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COMPUTATIONAL DESIGN, SYNTHESIS AND *IN-VITRO* EVALUATION OF NOVEL ARYL FLUORO HYDRAZIDE DERIVATIVES

K. Sreena *, P. Ashique, T. R. Pavithra and Pooja Lakshmi

Department of Pharmaceutical Chemistry, Crescent College of Pharmaceutical Sciences, Payangadi, Kannur - 670358, Kerala, India.

Keywords:

4-Fluorobenzhydrazide, 3-Bromo-2-fluorobenzaldehyde, *In-silico* study, Anti-microbial activity

Correspondence to Author:
K. Sreena

Professor,
Department of Pharmaceutical Chemistry, Crescent College of Pharmaceutical Sciences, Payangadi, Kannur - 670358, Kerala, India.

E-mail: sreenasujith@gmail.com

ABSTRACT: Infectious diseases continue to be a major cause of morbidity and mortality, and the current antimicrobial resistance crisis has the potential to worsen this problem. To address this issue, new antimicrobials and strategies for fighting antimicrobial resistance are needed. In this study, we synthesized two arylflouro hydrazide derivatives by reacting various selected hydrazides (4-Fluorobenz-hydrazide) and different substituted aromatic aldehydes (3-Bromo-2-fluoro benzaldehyde and 5-Bromothiophene-2-carboxaldehyde). The compounds were characterized using IR, 1H NMR, and 13C NMR. The synthesized derivatives were also pharmacologically evaluated using molecular modeling. The biological activity was assessed using an antimicrobial assay, which showed significant activity compared to the standard Ampicillin. Among the synthesized compounds, PD2B exhibited a higher zone of inhibition with 10 mm in *E. coli* and 12 mm in *B. subtilis*, whereas PD2F showed a zone of inhibition with 3 mm in E. coli and 8 mm in *B. subtilis*.

INTRODUCTION: Hydrazide constitutes a class of organic compounds which attracts the attention of medicinal chemists due to the fact that they contain azomethine (–NH–N=CH–) group connected with carbonyl group, which is responsible for their different pharmaceutical applications [1]. While hydrazines have traditionally been employed as reagents for the derivatization and characterization of carbonyl compounds, the N-N linkage has recently been used as a key structural modification in various bioactive agents [2].

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The main route to synthesizing hydrazide derivatives is reacting hydrazides with corresponding aldehydes.

Hydrazide as Antimicrobial Agents: An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill or inhibit the growth of microbes. Drugs in this class differ from all other drugs in that they are designed to inhibit or kill the infecting organism and to have no or minimal effect on the recipient.

The extensive use of antibiotics has led to the appearance of multi-drug-resistant microbial pathogens. This highlights the constant need for developing new classes of antimicrobial agents and alteration of known drugs to allow them to retain their physiological action while reducing their resistance to the pathogen. In this study we

synthesized novel aromatic fluorinated hydrazide derivatives from fluorinated aromatic hydrazide and different aromatic aldehydes, which exhibit potent antimicrobial activity due to their high affinity towards Penicillin Binding Proteins (PBP) [3]. These newly synthesized compounds show similar activity as that of synthetic penicillin's.

The Need for Novel Antibacterial Agents: The prevalence of drug-resistant bacteria is growing at an alarming rate in developing and developed countries. From this statement alone, it should be clear that the need to develop novel antibacterial agents is of utmost importance. In the current antibacterial drug pipeline, there is only a miniscule glimmer of hope [3, 4]. This rapid increase in resistant bacteria, coupled with the slow development of novel agents has led some experts to call this time the "dawn of the post-antibiotic era". There exists a perpetual need for new antibiotics. Most drugs will be just as effective in the future as they are today, but that is not the case with antibiotics. Eventually, the inevitable rise of resistance will erode the utility of today's antibiotics [5, 13]. Three factors intensify this supply problem by discouraging antibiotic development [6]. First, antibiotics are used in smaller quantities than other drugs. However, most newly approved drugs can be prescribed to all who may benefit from their use. These factors ultimately result in this quandary. Resistance is on the rise while antibiotic discovery and development are declining [7, 15, 18].

These drugs act by binding onto Penicillin-binding proteins (PBPs), a group of proteins characterized by their affinity for and binding of penicillin. They are a normal constituent of many bacteria; the name reflects how the protein was discovered. All β-lactam antibiotics (except for tabtoxinine-β-lactam, which inhibits glutamine synthetase) bind to PBPs, essential for bacterial cell wall synthesis [8, 11]. PBPs are members of a subgroup of enzymes called Trans peptidases. Specifically, PBPs are DD-trans peptidases.

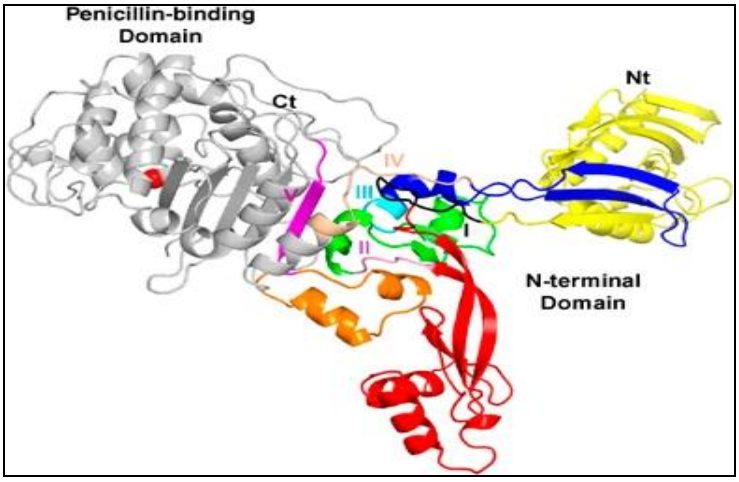


FIG. 1: 3-D STRUCTURE OF PENICILLIN BINDING PROTEIN (PBP) Downloaded from https://academic.oup.com/femsre/article/32/2/234/2683944 on 26 September 2022

PBPs bind to β-lactam antibiotics because they are similar in chemical structure to the modular pieces that form the peptidoglycan. When they bind to penicillin, the β-lactam amide bond is ruptured to form a covalent bond with the catalytic serine residue at the PBPs active site. Ampicillin is the standard drug used in this study, an antibiotic used to prevent and treat several bacterial infections, such as respiratory tract infections, urinary tract infections, meningitis, salmonellosis and endocarditis. Ampicillin is used to treat infections by many Gram-positive and Gram-negative bacteria [12, 13]. Ampicillin is in the penicillin group of beta-lactam antibiotics and is part of the amino penicillin family. It is roughly equivalent to amoxicillin in terms of activity. Ampicillin can penetrate Gram-positive and some Gram-negative bacteria. It differs from penicillin G or benzyl penicillin, only by the presence of an amino group. Ampicillin acts as an irreversible inhibitor of the enzyme Tran's peptidase, which is needed by bacteria to make the cell wall.

Test Organism: *Escherichia coli* (*E. coli*) and *Bacillus subtilis* (*B. subtilis*) are the test organism used. Escherichia coli also known as *E. coli* is a

Gram-negative and non-sporulating bacterium, facultatively anaerobic, rod-shaped, coliform bacterium of the genus Escherichia that is commonly found in the lower intestine of warm blooded organisms, nonsporulating coliform bacterium. Cells are typically rod-shaped, about 2.0µm long and 0.25–1.0µm in diameter, with a cell volume of 0.6–0.7 µm. Antibiotics can effectively treat *E. coli* infections outside the digestive tract and most intestinal infections but are not used to treat intestinal infections by one strain of these bacteria [14, 26]. *Bacillus subtilis*, also known as the haybacillus or grassbacillus is a Gram-positive, catalase-positive bacterium, found in soil and the gastrointestinal tract of ruminants, humans and marine sponges. As a member of the genus Bacillus, *B. subtilis* is rod-shaped and can form a tough, protective endospore, allowing it to tolerate extreme environmental conditions. *B. subtilis* cells are typically rod-shaped and are about 4–10 micrometers (µm) long and 0.25–1.0 µm in diameter, with a cell volume of about 4.6 fL at stationary phase.

MATERIAL AND METHODS: The chemicals and reagents were procured from Sigma Aldrich, Lobachemie, and Nice Chemicals, Mumbai, India. Melting points were determined by the open capillary method and were uncorrected. IR spectra were recorded on Bruker FT-IR (Shimadzu 8201 PC) spectrophotometers and values are expressed in cm-.1HNMR and 13C-NMR spectra were recorded on Bruker Avance-500, FTNMR spectrometer (Bruker, Chandigarh) at 500MHz and the chemical shifts are reported in parts per million (δ value), taking TMS (δ 0 ppm for 1H NMR) as the internal standard. Mass spectra were recorded using LC-ESI Technique on the ESI-MS Q-ToF Micro Waters Mass Spectrometer instrument (NIPER, Punjab).

***In-silico* Study:** All computational analysis was carried out on a Windows 10 Pro OS platform on a Desktop with an Intel(R) Pentium(R) CPU J3710 @ 1.60GHz 1.60 GHz and 4 GB RAM.

Physiochemical Properties: Molinspiration Molecular Viewer allows the visualization of molecules which is encoded as SMILES or SD file for the calculation of important molecular description (Log P, Polar surface area, Number of hydrogen bond donors, Number of hydrogen bond acceptors, etc.) as well as prediction of bioactivity score of important drug targets.

Pharmacokinetic Study by Swiss ADME: Swiss ADME is a web tool giving free access to physiochemical properties (Molecular weight, Molar refractivity, Polar surface area), pharmacokinetics (substrate or non-substrate of P-gp, CYP inhibition), drug-likeness of the potent molecule.

Pass Online: Prediction of Activity Spectra for Substances (PASS) is a computer program that estimates a drug-like organic compound's probable biological activity profile based on its structural formula. It provides output information as a list of predicted types of activity with an estimated probability of each kind of activity,, to be active‟ Pa and to be inactive‟ Pi, which may vary from zero to one. If Pa> 0.7, the changes of finding experimental activity are rather high. If 0.5 <Pa< 0.7, the compounds will be less similar to known pharmaceutical agents. If Pa< 0.5, the compound is found to be a new chemical class for biological activity.

Molecular Docking: Docking small molecules and compounds into the receptor's binding site and estimating the complex's binding affinity is an important part of structure-based drug design. AutodockVina achieves molecular docking. The 3D crystallographic structure of proteins is uncovered from the protein data bank (PDB ID-3ITB) AutodockVina is an open-source program offering a complete molecular viewer and graphical support for all the steps inevitable for setup and docking analysis [5, 6]. PyMOL produces a high-quality 3D image of protein as well as its visualization. PyRx is for docking analysis.

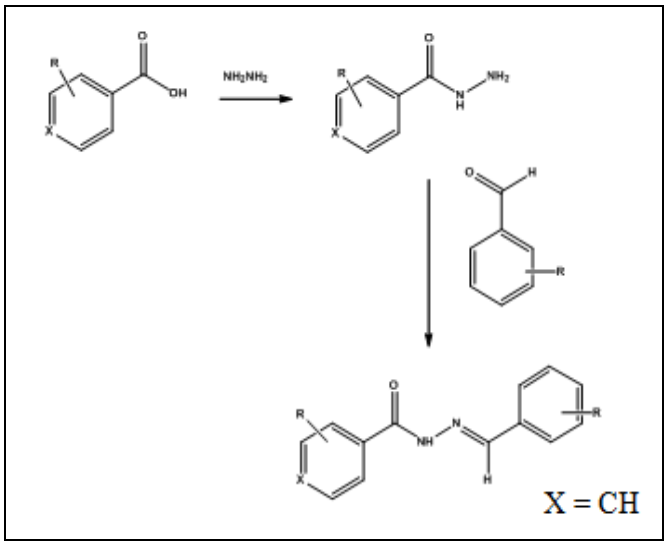
Protein Preparation: The structure downloaded from PDB database is unsuitable for docking studies. PyMOL produces high-quality 3D images of these proteins. The structure should clear up with water molecules (HOH), small molecules, and detergents (DSN). It is achieved by inserting various commands like “remove<>resn<> HOH/DSN” (for water molecules or detergents). Hydrogen atom should be added to the structure of the protein

Ligand Preparation: The 2D chemical structures of ligands are drawn using ACD Lab Chemsketchver 12.0 or Chemdraw Ultra 12.0 and generated smiles notation. This smile notation is being converted into 3D PDB format with the help of a freely accessible Online SMILES Translator.

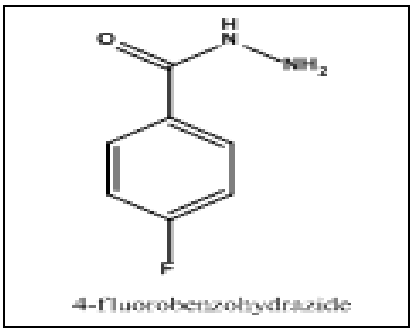
Docking using AutodockVina: Docking is performed in PyRX where both the derivative and receptor are loaded in the navigation pane. Then the protein is converted into macromolecule and derivative into ligand molecule. After the preparation, click on AutodockVina Wizard start button and adjust the grid size. After the completion of process, docking value is expressed in terms of binding affinity (Kcal/mol) with RMSD upper bound and lower bound value. Autodock Vinaconvert PDB to PDBQT which is followed by additional step by adding polar contacts to find out the types of amino acid interactions during ligand-receptor binding.

Chemistry: The compounds were synthesized per the following scheme; General procedure for synthesizing Fluoro hydrazide Derivatives [10, 11]. A mixture of hydrazide (0.5g, 0.0036 mol) and substituted aromatic aldehyde (0.0036 mol) was stirred in 10 ml water for the prescribed time period mentioned in **Table 1** at room temperature.

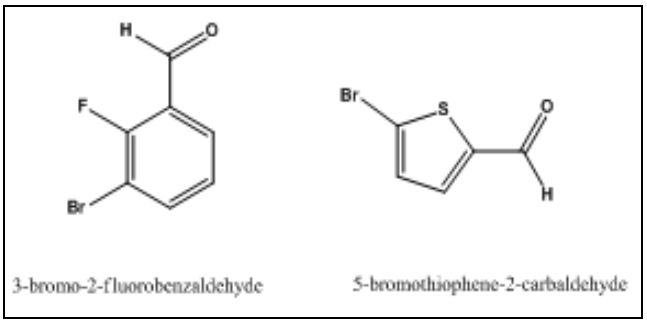
In a few minutes, the temperature of the reaction mixture was raised due to the heat that evolved during the exothermic reaction, but it should not be allowed to exceed 20°C above room temperature. The crystalline product was filtered, washed with water, dried, and recrystallized from ethanol.



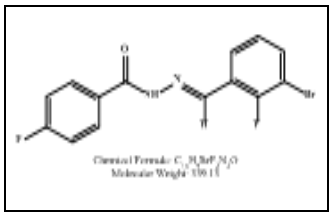
Hydrazide:

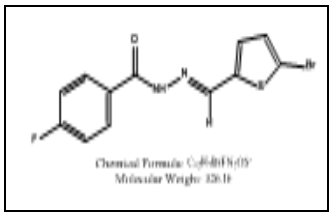


Substituted Aromatic Aldehyde:



Structure of Synthesized Compounds PD2B PD2F:





Biological Evaluation:

Chemicals: Agar-Agar was purchased from Finar Limited, Ahmedabad. Nutrient agar (contains Agar, Peptic digest of animal tissue, Sodium chloride, Yeast extract, Beef extract) was purchased from SiscoResearch Laboratories, New Mumbai, India. Dimethyl sulfoxide (DMSO) was purchased from Merck Specialities Private Limited, Mumbai.

Determination of Antimicrobial Activity: The agar well diffusion method is widely used to evaluate the antimicrobial activity of newly synthesised compounds which shows activity against Escherichia coli (*E. coli*) [19, 20]. The agar plate surface is inoculated by spreading a volume of the microbial in-oculum over the entire agar surface. Then, a hole with a 6 to 8-mm diameter is punched aseptically with a sterile cork borer or a tip. Each test compound (0.05g) was dissolved in

5ml of dimethyl sulfoxide (50µg/ml). The solution of each test compound were added separately in the wells and petridishes were subsequently incubated [16, 17]. Ampicillin was used as standard (reference) drug and dimethyl sulfoxide as a control which didn't reveal any inhibition. The zone of inhibition produced by each compound was measured in mm; the results are presented in **Table 5**.

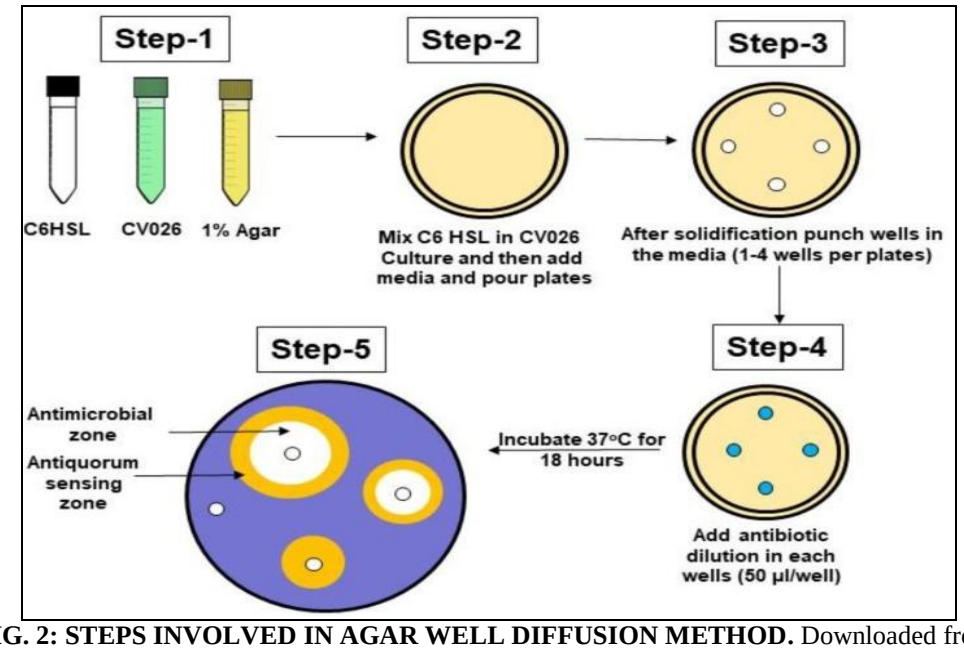


FIG. 2: STEPS INVOLVED IN AGAR WELL DIFFUSION METHOD. Downloaded from: https://www.biorxiv.org/content/biorxiv/early/2020/05/16/2020.05.15.097790/F10.large.jpg

TABLE 1: PHYSIOCHEMICAL PROPERTIES OF SYNTHESIZED COMPOUNDS

Compound		PD2B	PD2F
	Hydrazide	4-Flourobenzohydrazide	4-Flourobenzohydrazide
	Aldehyde	3-Bromo-2-flourobenzaldehyde	5-Bromothiophene-2-carbaldehyde
	Reaction Time (hrs)	1.5	1.5
	Melting Point (^{0}C)	178-195°C	136-144°C
TLC	R_f Value	0.7	0.74
	Solvent system	Ethylacetate: Ethanol (1:0.5)	Ethylacetate: Toluene (1:1)
	Recrystallization Solvent	Ethanol	Ethanol
	Yield (%)	72.5%w/w	68.8%w/w

RESULTS AND DISCUSSION:

***In-silico* Studies:** Pharmacokinetics parameters of these derivatives were calculated using Molinspiration Online software. From all these parameters **Table 2**, the compounds obeying Lipinski's rule of five was selected of five were selected for docking studies.

TABLE 2: ANALYSIS OF LIPINSKI'S RULE OF FIVE BY MOLINSPIRATION

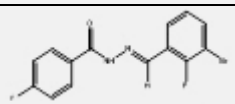
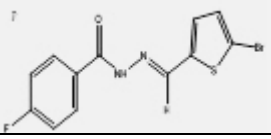
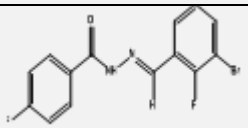
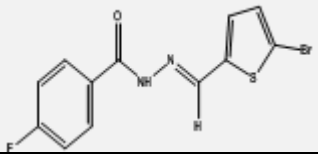
Compound ID	Structure	MW (g/mol)	HA	HD	LogP	nrotb	Violation
PD2B		339.14	3	1	4.12	3	0
PD2F		327.18	3	1	4.07	3	0

TABLE 3: PHARMACOKINETIC STUDY BY SWISS ADME

Compound ID	GI Absorption (High/Low)	BBB Permeant (Yes/No)	P-gp substrate (Yes/No)	PAINS (alert)
PD2B	High	Yes	No	0
PD2F	High	Yes	No	0

The designed molecules were docked against the selected Penicillin-binding protein (3ITB). The best and stable pose was selected based on the docking score and the basis of multiple interactions. Comparing the binding structure of the entire 2 synthesized molecules, the hydrazide holds a key group for binding affinity in the binding pocket. Among the synthesized PBP Inhibitors, compound PD2B has the highest binding affinity towards the protein, and PD2F has the least binding affinity. The five-membered heterocyclic may reduce the affinity and fitting of the drug in the binding pocket for the desired activity. The presence of electronegative atoms on both end of a designed compound may increase the binding affinity.

TABLE 4: DOCKING RESULTS

Sl. no.	Compound	Structure	Docking score	Interacting residue
1	PD2B		-9.238	ALA A:39 SER A:40 LYS A :43 LEU A:149 ARG A:194 THR A:210 GLY A:211 THR A:212
2	PD2F		-8.814	ALA A:39 LYS A:43 SER A:83 ASN A:108 LEU A:149

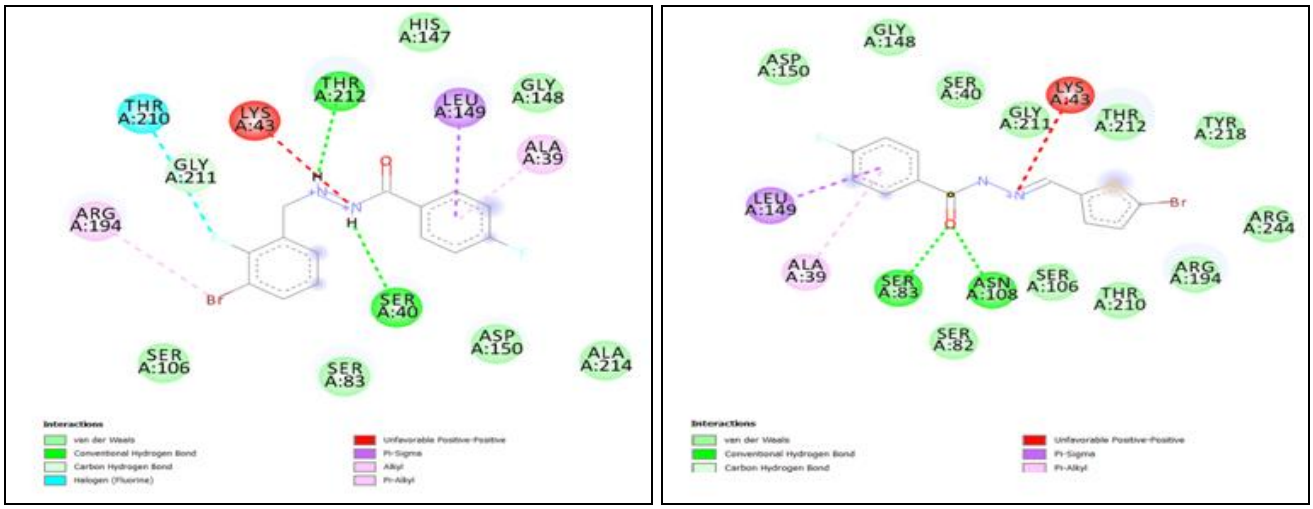


FIG. 3: BINDING INTERACTION OF COMPOUND PD2B AND PD2F

Chemistry: Two aryl fluoro hydrazide derivatives were designed and synthesized by the reaction of equimolar amounts of the selected Hydrazides (4-Fluorobenzhydrazide) and different substituted aromatic aldehydes (3-Bromo-2-fluorobenzal-dehyde, 5-Bromothiophene - 2 - carboxaldehyde). The compound PD2B, PD2F took 1.30 hr to complete the reaction compound. The progress of the reaction was monitored by TLC. The compounds' yield ranged from 60-75% with reasonable purity. All the synthesized derivatives were found to have a sharp melting point.

Characterization of the Synthesized Compounds: 1. N'-[(E)-(3-bromo-2-fluorophenyl) methylidene]-4-fluorobenzohydrazide (PD2B): White powder (EtOH); MP=178-195oC, Yield: 72.5%w/w, IR (ZnSe) peaks: 3449.84cm-1(NH stretching) 3040.91cm-1 (Aromatic CH) 1666.57 cm-1 (C=O Stretching) 1577.52 cm-1 (C=N). 1HNMR (500MHz, DMSO-D6): δppm=7.22-7.99 (m, 7H, ArH) 8.63 (s, 1H, CH) 12.07 (br, 1H, NH). 13CNMR (500MHz, DMSO-D6): δppm=116.04, 116.21, 120.98, 124.12, 125.84, 126.31, 126.83, 130.01, 131.00, 132.65, 135.29, 140.26, 145.43, 162.60.ESI-MS: 340.14 (M+1)

2. N'-[(E)-(5-bromothiophen-2-yl) methylidene]-4-fluorobenzohydrazide (PD2F): White powder (EtOH); MP=136-144oC,Yield:68.8%w/w, IR (ZnSe) peaks: 3554.96cm-1 (NH stretching) 3050.55cm-1(Aromatic CH) 1661.75cm-1 (C=O

stretching) 1579.50cm-1 (C=N) 1HNMR (500MHz, DMSO-D6): δppm=7.24-7.92 (m, 6H, ArH) 8.54 (s, 1H, CH) 11.88 (br, 1H, NH). 13CNMR (500MHz, DMSO-D6): δppm=115.36, 115.98, 116.12, 130.24, 130.82, 130.88, 131.85, 132.12, 141.51, 142.72, 163.88, 165.53.ESI-MS: 328.21(M+1)

The synthesized derivatives were pharmacologically evaluated. The evaluation was carried out by antimicrobial assay. Among the compounds tested for antibacterial activity, PD2B showed the highest zone of inhibition against *E. coli* and *B. subtilis* as compared to the standard drug Ampicillin and other synthesized derivatives [18, 19]. PD2F also shows the highest zone of inhibition than Ampicillin. The results show that a fluorine substituent present at the para position of phenyl ring enhances the antibacterial activity. The biological activity calculated using microbial assay was by molecular modeling study.PD2B was identified as a potent molecule during Insilco evaluation. Hence, it can be concluded that computational tools are highly effective in identifying potent molecules even before synthesis.

TABLE 5: ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compound ID	Zone of inhibition in mm	
	(*E. coli*)	(*B. subtilis*)
PD2B	10	12
PD2F	3	8
Standard (Ampicillin)	3	4
Control (DMSO)	Nil	Nil

FIG. 3: ZONE OF INHIBITION IN SYNTHESIZED COMPOUNDS AGAINST *E. COLI*

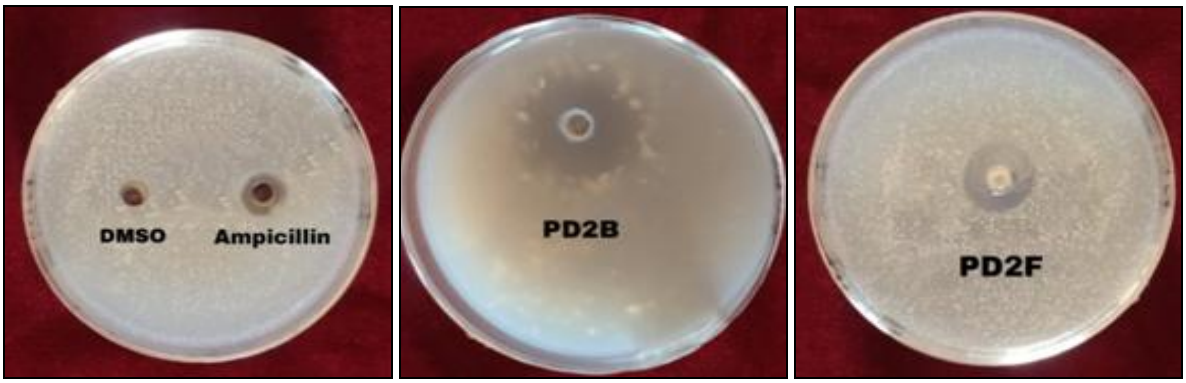


FIG. 4: ZONE OF INHIBITION IN SYNTHESIZED COMPOUNDS AGAINST *B. SUBTILIS*

CONCLUSION: From this study, we concluded that all the designed compounds were capable of acquiring a comfort zone with the target enzyme during the docking studies. Results of molecular docking showed that PD2B and PD2F were able to interact with the active site in an efficient manner, when compared with the co-crystallized ligand. It was found that the secondary amine and oxygen of hydrazone in 4-chloro-N'-(4-fluorobenzylidene) benzohydrazide (DR-4) had particular hydrogen bonds and the hydrophobic interactions with Tyr 435, Leu 171. The two benzene ring structure forms Pi-Pi stacking interaction with Tyr 398, Tyr 326 and Tyr 435. This lead molecule was found to be most active against MAO-B isoforms among the designed compounds. These molecules were taken forward for synthesis. We have successfully developed a simple and efficient method for

synthesizing designed compounds identified by molecular modeling studies. All the compounds were synthesized by simple stirring at room temperature for a period ranging from 1-2 hrs. TLC monitored the progress of the reaction. The compounds' yield ranged from 60-75% with reasonable purity. All the synthesized compounds were recrystallized twice with ethanol to get better purity necessary for the spectral studies.

Spectral studies using IR, 1H NMR, 13C NMR spectroscopy indicated the formation of hydrazide derivatives. Mass spectrometry also gave the molecular mass of synthesized compounds, confirming the structure of the hydrazide derivatives

These synthesized derivatives were further evaluated, which was carried out through a well diffusion assay and analysis of inhibitory activity. From the antimicrobial activity, it was revealed that the compound PD2B was found to be more active among the 2 tested compounds. It can be concluded from the antimicrobial study that PD2B is more potent than the standard drug Ampicillin. Compound PD2F was also found to be a potent antimicrobial agent.

In-vivo evaluation of the synthesized molecules in small animals must be performed to establish the compounds' effectiveness. We believe this study may provide valuable information to researchers working on developing Aryl fluoro derivatives as antimicrobial agents.

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CONFLICTS OF INTEREST: The authors declared no conflict of interest.

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