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MOLECULAR DOCKING STUDIES OF SOME NOVEL *N'*-ARYLSUBSTITUTED PYRROLE ANALOGS

Shrinivas D. Joshi^{*} S. R. Prem Kumar, and Venkatrao H. Kulkarni

Novel Drug Design and Discovery Laboratory, Department of Pharmaceutical Chemistry, S. E. T's College of Pharmacy, Sangolli Rayanna Nagar, Dharwad 580 002, Karnataka, India.

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ABSTRACT

In present work, Surflex docking has been carried out on a series (23 compounds bearing *N'*-arylsubstituted pyrrole heterocyclic molecules) of *M. tuberculosis* inhibitors. SYBYL-X 2.0 package (Tripos Inc., St. Louis, USA) was used for the study. Surflex-docking shown that the peptide connection between the aryl substitution and pyrroly moiety was significant to exhibit receptor and molecular interactions, and it was also found that the pattern of binding of established compounds is same as that of the ligand 1-cyclohexyl-*N*-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide, which gives an idea in understanding the specific activity of compounds towards the receptor.

Corresponding author

Dr. Shrinivas D. Joshi

Novel Drug Design and Discovery Laboratory,

Department of Pharmaceutical Chemistry, Soniya Education Trust's College of Pharmacy,

Sangolli Rayanna Nagar, Dharwad 580 002, India

shrinivasdj@rediffmail.com.

Tel.: +91 9986151953; Fax: +91 836 2467190

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INTRODUCTION

Pyrrole derivatives play an important in medicine fields. In particular, they are used as antibacterial, antifungal, antiproliferative, antiviral and antitubercular agents^[1-4]. Besides, pyrroles also played a major role in the development of heterocyclic compounds, and they are also used comprehensively in organic synthesis^[5]. Pyrrole which is an important heterocycle in plant and animal kingdom since its participation as a subunit of chlorophyll in plant cells and heme and vitamin B₁₂ in animal cells. Joshi and co-workers have reported some pyrrole derivatives and which have shown significant antimycobacterial activities^[6,7]. Literature shows that pyrrole ring and peptide linkage is the major medicinal key player in inhibition *M. tuberculosis* growth.

The docking study reveals structural features required for binding of ligand with amino acid residues and the co-factor present in the active site of the enzyme. Among the important class of pharmacophores responsible for antitubercular and antibacterial activity, pyrrole analogues are considered to be the worthwhile lead structures for the design and synthesis of more active and broad spectrum antitubercular agents. In our former reports, we have described synthesis and docking studies of different heterocyclic compounds^[8-10]. In continuation of these studies, here we report docking studies on pyrrole heterocyclic products as antitubercular agents.

The compounds^[11-12] selected for molecular modeling studies (Table 1) and 4TZK have carboxamide moiety in common, which recommended that *M. tuberculosis* enoyl ACP reductase (InhA) complexed with 1-cyclohexyl-*N*-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide enzyme could be the discerning target for the current study. Hence, the reported crystal structure of the *Mycobacterium tuberculosis* (*M. tuberculosis*) PDB code 4TZK was used.

EXPERIMENTAL

Molecular Modeling

Molecular modeling was done using Sybyl-X, version 2.0^[13], Surflex-Dock algorithm of sybyl was used for docking of compounds. The crystal structure of *M. tuberculosis* enoyl ACP reductase (InhA) complexed with 1-cyclohexyl-*N*-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide were downloaded from the Protein Data Bank (PDB entry code 4TZK, PDB extracted from the Brookhaven Protein Database <http://www.rcsb.org/pdb>) and used for initial docking studies. Co-crystallized ligand and water molecules were removed from the structure, H-atoms were added and side chains were fixed during protein preparation. The structure was then subjected to an energy refinement procedure. Gasteigere-Huckel charge^[14] were then calculated for the ligand, while Amber 7FF02 was used for the protein. The prototype was then subjected to energy minimization following the gradient termination of the Powell method for 3000 iterations using Tripose force field with non-bonding cutoff set at 9.0 and the dielectric constant set at 4.0. The binding of the pyrrole derivatives was also estimated using a variety of scoring functions that have been compiled into the single consensus score (CScore). The CScore module (Total Score) available in Sybyl includes the G_Score, PMF_Score, D_Score and ChemScore scoring functions.

Molecular Docking studies

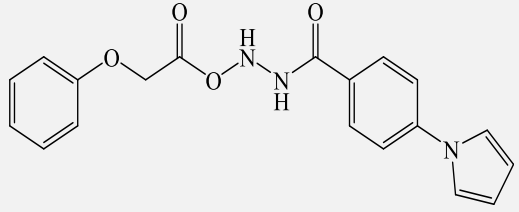
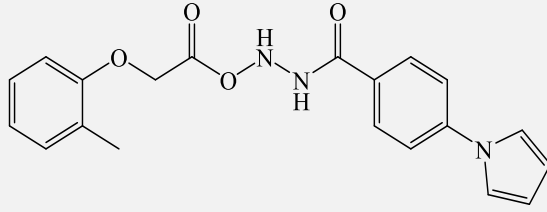
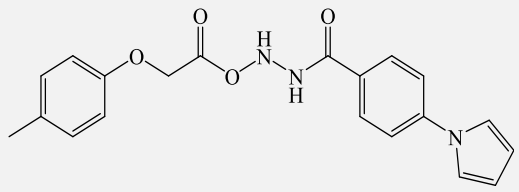
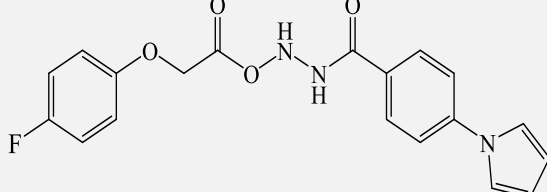
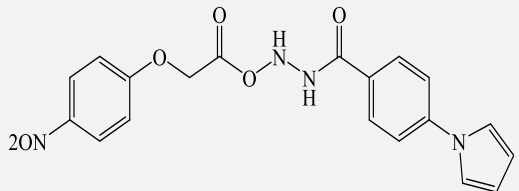
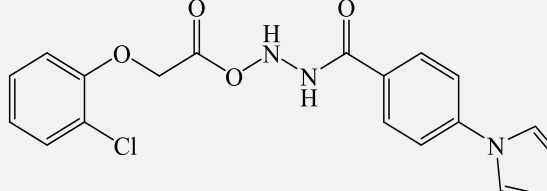
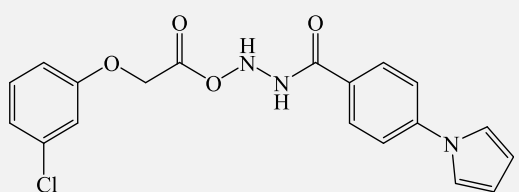
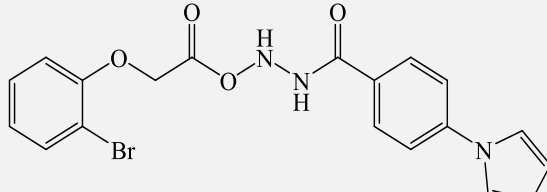
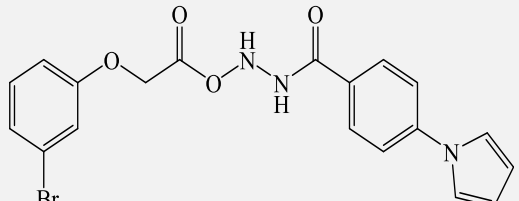
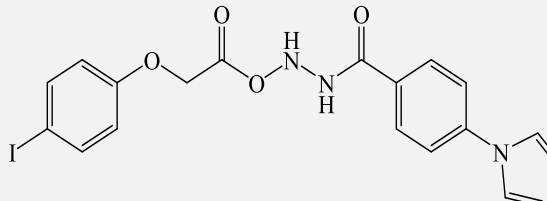
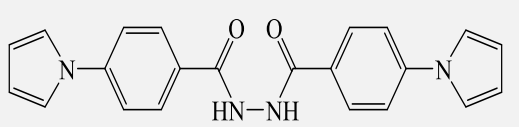
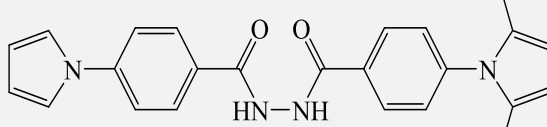
To investigate the comprehensive intermolecular interactions between the ligand and the target protein, a program Surflex-Dock was used. Three-dimensional structure information on the target protein was taken from the PDB entry 4TZK. Processing of the protein included the deletion of the ligand and the solvent molecules as well as the addition of hydrogen atoms. All the 23 inhibitors were docked into the active site of enzyme as shown in figures 1A and 1B. The predicted binding energies of the compounds are listed in Table 2. As depicted in the figures 3A, 3B and 3C, compound 4 showed five hydrogen bonding interactions at the active site of the enzyme, two hydrogen bonding interactions were raised from the carbonyl group of amide with hydrogen atom of amino acid residue TYR158 (C=O ----- H-TYR158, 1.90 Å) and hydrogen atom of NAD⁺ (C=O ----- H- NAD⁺, 1.84 Å), another two interactions raised from the interactions of the hydrogen atom of NH group of amide linkage with oxygen atom of amino acid residue TYR158 and nitrogen atom of NH group of amide linkage with hydrogen atom of amino acid residue TYR158 (NH ----- O-TYR158, 2.66 Å, N-----H-TYR158, 2.80 Å) and phenyl fluorine showed the interaction with hydrogen atom of glycine (F-----H-GLY104, 2.48 Å). Further, as depicted in figures 4A, 4B and 4C, compound 8 showed four hydrogen bonding interactions at the active site of the enzyme, oxygen atom of carbonyl group of amide makes a hydrogen bonding interaction with hydrogen atom of amino acid residue TYR158 (C=O ----- H-TYR158, 1.90 Å) and hydrogen atom of NAD⁺ (C=O ----- H- NAD⁺, 1.84 Å), also another two interactions raised from the interactions of the hydrogen atom of NH group of amide linkage with oxygen atom of amino acid residue TYR158 and nitrogen atom of NH group of amide linkage with hydrogen atom of amino acid residue TYR158 (NH ----- O-TYR158, 2.57 Å, N-----H-TYR158, 2.76 Å). Complex (ligand-protein), and internal (ligand-ligand) energies are similar as that of ligand 4TZK, which has been depicted in figures 2A, 2B and 2C. Helmholtz free energies of interactions for protein-ligand atom pairs for all compounds showed similar to that of ligand. Scoring of compounds with respect to the reward for hydrogen bonding, lipophilic contact, and rotational entropy, along with an intercept terms revealed that compounds has similar interactions with the protein as that of ligand.

All the compounds showed consensus score in the range 7.29-2.01, indicating the summary of all forces of interaction between ligands and the enzyme. Charge and van der Waals interactions between protein and ligands varied from -96.72 to -175.61. The Helmholtz free energies of interactions for protein ligands atom pairs range between -23.95 and -75.62. However, its H-bonding, complex (ligand-protein), and internal (ligand-ligand) energies range from -157.17 to -306.67. These scores show that molecules preferentially bind to the enzyme in contrast to the reference 4TZK ligand (Table 2), on the other hand amino acids ALA176, ALA179, ALA198, ALA201, GLY96, GLY104, GLY202, GLY205, GLY255, LEU168, ILE95, ILE202, and ASN231, ASN234, ASN255, ASP223, GLU219, LYS118, TYR113, TYR158 played hydrophobic and hydrophilic interactions that are essential for inhibiting the enoyl ACP reductase enzyme (figures 5 and 6).

The docking results provided detailed structurally important binding features between pyrrole derivatives and the enzyme. Based on the docking score, it may be concluded that the compounds showed good interaction with the enzyme active site compared to the ligand 1-cyclohexyl-*N*-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide.

The Lipinski's 'rule of 5' was calculated for all the **23** compounds. The poor absorption or permeation is most likely when, there are more than 5 H bond donors, the molecular weight is above 500, the cLogP is above 5 and there are more than 10 H-bond acceptors^[15]. We have calculated theoretical cLogP, molecular weight (MW) and number of hydrogen bond donors and acceptors using sybyl-X.2.0. Observing the results in Table 3 it can be said that compounds **1-23** mollified the physicochemical parameters assortment established by the Lipinski's rule. Analysis of the docking study provided details on the fine relationship connecting structure and activity, and offer proofs for structural modifications that can improve the activity. If all these compounds are synthetically modified, then a potent *M. tuberculosis* inhibitor can be generated with effective antitubercular activity.

TABLE 1: Structures and inhibitory activity of novel pyrrole derivatives (1-23) used for docking study.

Comp.	Structure	MIC	Comp.	Structure	MIC
1		3.12	2		25
3		12.5	4		3.12
5		6.25	6		3.12
7		3.12	8		3.12
9		3.12	10		6.25
11		12.5	12		6.25

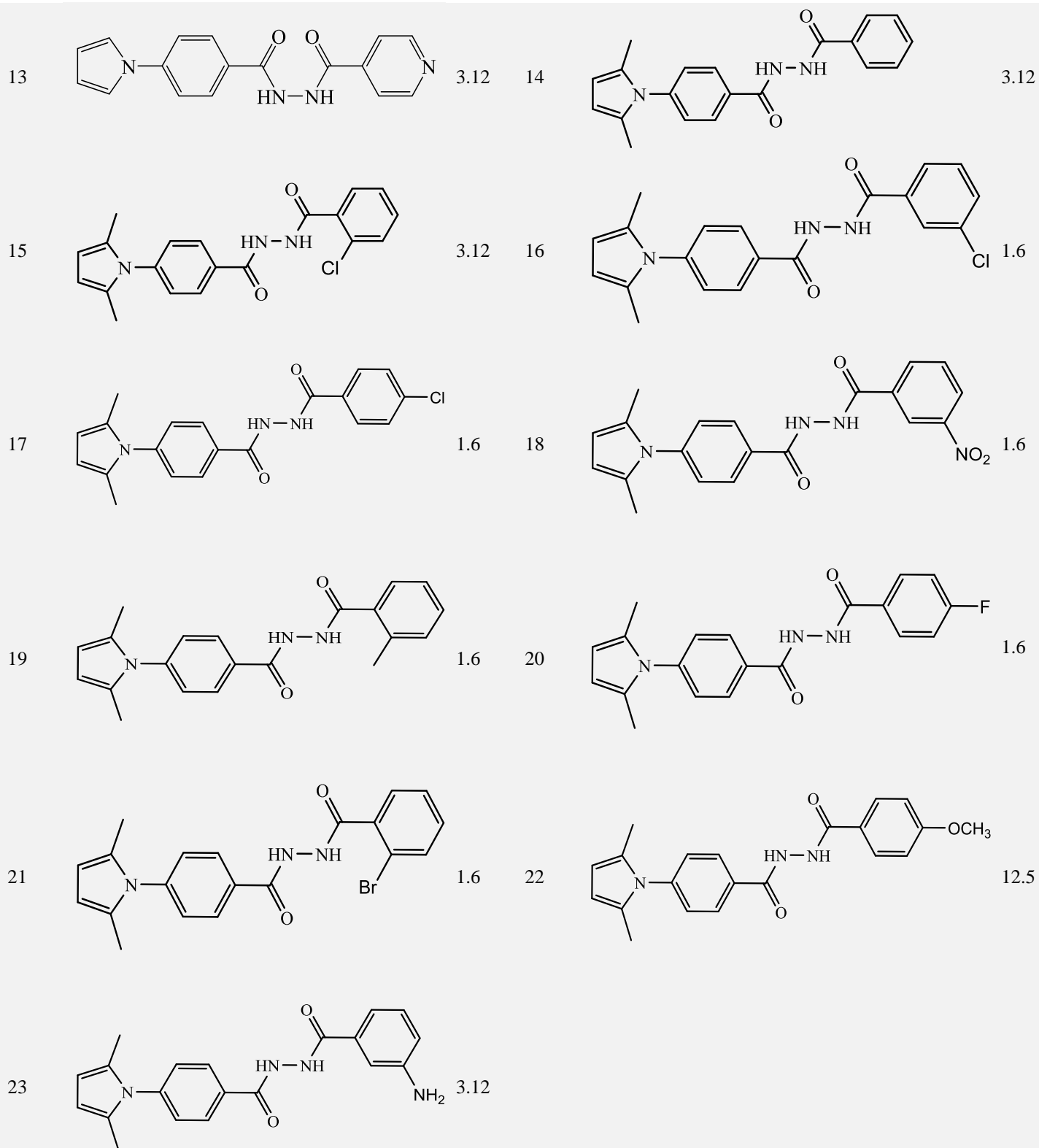


Table 2. Surflex Docking score (kcal/mol) of the pyrrole derivatives.

Compounds	C Score ^a	Crash Score ^b	Polar Score ^c	D Score ^d	PMF Score ^e	G Score ^f	Chem Score ^g
4TZK	8.73	-1.39	1.18	-168.11	-49.19	-285.29	-37.47
1	7.29	-4.20	1.64	-132.90	-64.50	-251.46	-33.24
2	6.09	-1.16	1.24	-128.34	-72.41	-202.48	-36.98
3	6.91	-2.03	0.44	-175.61	-23.95	-336.72	-36.38
4	7.97	-1.38	1.61	-138.17	-59.30	-252.07	-31.86
5	7.54	-1.49	1.59	-149.51	-75.62	-282.13	-31.88
6	7.65	-1.63	1.82	-139.86	-55.80	-270.82	-34.36
7	7.31	-1.41	1.63	-146.63	-65.55	-270.54	-35.44
8	7.98	-1.46	1.59	-145.45	-63.35	-268.86	-34.71
9	7.10	-2.08	1.68	-149.30	-68.65	-276.77	-35.12
10	7.34	-1.67	1.41	-157.90	-68.05	-298.79	-34.87
11	6.47	-2.98	2.02	-155.91	-58.52	-275.56	-44.70
12	2.01	-6.38	0.06	-164.76	-37.65	-306.67	-42.70
13	4.95	-1.37	1.67	-115.27	-57.28	-209.92	-34.94
14	5.65	-0.91	2.08	-109.54	-66.38	-188.16	-32.64
15	4.83	-1.29	1.98	-116.52	-62.66	-199.99	-34.53
16	4.77	-1.94	0.07	-131.64	-64.64	-263.34	-33.50
17	5.07	-1.04	1.33	-119.38	-66.90	-206.25	-34.78
18	6.10	-2.02	1.15	-126.57	-62.82	-240.04	-33.93
19	5.71	-1.99	0.00	-127.97	-47.50	-267.16	-31.14
20	4.74	-0.96	2.04	-106.40	-73.12	-166.57	-32.16
21	3.08	-1.25	1.76	-96.72	-35.02	-157.17	-28.83
22	6.74	-1.65	1.86	-126.57	-56.18	-233.02	-37.63
23	6.32	-1.68	1.56	-118.81	-66.00	-237.83	-35.82

^a CScore (Consensus Score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score.

^b Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favourable. Negative numbers indicate penetration.

^c Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds.

^d D-score for charge and van der Waals interactions between the protein and the ligand.

^e PMF-score indicating the Helmholtz free energies of interactions for protein-ligand atom pairs (Potential of Mean Force, PMF).

^f G-score showing hydrogen bonding, complex (ligand-protein), and internal (ligand-ligand) energies.

^g Chem-score points for H-bonding, lipophilic contact, and rotational entropy, along with an intercept term.

Table 3. QSAR parameters: cLogP, molecular weight (MW), number of H bond donors and H bond acceptors value for compounds 1-23.

Compounds	cLOG P	Acceptor	Donor	Lipinski_Viol	MW
1	3.69	7	2	0	351.35
2	4.19	7	2	0	365.38
3	4.19	7	2	0	365.38
4	3.97	7	2	0	369.34
5	0.40	10	2	0	396.35
6	4.31	7	2	0	385.80
7	4.54	7	2	0	385.80
8	4.46	7	2	0	430.25
9	4.69	7	2	0	430.25
10	4.95	7	2	0	477.25
11	4.90	6	2	0	370.40
12	5.90	6	2	1	398.45
13	2.71	6	2	0	306.31
14	4.65	5	2	0	333.38
15	4.61	5	2	0	367.82
16	5.44	5	2	1	367.82
17	5.44	5	2	1	367.82
18	1.36	8	2	0	378.38
19	4.81	5	2	0	347.10
20	4.87	5	2	0	351.37
21	4.67	5	2	0	412.28
22	4.73	5	2	0	363.41
23	3.70	6	3	0	348.39

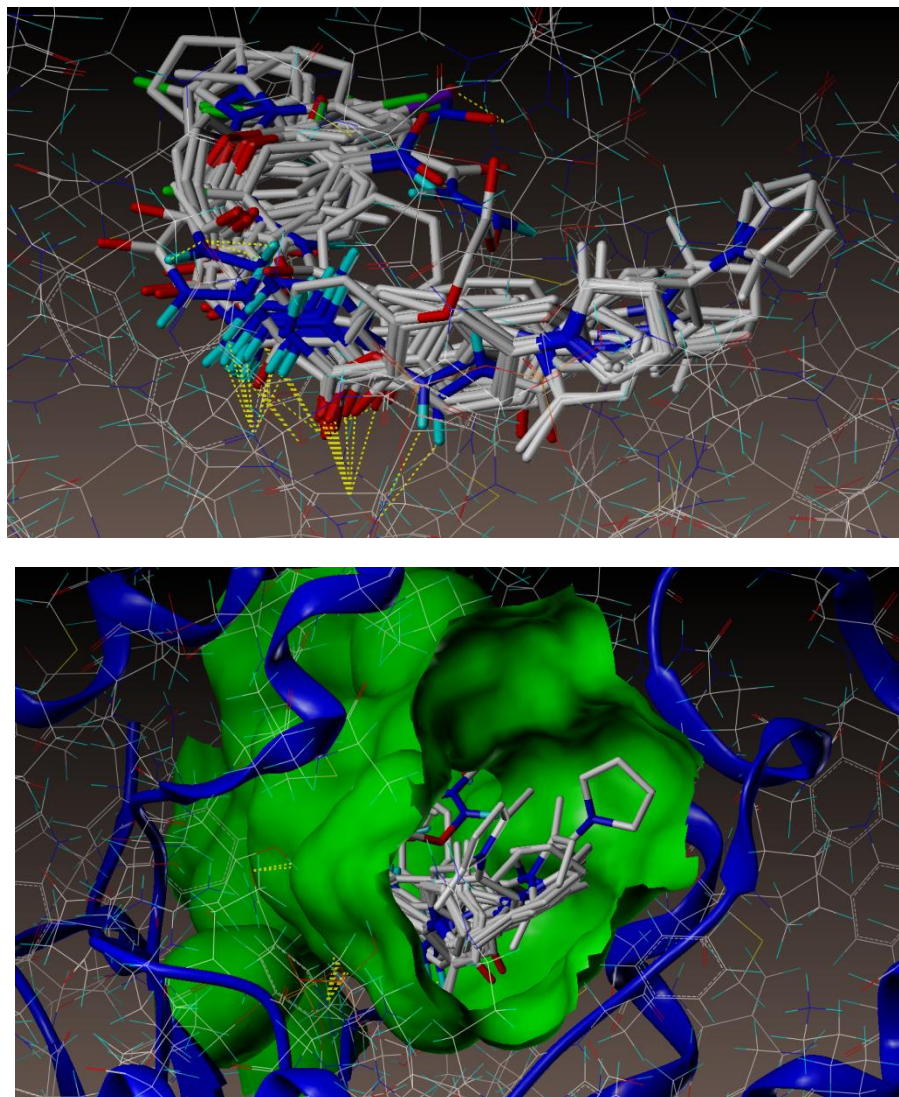


Figure 1. A) Docked mode of all 23 compounds, B) inside the proposed binding pocket of InhA (PDB ID: 4TZK).

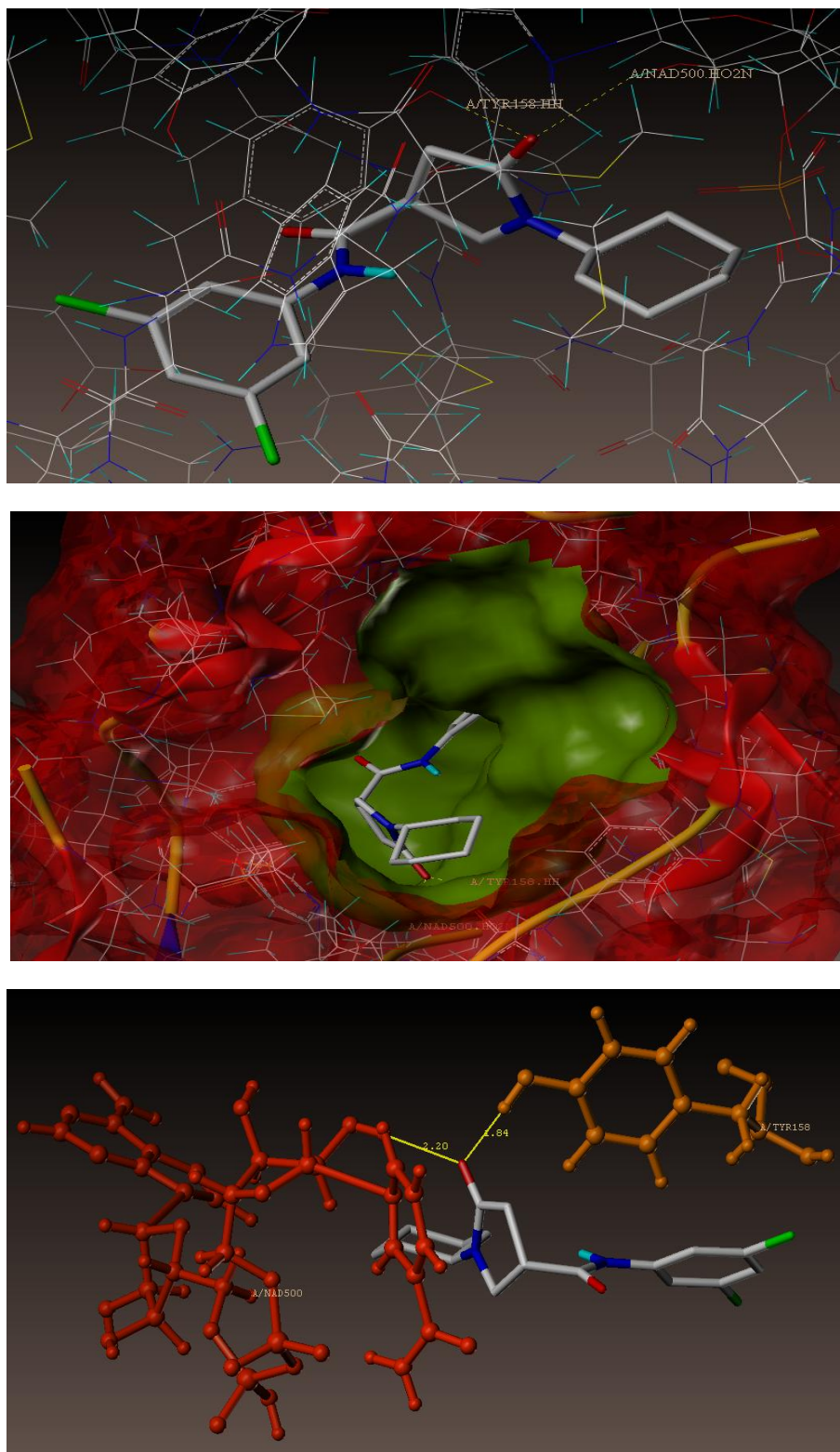


Figure 2. (A) Docked mode of 4TZK_ligand; (B) Inside proposed binding pocket of InhA; (C) 3D docked view of the 4TZK_ligand. Binding site residues; grey colored Tyr158 amino acid, red colored co-factor NAD⁺ and the molecule is colored according to atom type.

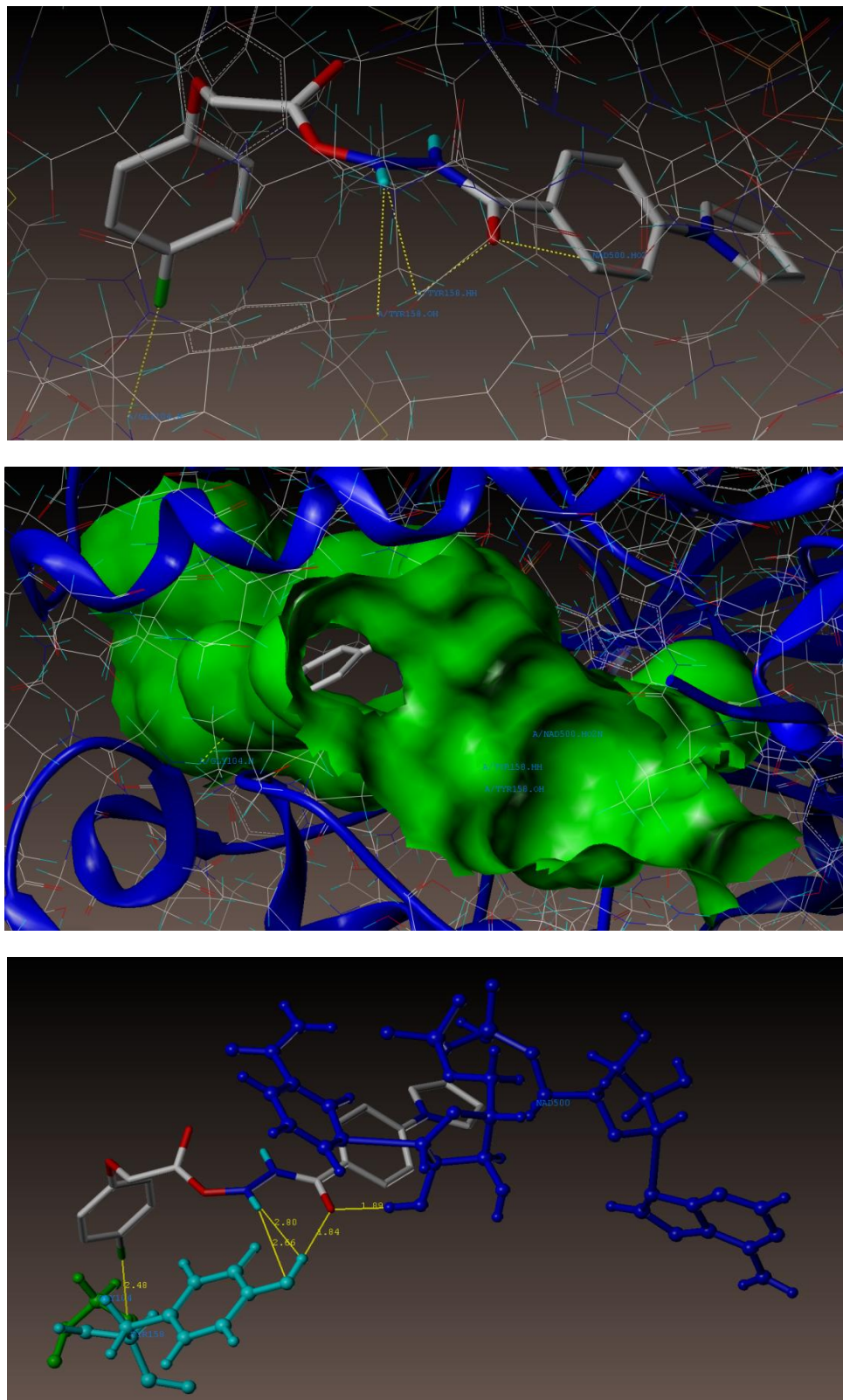


Figure 3. (A) Docked mode of compound 4; and (B) Inside the proposed binding pocket of InhA (PDB ID: 4TZK); (C) 3D docked view of the compound 4. Binding site residues; cyan colored Tyr158 amino acid, blue colored co-factor NAD+ and the molecule is colored according to atom type.

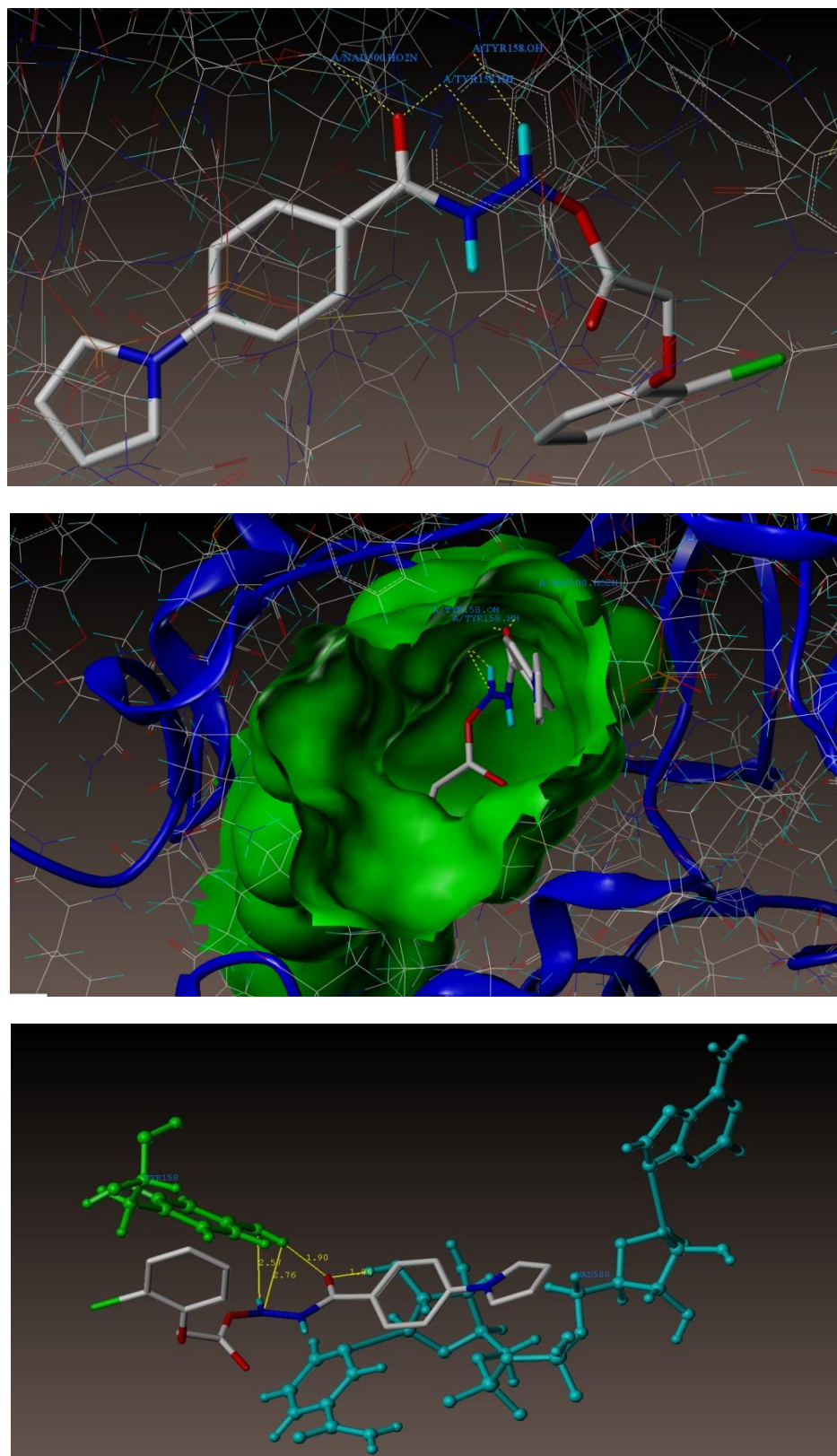


Figure 4. (A) Docked mode of compound 8; and (B) Inside proposed binding pocket of InhA (PDB ID: 4TZK); (C) 3D docked view of the compound 8. Binding site residues; green colored Tyr158 amino acid, cyan colored co-factor NAD⁺ and the molecule is colored according to atom type.

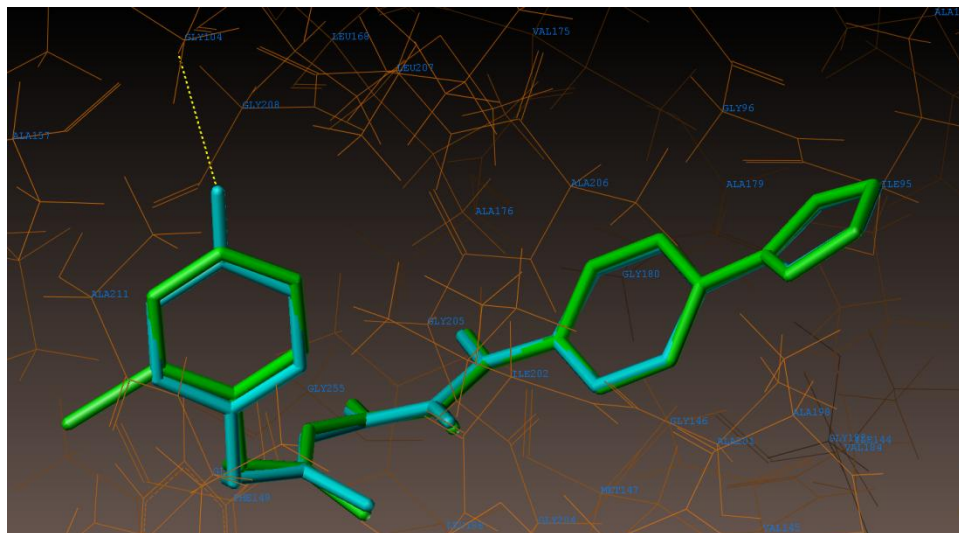


Figure 5. Hydrophobic Interaction of compound 4 and 8 with crystal structure of enzyme PDB 4TZK.

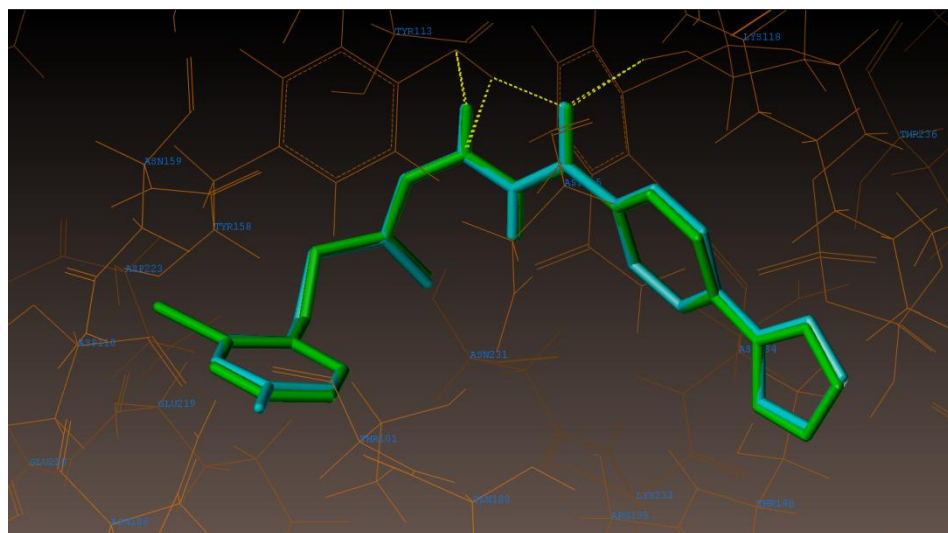


Figure 6. Hydrophilic Interaction of compound 4 and 8 with crystal structure of enzyme PDB 4TZK.

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