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DESIGN, SYNTHESIS, *IN-VITRO* AND *IN-SILICO* ANTIMYCOBACTERIAL ACTIVITY SCREENING OF NOVEL N´- [3-(SUBSTITUTED PHENYL AMINO) CHLOROACETYL]-4-(1H-PYRROLE-1-YL)-BENZOHYDRAZIDE DERIVATIVES

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ABSTRACT

In the present inquiry, *N′-[3-(substituted phenylamino) chloroacetyl]-4-(1H-pyrrol-1-yl) benzo-hydrazide* was reacted with various substituted primary amines to produce a new series of pyrrole derivatives. The synthesized compounds were thoroughly characterized using spectroscopic approaches, including IR, ^{1}H NMR, and ^{13}C NMR, to establish their structural integrity. The antimycobacterial activity of these substances was tested against Mycobacterium TB strain H37Rv using the Microplate Alamar Blue Assay (MABA) technique. Among the studied compounds, R-2 and R-3 displayed high antitubercular activity, with a minimum inhibitory concentration (MIC) of 31.25 µg/mL, while R-1 and R-4 showed moderate activity, with an MIC of 62.5 µg/mL. To further study the binding interactions of these drugs with the M. tuberculosis enoyl-reductase (InhA) enzyme (PDB: 5JFO), in silico molecular docking experiments were done. The docking findings demonstrated high binding affinities, with compounds R-1, R-2, R-3 and R-4 having binding energies of -8.2, -7.6, -6.5, and -7.8 kcal/mol, respectively, confirming their potential as InhA inhibitors. These findings emphasise the prospective antitubercular capabilities of the synthesized pyrrole derivatives.

KEYWORDS: Pyrrole, antimycobacterial activity, MABA method, ^{1}H NMR and ^{13}C NMR, tuberculosis.

INTRODUCTION

Tuberculosis is an infectious disease that severely affects the lungs. It is a pandemic disease and is caused by five different directly related mycobacteria, such as Mycobacterium africanum, Mycobacterium bovis, Mycobacterium microti, Mycobacterium canetti, and Mycobacterium tuberculosis.[1,3]

Mycobacterium tuberculosis has been the major causative agent of tuberculosis, a disease that affects the lungs, referred to as pulmonary TB, and some other parts as well, referred to as extrapulmonary TB.[2,13,11] Tubercle bacillus, preferably known as Mycobacterium tuberculosis, was identified by Robert Koch in 1882.[16] Ever since its discovery, it seems to have spread worldwide, affecting numerous people and causing numerous deaths. Tuberculosis is an airborne and transmissible disease. TB is also among the leading causes of death worldwide in comparison to AIDS and HIV.[16,3] According to the World Health Organization (WHO), in 2022, around 2 billion people were infected with TB. In 2017, 10 million new cases of TB, 1.6 million TB-related deaths, and 1.5 million TB-related deaths were observed in 2018.[7,13,16]

Tuberculosis can remain inactive in the body without causing any signs or symptoms of illness, through which many people become symptomless carriers of M. TB. According to the WHO, approximately 2 billion people worldwide are infected with M. tuberculosis who were previously quiescent.[4,6] The chances of a resurgence of TB in these patients are about 5–10%. The bacteria could be rejuvenated in patients with compromised immune systems, such as those with HIV. The chances of the development of TB in HIV-positive patients are expected to be 18 times higher than those without HIV. Tb reactivation occurs when the stalemate is broken and the bacterial burden soars, making the disease symptomatic.[7,11] Through treatment with standard anti-tubercular drugs like isoniazid, rifampicin, ethambutol, and pyrazinamide, TB can be cured and prevented. According to the reports of the WHO, there is a fall of only about 2% in the cases, while it should have been about 4–5%, according to the end strategy of the WHO, ending the pandemic.[16,3,12]

Immunological, radiographical, microscopical, bacterial culture, and clinical methods are employed for the diagnosis of TB, and immunological tests such as QuantiFERON-TB Gold (QFT) and the Tuberculin Skin

Test (Mantoux test) are mainly used for the purpose of screening and ruling out TB infection.[2,9,11] Radiography (Chest X-rays) is a screening tool used to diagnose active pulmonary TB, although it cannot help in detecting dormant TB infection. In sputum smear microscopy, the Tb bacteria are stained with Ziehl-Neelsen stain, but reduced sensitivity and a lack of differentiation between M. tuberculosis and other acid-fast bacilli are key caveats of this method. Sputum culture is highly specific for the diagnosis of TB, in which Lowenstein-Jensen medium is used to culture the TB bacteria. The symptoms of active pulmonary TB may include prolonged cough, low-grade fever, fatigue, loss of appetite, weight loss, and night sweats.[5,7,10]

Currently, there is no vaccine to prevent TB exposure in adults, either before or after exposure. Bacille Calmette-Guérin (BCG) protects infants and children moderately from severe types of TB.[8,12,10]

Current Treatment Regimen for Tuberculosis

The current treatment entails combining four antibiotics that were all discovered almost 60 years ago, which are the first-line treatment drugs: ethambutol (EMB), pyrazinamide (PZA), rifampicin (RIF), and isoniazid (INH). To guarantee high rates of treatment effectiveness and cure, this four-drug combination should be given under directly observed treatment (DOT) for at least six months. There are two stages to the treatment: the first is giving the four medications indicated above for two months, and the second is continuing the treatment with INH and RIF for the final four months to kill the dormant bacteria. These drugs are categorized as the first line of drugs for the treatment of tuberculosis. The second line of drugs for the treatment of M. tuberculosis are Amikacin, Kanamycin, Streptomycin, Cycloserine, and the third line of drugs are Clarithromycin, Linezolid, and Clavulanic acid.[4,12,14,10]

In recent years, the number of cases of individuals affected by tuberculosis has been increasing and is now the leading cause of death worldwide. The drugs that are currently in use for the treatment of tuberculosis have been ineffective or less effective due to the emergence of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. Due to this condition, there is an immediate need for the development of new potent antitubercular drugs with a novel mechanism that can fight against multidrug-resistant, extensively drug-resistant, and totally drug-resistant tuberculosis.[9,13,15]

Pyrrole is a five-membered heterocyclic compound that is aromatic. It is one of the most omnipresent heterocycles due to its association as a subunit of chlorophyll in plant cells and hemin and vitamin B12 in animal cells.[2,3,7]

It is an electron-rich ring, can react with numerous biomolecules and is susceptible to electrophilic attack, hence being an important constituent of many drugs like torvastatin, chlorfenapyr, premazepam, tolmetin, and zomepirac.[2,7,17] Pyrrole and its derivatives have exhibited numerous activities such as anti-tumor, analgesics, anti-inflammatory, anti-allergic, and antitubercular. It is used for corrosion inhibition, polymerization, and preservation in catalytic reactions. Among the many, antibiotics consisting of pyrroles are secluded from biological sources, and their activities are defined.[5,11,13]

Pyrrole and its derivatives have proven to be unquestionably helpful in recent times for suppressing and being effective in inhibiting Mycobacterium tuberculosis and some other mycobacteria.

Considering the aforementioned findings and the widespread applications of pyrrole and its derivatives in the management and prevention of many diseases.

In the quest for biologically more potent antitubercular compounds, we ideated to design, synthesize pyrrole-substituted hydrazide derivatives.

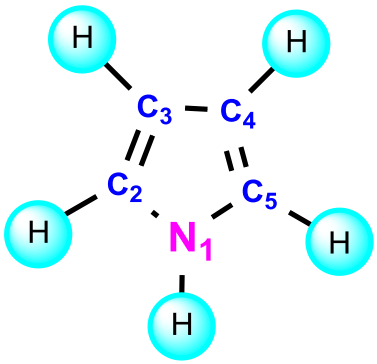
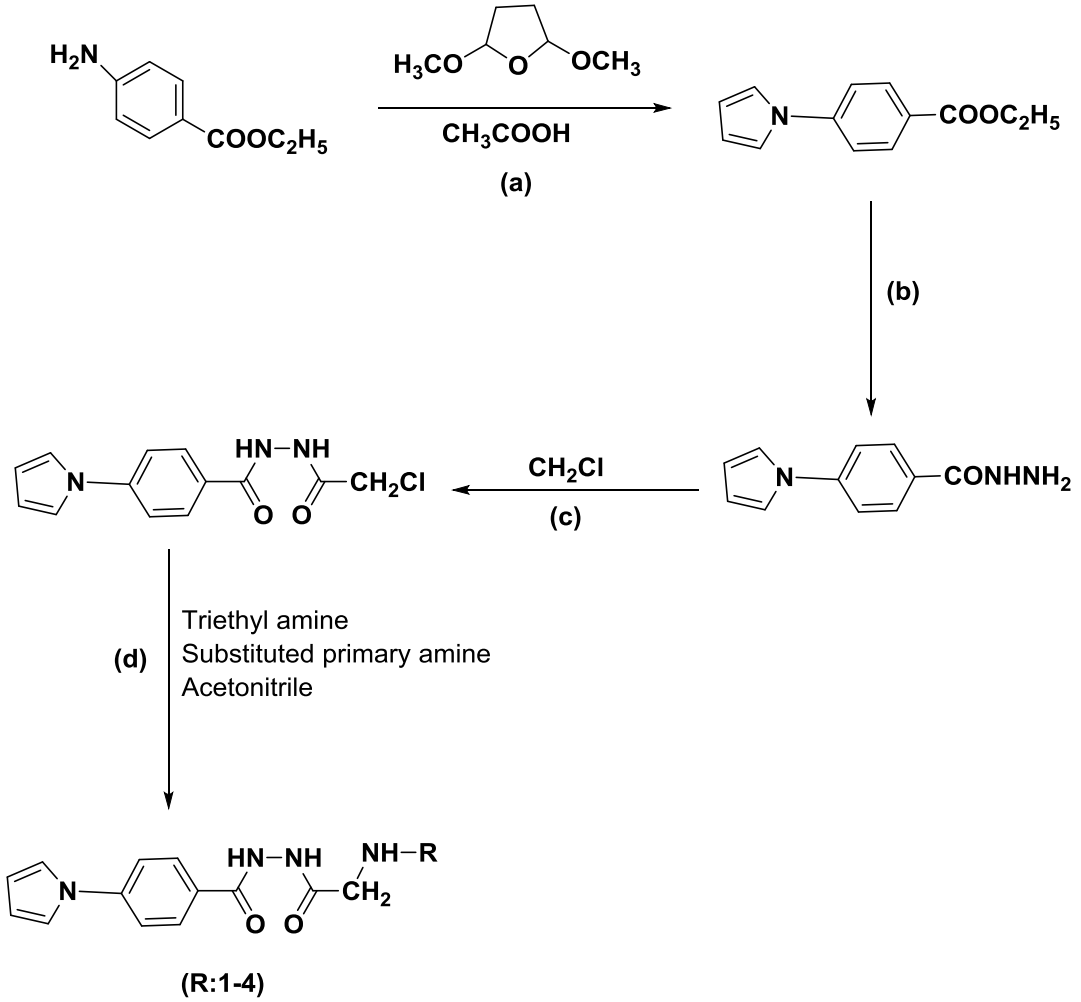


Figure 1: Pyrrole Structure.

Given pyrrole's known efficiency against M. TB and its structural versatility, we focused on developing and synthesizing new pyrrole-substituted hydrazide derivatives to produce powerful antitubercular medicines.

MATERIAL AND METHODS



Scheme: Synthetic pathway of compounds (R: 1- 4)

*Reagents and conditions: **(a)** 2,5-Hexanedione, pure acetic acid, stir for 45 min; **(b)** Hydrazine hydrate, ethanol, stir for 3 hr; **(c)** methylene chloride, chloroacetyl chloride,4hrs; **(d)** acetonitrile, triethylamine, 6hrs;

GENERAL PROCEDURE

Synthesis of ethyl 4-(1H-pyrrol-1-yl)benzoate (a)

For 45 minutes, a solution of 0.05 grams of ethyl 4-aminobenzoate in 7.5 milliliters of dried acetic acid and 0.05 milliliters of 2,5-dimethoxy tetrahydrofuran was refluxed at 150–160 degrees Celsius. After pouring the reaction liquid over crushed ice, the mixture was neutralized using a freshly made sodium bicarbonate solution. The separated solid product was filtered and recrystallized using ethanol.

Synthesis of 4-(1H-pyrrol-1-yl)benzo-hydrazide (b)

A combination of ethyl 4-(1H-pyrrol-1-yl)benzoate (I) (0.014 mol) with hydrazine hydrate (9.3 ml) in absolute ethanol (9.3 ml) was refluxed for 3 hours, and the reaction mixture was cooled. The crystalline substance produced was recrystallized from ethanol.

Synthesis of N´-(3-chloroacetyl)-4-(1H-pyrrole-1-yl)-benzo-hydrazide (c)

To a mixture comprising a solution of hydrazide (6.2 mmol) in dry methylene chloride (25 ml), chloro-acetyl chloride (6.8 mmol) was added and was refluxed for 4 hours. Later, it was filtered, dried, and the resultant solid product was recrystallized from ethanol.

Synthesis of N´-[3-(Substituted phenylamino)chloroacetyl]-4-(1H-pyrrole-1-yl)-benzohydrazide derivatives (R:1-4)

To a mixture of matching chloro derivative (4.2 mmol), the suitable amine (4.2 mmol), and triethylamine (8.4 mmol) in dry acetonitrile was refluxed for 6 hours, and the liquid was cooled, poured over crushed ice, and filtered. The residue was rinsed with cold water and then dried. The acquired crude product was recrystallized from ethanol to generate the named compounds.

IN SILICO STUDIES

Computer-Aided Drug Design (CADD) has emerged as a potent and efficient technique for discovering promising lead compounds and aiding the creation of innovative therapeutic medicines to address a varied array of ailments. The basic purpose of drug design is to discover and anticipate whether a certain molecule will

successfully attach to a chosen biological target and, if so, to evaluate the strength and stability of that association. To achieve this, computational techniques such as molecular mechanics and molecular dynamics simulations are utilized to quantitatively estimate the strength of intermolecular forces and interactions between a small molecule (potential drug candidate) and its biological target, such as a protein or enzyme. In a specific investigation, the three-dimensional structure of the Mycobacterium tuberculosis enoyl-reductase enzyme InhA in association with the inhibitor GSK625 was retrieved from the Protein Data Bank (PDB) under the accession number 5JFO. Molecular docking studies were subsequently conducted to explore the binding interactions using a suite of specialized software tools, including PyRx for virtual screening, Discovery Studio for visualization and analysis, Chem-Draw for chemical structure drawing, and Chem3D for molecular modelling and energy minimization. These integrated computational tools offer a deep knowledge of the molecular interactions crucial for drug development and optimization.

ANTIMYCOBACTERIAL ACTIVITY

The minimum inhibitory concentration (MIC) values for the synthesized compounds were assessed against the Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA), with isoniazid and rifampicin acting as reference medicines. Each well of a 96-well plate was filled with 100 µl of Middlebrook 7H9 broth, and serial dilutions of the test compounds were made directly in the plate, providing concentrations of 0.2, 0.4, 0.8, 1.6, 3.125, 6.25, 12.5, 25, 50, and 100 µg/ml. The plates were then sealed with parafilm, covered, and incubated at 37°C for 5 days. Following incubation, 25 µl of a freshly made 1:1 combination of Alamar Blue reagent and 10% Tween 80 was added to each well, and the plates were incubated for an additional 24 hours. A blue hue in a well showed no bacterial development, whereas a pink colour signified bacterial growth. The MIC was calculated as the lowest concentration of the molecule that retained the blue hue, preventing the transition to pink.

RESULTS AND DISCUSSION

N´-(3-chloroacetyl)-4-(1H-pyrrole-1-yl)-benzohydrazide (C)

Whitish yellow solid, M.P: 165-167 ^{0}C; Yield (%): 93%; Rf: 0.85; Mobile phase: Pet. Ether: Ethyl acetate (6:4)
Molecular formula: $C_{13}H_{12}ClN_3O_2$; Molecular weight: 277.71g/mol FT-IR (KBr, cm^{-1}): 3228.76 (-NH stretching); 3017(C-H stretching); 1682.95(C=O stretching; 1641.52(C=C stretching); 1511(NO_2 stretching).

^{1}H-NMR (500MHz, $CDCl_3$, δ ppm):10.54(s,1H,1NH), 10.38(s,1H,NH),7.97(d,2H,Ar-CH), 7.74(d,2H,Ar-CH), 7.50(t,2H,Ar-CH), 6.31(m,2H,Ar-CH), 4.20(d,1H,CH).

N'-(((5-nitropyridin-2-yl)amino)glycyl)-4-(1H-pyrrol-1-yl)benzohydrazide [R-1]

Crystaline yellowish solid, M.P: 143-145 ^{0}C; Yield (%): 93%; Rf: 0.81; Mobile phase: Pet. Ether: Ethyl acetate (7:3)
Molecular formula: $C_{18}H_{17}N_7O_4$; Molecular weight: 395.38g/mol FT-IR (KBr, cm^{-1}): 3488.77(-NH stretching); 3031(C-H stretching); 2854 (C-H stretching); 1638.67(C=O stretching) ^{1}H NMR (DMSO) 500 MHz (δ ppm): 11.04(d,1H,NH), 8.84(m,1H,Ar-CH), 8.13(m,1H,Ar-CH), 7.96(d,1H,Ar-CH), 7.82(m,1H,Ar-CH), 6.52(m,1H,Ar-CH), 6.3154 ^{13}C NMR (DMSO) 500 MHz (δ ppm): 146.7(1C,Pyridine), 134.36(3C,Pyridine),107.29(4C,Pyridine),163.05(5C,Pyridine),167.11(7C,C=O),163.05(8C,C=O),129.13(9C,Benzene),127.45(10C,Benzene),130.54(11C,Benzene),110.9(13C,Pyrrole),110.9(14C,Pyrrole),130.54(17C,Benzene), 127.45(18C,Benzene)

N'-(((3-hydroxypyridin-2-yl)amino)glycyl)-4-(1H-pyrrol-1-yl)benzohydrazide [R-2]

Crystaline yellowish solid, M.P: 155-157 ^{0}C; Yield (%): 93%; Rf: 0.79; Mobile phase: Pet. Ether: Ethyl acetate (7:3).
Molecular formula: $C_{18}H_{18}N_6O_3$; Molecular weight: 366.38g/mol FT-IR (KBr, cm^{-1}): 3360.19(-NH stretching); 2853.03(C-H stretching); 1637.24(C=O stretching); 1604.38(C=C stretching) ^{1}H NMR (DMSO) 500 MHz (δ ppm): 9.79(s,1H,OH), 7.91(m,2H,Ar-CH), 7.67(m,2H,Ar-CH), 7.48(m,2H,Ar-CH), 6.31(m,3H,CH), 4.53(m,2H,NH).

N'-(((6-chloropyridin-3-yl)amino)glycyl)-4-(1H-pyrrol-1-yl)benzohydrazide [R-3]

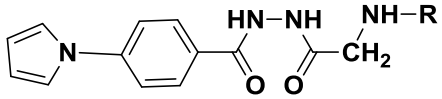
Crystaline yellowish solid, M.P: 128-130 ^{0}C; Yield (%): 93%; Rf: 0.91; Mobile phase: Pet. Ether: Ethyl acetate (7:3)
Molecular formula: $C_{18}H_{17}ClN_6O_2$; Molecular weight: 384.82g/mol FT-IR (KBr, cm^{-1}): 3225.90 (-NH stretching); 2923.03 (O-H stretching); 1637.24 (C=O stretching); 1604.38 (C=C stretching); 1505.80 (NO_2 stretching). ^{1}H NMR (DMSO) 500 MHz (δ ppm): 9.80(s,1H,NH),7.9(m,2H,Ar-CH), 7.70(m,2H,CH),7.48(m,2H,Ar-CH), 6.30(m,3H,CH).

N'-((pyridin-3-ylamino)glycyl)-4-(1H-pyrrol-1-yl)benzohydrazide [R-4]

Crystaline yellowish solid, M.P: 106-108 ^{0}C; Yield (%): 93%; Rf: 0.82; Mobile phase: Pet. Ether: Ethyl acetate (7:3)
Molecular formula: $C_{18}H_{18}N_6O_2$; Molecular weight: 350.38g/mol FT-IR (KBr, cm^{-1}): 3225.90 (-NH stretching); 3215.90 (-NH stretching); 2918.74 (-CH stretching); 1605.81 (C=C stretching) ^{1}H NMR (DMSO) 500 MHz (δ ppm): 11.04(s,1H,NH),8.01(d,3H,Ar-CH), 7.91(m,2H,Ar-CH),7.83(m,2H,Ar-CH),7.76(m,3H,Ar-CH),7.71(m,5H,CH).

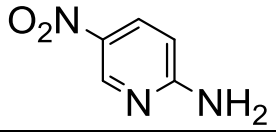
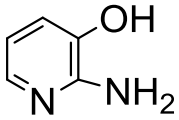
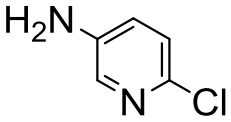
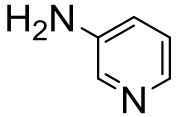
Antimycobacterial activity

The synthesized compounds **R-1, R-2, R-3,** and **R-4** were screened for their antitubercular activity by the MABA method against M. Tuberculosis $H_{37}Rv$ strain using Isonazid and Rifampicin as standard or reference drugs.



(R:1-4)

Table 1: Antimycobacterial activity of the compounds (R:1-4).

Code	Compound	MIC values in µg/ml
R-1		62.5
R-2		31.25
R-3		31.25
R-4		62.5
5	Rifampicin	0.98
6	Isoniazid	1.95

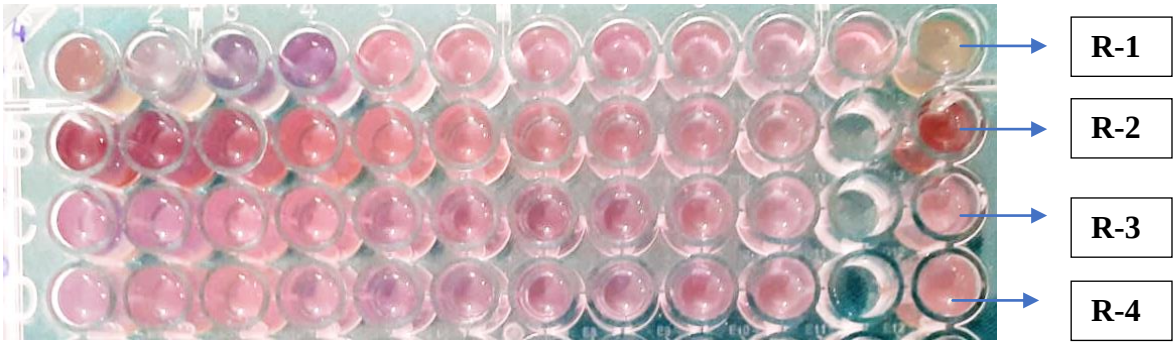


Figure 2: In vitro activity of the synthesized compounds.

In silico studies

The crystal structure of M. tb enoyl-reductase InhA was downloaded from the Protein Data Bank (PDB ID: 5JFO).

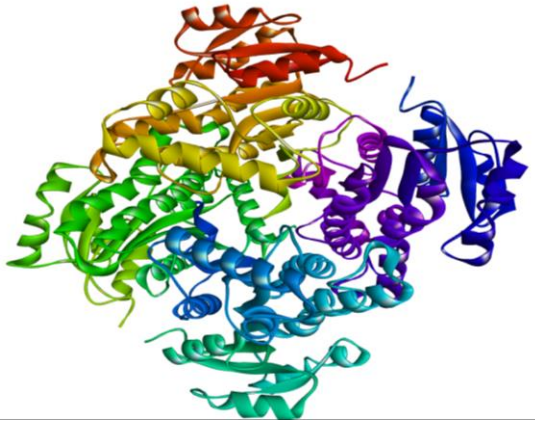


Figure 3: 3D Protein structure of 5JFO.

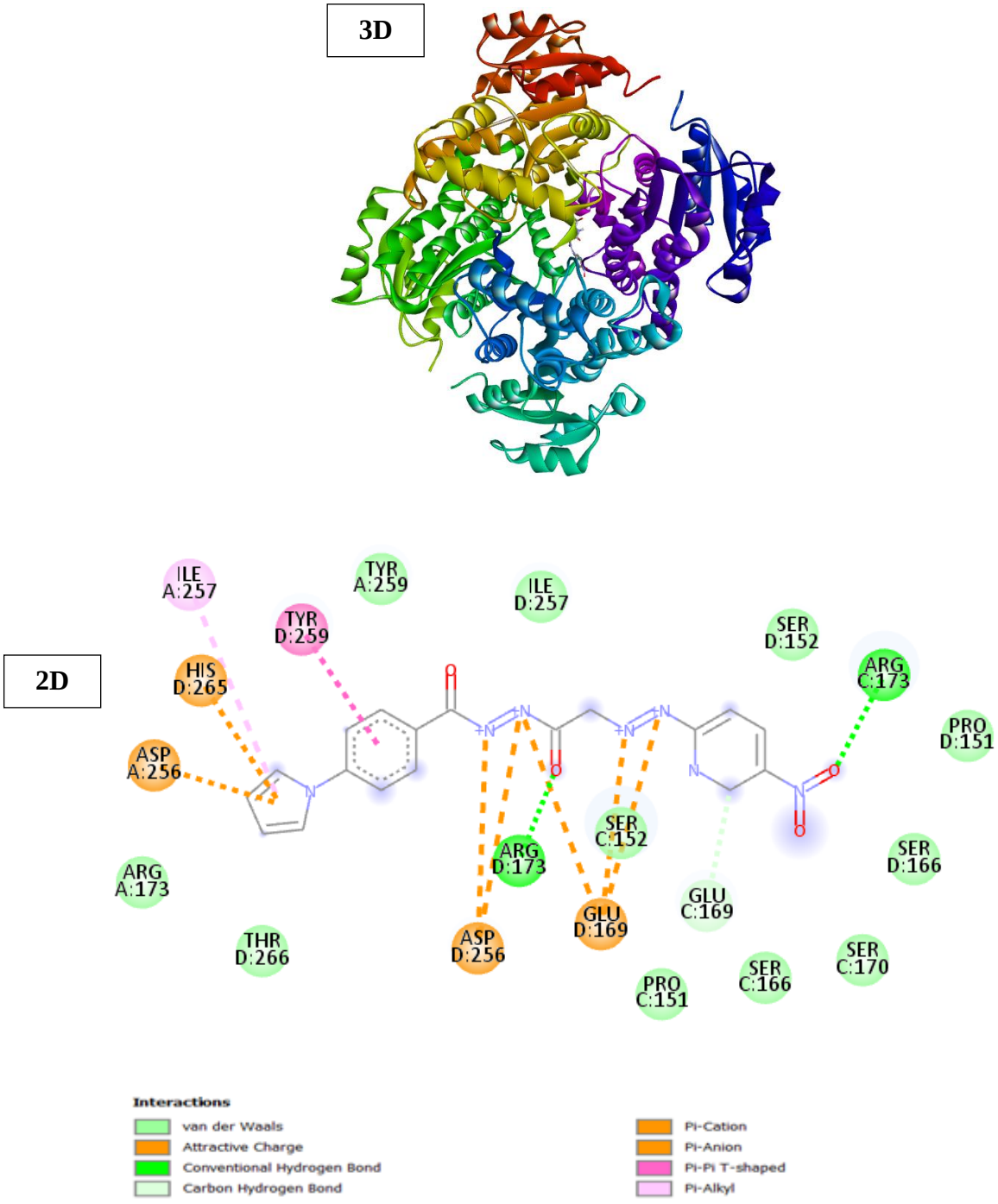


Figure 4: 3D and 2D [R-1] docked with protein 5JFO.

Table 2: Binding affinity of compound [R-1] docked with 5JFO.

5JFO with 4A	Binding affinity	RMSD/UB	RMSD/LB
1	-8.2	0	0
2	-8.1	11.02	8.778
3	-8.1	5.856	4.023
4	-7.9	10.999	6.103
5	-7.9	8.544	5.283
6	-7.8	8.419	4.908
7	-7.8	13.162	9.636
8	-7.6	9.856	6.05
9	-7.6	6.995	5.371

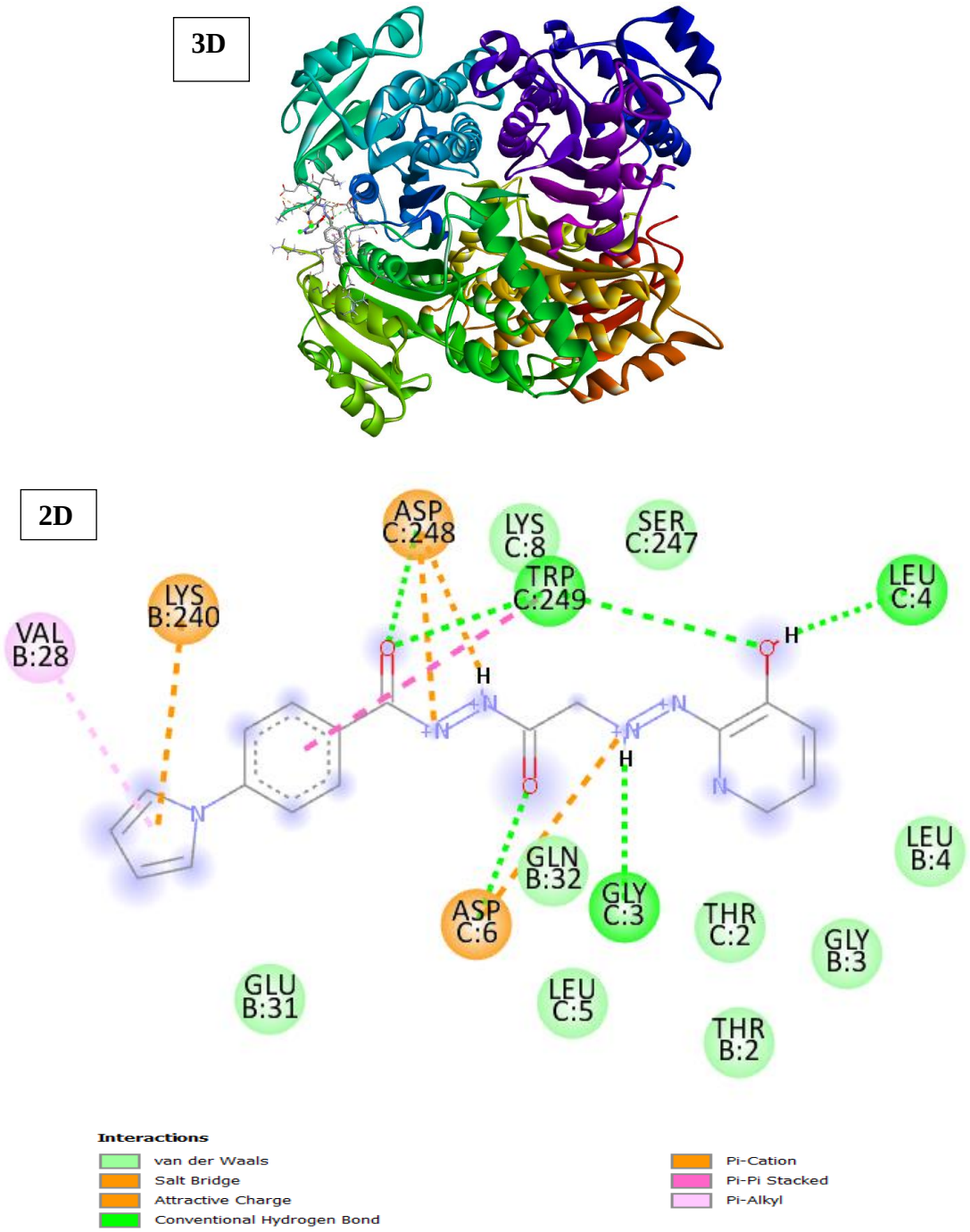


Figure 5: 3D and 2d structure [R-2] docked with the protein 5JFO

Table 3: Binding affinity of compound [R-2] docked with 5JFO.

5JFO with 4B	Binding affinity	RMSD/UB	RMSD/LB
1	-7.6	0	0
2	-7.2	29.015	26.863
3	-6.9	32.758	30.509
4	-6.8	48.174	46.454
5	-6.8	32.775	31.134
6	-6.7	47.206	45.828
7	-6.2	47.6.3	46.112
8	-6.2	20.687	17.835
9	-6.2	48.931	47.149

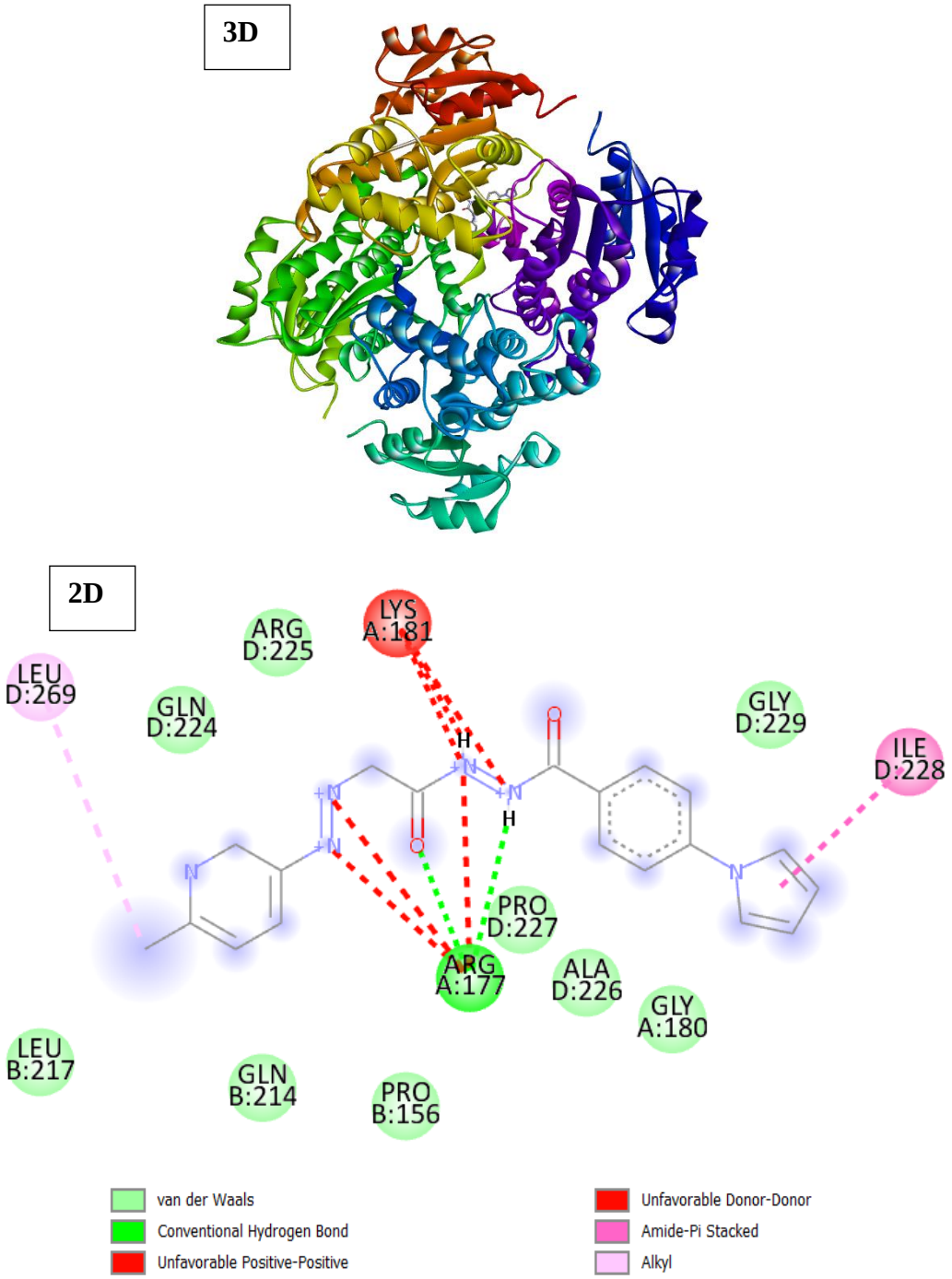


Figure 6: 3D and 2D structure of [R-3] docked with 5JFO protein.

Table 4: Binding affinity of compound [R-3] docked with 5JFO.

5JFO with 4C	Binding affinity	RMSD/UB	RMSD/LB
1	-6.5	0	0
2	-6.3	31.283	27.217
3	-6.2	11.726	10.037
4	-6.1	36.907	34.248
5	-6.1	50.74	47.259
6	5.9	45.698	43.183
7	5.7	33.531	31.932
8	-5.6	44.886	42.951
9	-5.6	50.973	48.804

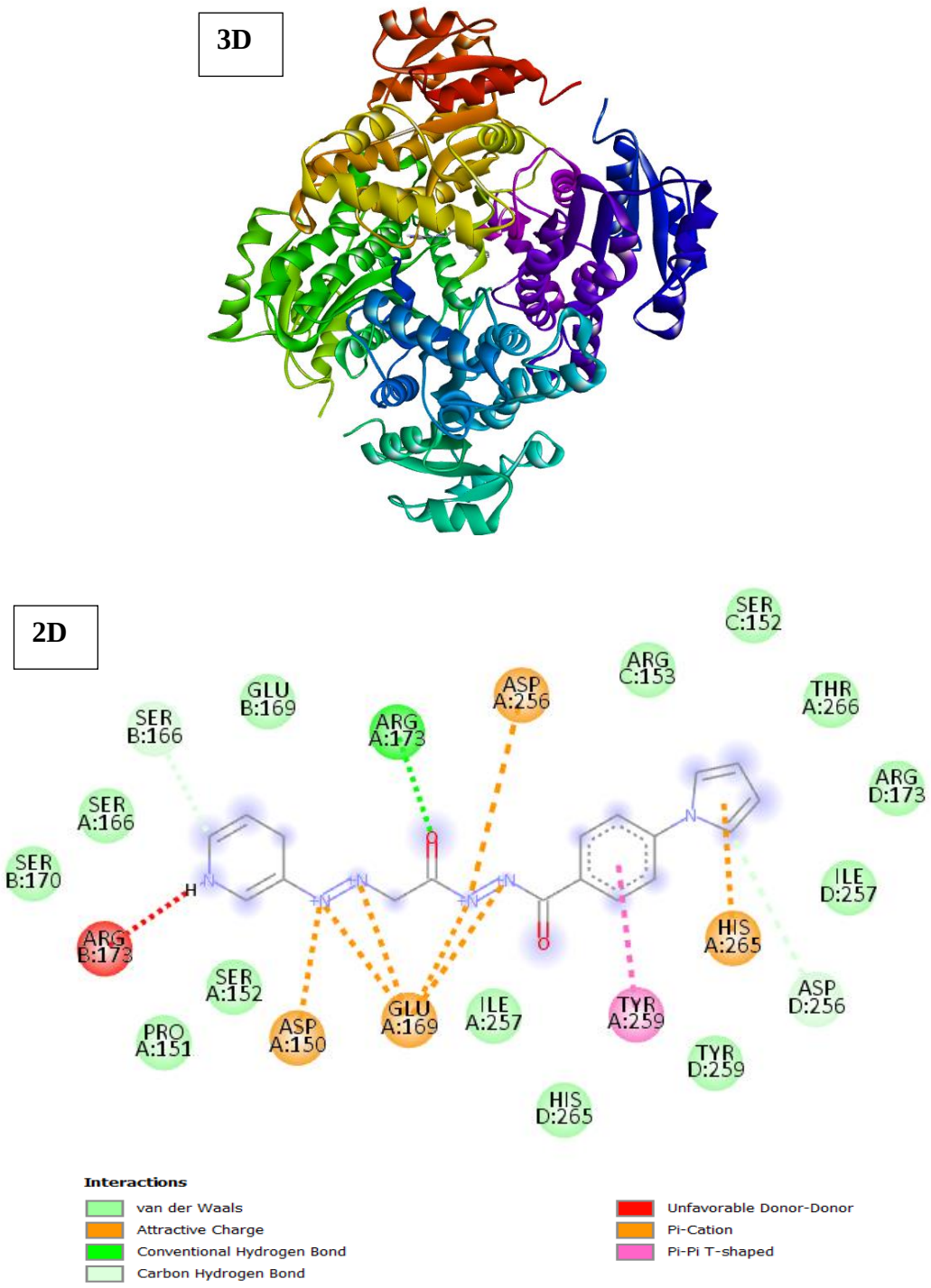


Figure 7:3D and 2D structure of [R-4] docked with the protein 5JFO.

Table 5: Binding affinity of compound R-4 docked with 5JFO.

5JFO with 4D	Binding affinity	RMSD/UB	RMSD/LB
1	-7.8	0	0
2	-7.5	9.793	8.6
3	-7.4	7.162	6.17
4	-7.4	8.227	7.272
5	-7.3	11.617	7.996
6	-7.3	7.015	5.656
7	-7.3	11.849	7.431
8	-7	9.53	7.721
9	-7	25.788	24.018

The binding affinities of drugs R-1, R-2, R-3 and R-4 when docked with the protein were estimated and were found to be satisfying in all four compounds. The drugs R-1, R-2, R-3, and R-4 exhibited greater affinities with values -8.2, -7.8,-6.5, and -7.6.

Table 6: Binding affinity of compounds R-1, R-2, R-3, and R-4 when docked with 5JFO.

Compounds	Binding affinity	RMSD/UB	RMSD/LB
R-1	-8.2	0	0
R-2	-7.6	0	0
R-3	-6.5	0	0
R-4	-7.8	0	0

DISCUSSION

By the reaction of ethyl-4-aminobenzoate and 2,5-dimethoxy tetrahydrofuran in dried acetic acid, compound **(a)** was synthesized. The synthesized compound **(a)** was then reacted with hydrazine hydrate in absolute ethanol to obtain compound **(b)**. Compound **(b)** was reacted with chloroacetyl chloride in dry methylene chloride to give compound **(c)**, and the obtained compound **(c)** was further reacted with substituted primary amines with triethylamine in dry acetonitrile to give compounds **R-1, R-2, R-3,** and **R-4.** The synthesized compounds were subjected to spectral characterization through FT-IR, ^{1}H, and ^{13}C NMR.

In the IR spectra of compounds **R:1-4** broad stretching at around 3200-3500 cm $^{-1}$ were due to NH while strong stretching band at around 2800-3200 cm $^{-1}$ were due to C-H and strong stretching band at around 1638.67 cm $^{-1}$ was due to C=O and strong stretching band at around 1605.38 cm $^{-1}$ was due to C=C.

^{1}H NMR spectrum showed a singlet around δ 7.70 (NH-Pyrrole), around δ 8.2 (Benzene), around δ 11.04 (NH) δ 4.3(NH).

^{13}C NMR spectrum data of R-1 146.7(1C,Pyridine), 134.36(3C,Pyridine), 107.29(4C,Pyridine), 163.05(5C,Pyridine), 167.11(7C,C=O), 163.05(8C,C=O), 129.13(9C,Benzene), 127.45(10C,Benzene), 130.54(11C,Benzene), 110.9(13C,Pyrrole), 110.9(14C,Pyrrole),130.54(17C,Benzene), 127.45(18C,Benzene).

Antimycobacterial activity of the synthesized compounds was carried out by using the $H_{37}R_v$ strain by the MABA method. Compounds **R-2** and **R-3** exhibited good antimycobacterial activity with an MIC value of 31.25 µg/ml, and compounds **R-1** and **R-2** exhibited moderate antimycobacterial activity, 62.5 µg/ml against standard isoniazid and rifampicin.

In-silico studies of the synthesized compounds was carried out using Discovery Studio, PyRx, Chem Draw and Chem Draw 3D.The binding affinities of compounds **R-1, R-2, R-3,** and **R-4** were found to be -8.2,-7.6,-6.5 and -7.8 respectively.

CONCLUSION

A novel series of pyrrole derivatives were synthesized by the reaction between N´-[3-(substituted phenylamino)chloroacetyl]-4-(1-H-pyrrol-1-yl)-benzohydrazide and substituted primary amines in the presence of triethylamine and acetonitrile and the these synthesized compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR. The synthesized compounds were further screened for its antimycobacterial activity against bacteria *Mycobacterium tuberculosis* H_{37} R_V strain by MABA method using isoniazid and rifampicin as reference drugs. The compounds **R-2** and **R-3** exhibited good anti-TB activity with an MIC value of 31.25 µg/ml and compounds **R-1** and **R-4** exhibited moderate anti-TB activity with an MIC value of 62.5 µg/ml. *In silico* studies was carried out using the software Discovery Studio and PyRx and the docking studies revealed that compounds **R-1, R-2, R-3,** and **R-4** binds with binding affinities -8.2,-7.6,-6.5 and -7.8 respectively to the protein 5JFO.Hence, we conclude that this study will help and guide for further development and designing and synthesizing more effective pyrrole derivatives for the treatment of Tuberculosis.

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