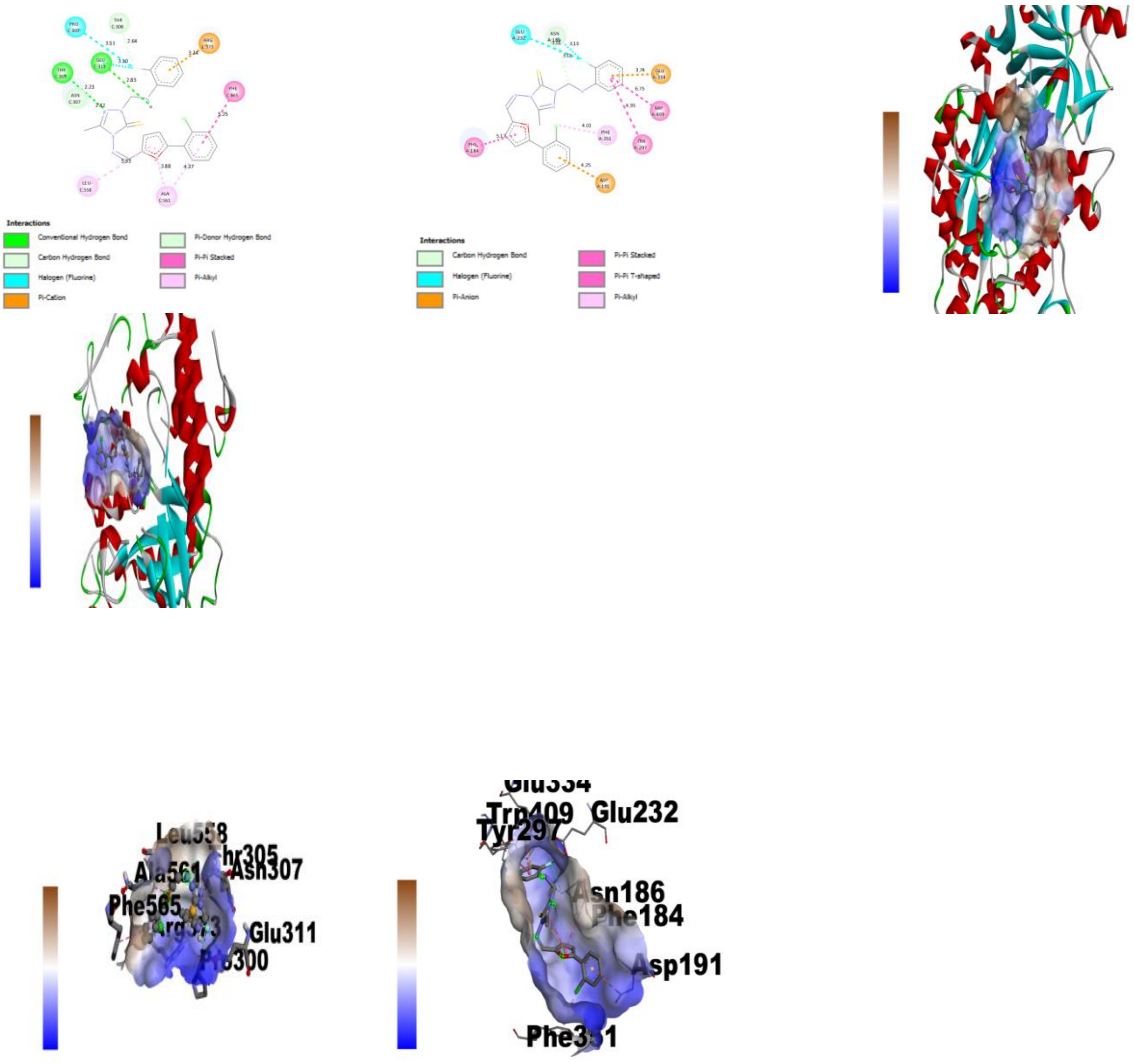


Figure 11: 2D diagrams, binding pocket and hydrophobic pocket of Compound 4R

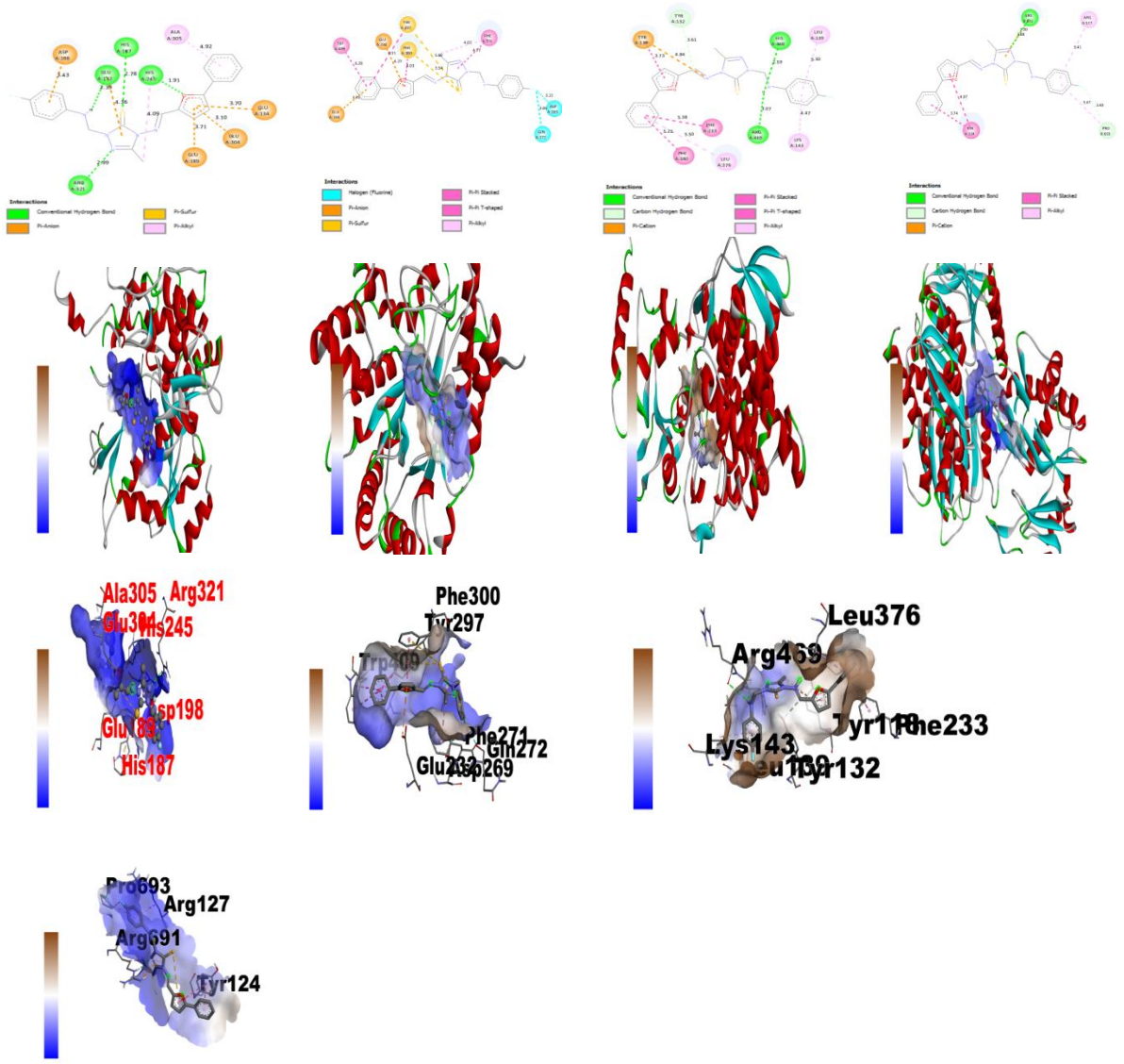


Figure 12: 2D diagrams, binding pocket and hydrophobic pocket of Compound 5R

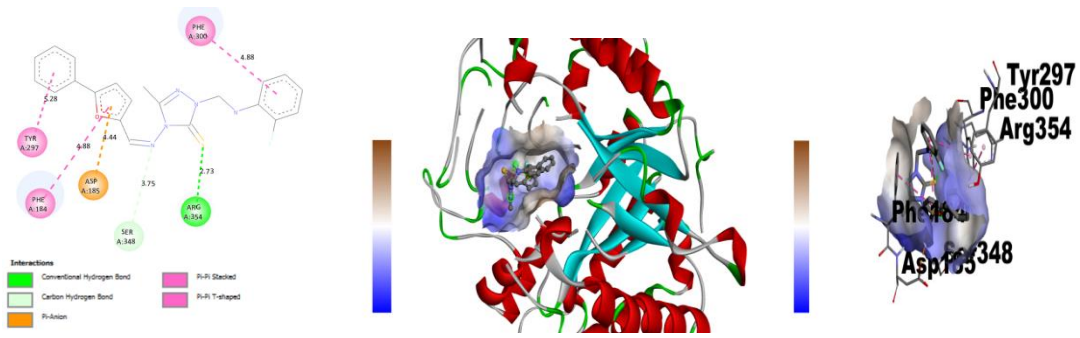


Figure 13: 2D diagrams, binding pocket and hydrophobic pocket of Compound 6R

Result and discussion

A series of 1-(Amino/Fluro methyl - 3 Alkyl subbed - 4-arylidiene) Amino - 1,2,4-triazole were synthesised and they screened for antibacterial movement against B.Subtilis and A.aerogenes by utilizing plate dispersion method . Hence we found that compounds containing fluorine at para position showed significant activity than other substituents and when these compounds were screened for docking studies as well as ADMI studies compound 5R showed highest binding activity when compared to other compounds.

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CONFLICT OF INTEREST:

No conflict of interest.

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