Frontiers in Health Informatics www.healthinformaticsjournal.com
ISSN-Online: 2676-7104
2024; Vol 13: Issue 5 Open Access

Computational ADMET Profiling and Docking Study of N-Substituted Quinoline Hydrazone Derivatives

Nilesh M. Jangade[1*], Manoj S. Charde[2]

[1*]Assistant Professor, Department of Pharmaceutical Chemistry, Bharati Vidyapeeth College of Pharmacy, Palus, Maharashtra, India.
[2]Assistant Professor, Department of Pharmaceutical Chemistry, Government College of Pharmacy, Karad, Maharashtra.

***Correspondence Author:** Nilesh M. Jangade
*Department of Chemistry, Department of Pharmaceutical Chemistry, Bharati Vidyapeeth College of Pharmacy, Palus, Maharashtra, India.
nilesh.jangade108@gmail.com

Cite this paper as: Nilesh M. Jangade, Computational ADMET Profiling and Docking Study of N-Substituted Quinoline Hydrazone Derivatives. *Frontiers in Health Informatics*, 13 (5), 14-20

Abstract
The Mycobacterium Tuberculosis (MTB) is the cause of tuberculosis, a persistent lung ailment. It is recognized as one of the worst illnesses, and it poses a serious threat to humankind when it coexists with HIV infection. A computational modeling method called molecular docking used to build complexes between interacting molecules. The 2D and 3D potential structures of the derivatives designed using the ChemDraw software. Pymol software used to transform these drawn structures into the PDB format, which was needed for ADMET screening and docking investigations. In ADMET study were carried using the web tools AdmetSAR. Protein data bank (PDB) was used to derive 3D protein structures. This study focuses on investigating the binding mode; interactions against mycobacterial ATP synthaze using virtual screening conducted with AutoDock 4.2. Derivative **4c** exhibited strong binding interaction than 4a, 4g, 5c and 5d with target ATP synthaze. The ADMET study shown that all derivatives are promising and safe.

Keywords: Quinoline 3-carbaldehyde hydrazone, ATPsynthaze, ADMET and Molecular docking etc.

1. Introduction

Molecular docking is an in silico method that determines the correct binding posture of a protein-ligand pair. It evaluates its efficacy by employing many scoring techniques to ascertain the ideal posture generated by every molecule [1]. Docking techniques optimize many parameters, including as hydrophobic, steric and electrostatic interactions, and calculate their binding free energies to fit a ligand into the target protein's binding site [2]. Protein data bank (PDB) was used to derive 3D protein structures [3].

Molecular docking uses computer modeling to construct complexes between interacting molecules. Virtual screening of large chemical libraries is enabled by molecular docking, which also suggests structural hypotheses for lead optimization in drug development.

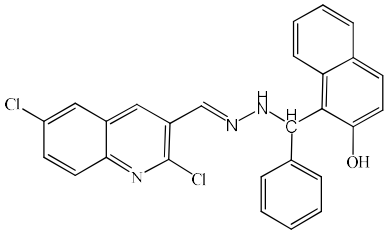
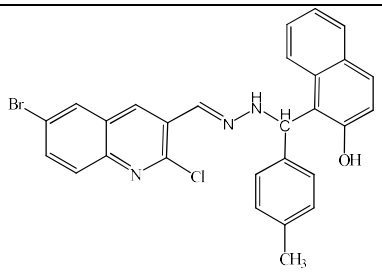
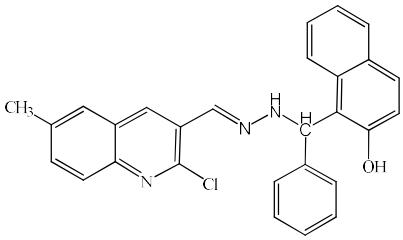
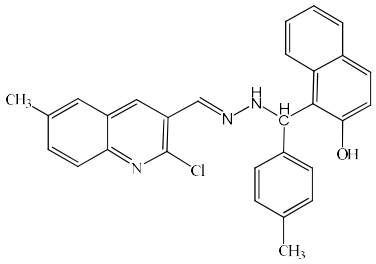
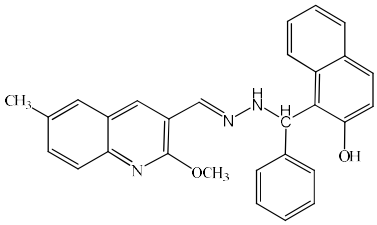
The Mycobacterium Tuberculosis (MTB) is the cause of tuberculosis, a persistent lung ailment. It is recognized as one of the worst illnesses, and it poses a serious threat to humankind when it coexists with HIV infection. Two main reasons contribute to the prevalence of tuberculosis (TB) worldwide: MDR-TB (multidrug-resistant tuberculosis) and the AIDS virus [4]. The bulk of TB cases reported from developing countries, and the proportion of TB patients who are also HIV-positive is rising. 10.1 million cases (or 4.5%) of tuberculosis were reported in 2020; by 2021, that number had increased to 10.6 million cases. In the same period, the occurrence rate of tuberculosis increased by 3.6%, leading to almost 187 thousand deaths among people living with HIV [5].

Quinoline is commonly found in natural compounds and serves as a precursor for numerous synthetic derivatives with diverse pharmacological activities, including antimalarial [6-7], antihypertensive [8], anticancer [9] and antifungal [10] properties. The presence of both non-polar and polar moieties in new *N*-

substituted quinoline 3-carbaldehyde hydrazone derivatives makes it suitable for permeation into bacterial cells [11].

The computational process of locating and properly attaching a ligand to a receptor is the focus of molecular docking. The binding mechanism and interaction of new N-substituted quinoline 3-carbaldehyde hydrazone derivatives **Table 1** with the mycobacterial ATP synthaze were investigated in this study using virtual screening with AutoDock4.2. One essential metabolic enzyme needed for the production of ATP is the ATP synthase. Consequently, ATP synthaze is seems to be a promising target in the ongoing research to discover anti-tubercular medications. Physicochemical Property, Lipophilicity, ADME and toxicological characteristics of bioactive molecules was estimated using online web tools admetSAR. Bioactivity scores for various targets using the Molinspiration software can be predicted.

Table 1: New *N*-substituted quinoline 3-carbaldehyde hydrazone derivatives

Compound	Structure	Compound	Structure
4a		5c	
4c		5d	
4g			

2. Material and Method:

2.1 Preparation of Ligands

The 2D and 3D potential structures of the derivatives designed using the ChemDraw software. Pymol software used to transform these drawn structures into the PDB format, which was needed for ADMET screening and docking investigations.

2.2 Selection and Preparation of Protein

The ATP synthaze selected for the docking study based on the Swiss Target Prediction Report. The three-dimensional crystallographic structure of ATP synthaze obtained using the PDB.

2.3 Predictions of Pharmacokinetics (ADME) and Toxicology:

The ADME and toxicological characteristics of bioactive molecules predicted using AdmetSAR software. Based on the compound's structure, these tools compute pharmacokinetic and toxicological characteristics. Pharmacokinetic properties of the compounds (Absorption, Distribution, Metabolism and Excretion) can be predicted using AdmetSAR software. Some of the important components include;

1. GI Absorption: Predicts whether the compound has high or low gastrointestinal absorption.
2. p-gp Substrate: Predicts if the compound is a substrate for P-glycoprotein, which affects drug transport and bioavailability.
3. BBB (Blood-Brain Barrier) Permeability: Indicates whether the compound can cross the blood-brain barrier.

AdmetSAR software was employed to estimate the various ADMET characteristics of the most well-known compound. Toxicity predictions for the compounds can also be done using AdmetSAR software:

1. The AMES toxicity test was utilized to assess the mutagenicity of the compound. The processed ligand showed a negative AMES toxicity test result for the compound, indicating that it is non-mutagenic.
2. Ames Mutagenesis: Predicts the likelihood of the compound causing genetic mutations (mutagenicity).
3. Carcinogenicity: Predicts the potential of the compound to cause cancer.
4. Acute Oral Toxicity: Indicates the acute toxicity of the compound when administered orally.
5. Acute Toxicity LD50: The lethal dose required to kill 50% of a test population, expressed in mol/kg.

These informations collectively provide a comprehensive overview of the drug-likeness, bioactivity, pharmacokinetics, and toxicity of the compounds, which are crucial for evaluating their potential as therapeutic agents.

2.4 Drug Likeness Score:

Evaluation synthetic compounds for its drug-likeness features is done by using admetSAR Web tool. For drug design, the concept of drug-likeness is employed. To assess drug-likeness, the Lipinski rule of five is considered which Provides drug-likeness metrics based on criteria such as Lipinski's rule of five and other pharmaceutical benchmarks.

2.5 Physicochemical Properties:

Physicochemical Property and Lipophilicity was estimated using online web tools admetSAR for property calculations. Compounds evaluated based on their physicochemical properties and Lipinski's rule of five, which is used to predict the drug-likeness of a compound. The properties listed include:

1. Molecular Weight (Mol. Wt.): A measure of the mass of a molecule.
2. Hydrogen Bond Acceptors (H-accepter): Number of atoms in a molecule that can accept hydrogen bonds.
3. Hydrogen Bond Donors (H-donor): Number of hydrogen atoms that can be donated in hydrogen bonding.
4. Rotatable Bonds: Number of bonds in a molecule that can freely rotate, affecting the molecule's flexibility.
5. Log P: The partition coefficient, which indicates the lipophilicity of a compound.
6. Total Polar Surface Area (TPSA): The surface area of a molecule that is polar, which impacts drug absorption and permeability.

2.6 Bioactivity Score:

Bioactivity scores for various targets using the Molinspiration software can be predicted. The scores are typically presented as negative values, where values closer to zero indicate higher predicted bioactivity.

1. GPCR Ligand: Compounds acting on G-Protein-Coupled Receptors.
2. Ion Channel Modulator: Compounds modulating ion channels.
3. Kinase Inhibitor: Compounds inhibiting kinase enzymes.
4. Nuclear Receptor Ligand: Compounds interacting with nuclear receptors.
5. Protease Inhibitor: Compounds inhibiting protease enzymes.
6. Enzyme Inhibitor: Compounds inhibiting various enzymes.

2.7 Computatıonal Methodology:

The binding mechanism and interaction of newly discovered N-Substituted Quinoline 3-Carbaldehyde hydrazone derivatives with the mycobacterial ATP synthaze were studied [12] using virtual screening with AutoDock4.2. The RCSB database was used to retrieve the crystal structure of ATP synthaze using the source code 4V1F.pdb. Bedaquiline (BDQ) is a novel adenosine triphosphate (ATP) synthaze inhibitor that is specific to Mycobacterium. The BDQ material targets the membrane-embedded rotor (c-ring) of the mycobacterial ATP synthaze. The ATP synthaze is an essential metabolic enzyme required for ATP synthesis. Consequently, ATP synthaze found to be a promising target in the ongoing research to discover anti-tuberculosis drugs. The Discovery studio visualizer was used to create the atomic coordinates of new compounds that are N-Substituted Quinoline 3-Carbaldehyde hydrazone derivatives.

In this instance, the BDQ binding site is treated as the ATP synthaze active site for virtual screening by the AutoDock4.2 software. New N-Substituted Quinoline 3-Carbaldehyde hydrazone derivatives were molecularly docked using a 40 x 40 x 40 grid box with 0.375 grid spacing. The pharmacological component consisted of a flexible molecule, but the 4VIF receptor protein was maintained rigid for docking. The Lamarckian genetic algorithm ran with its default settings [13]. Drug output conformations were further classified using an all-atom RMSD with a cut-off of 4. The binding energy, van der Waals energy, intermolecular energy, and cluster size of various output conformations compared in accordance with previous studies [14–17].

3. Results and Discussion:

3.1 Physicochemical Properties and Drug Likeness Prediction:

A compound's physicochemical properties are carefully studied when determining how drug-like it is to see if they meet standards like the Lipinski rule of five.

Various factors are considered, encompassing features like topological polar surface area (TPSA), logP, hydrogen bond donors (HBD), count of rotatable bonds, molecular mass, molar refractivity, quantity of rotatable bonds, and hydrogen bond acceptors (HBA). The results, presented in **Table 2**, provide a summary indicating that all derivatives strictly adhere to the Lipinski Rule of Five without any breaches.

Table 2: Physiochemical properties and drug likeness

	Physicochemical Properties						Drug Likeness		
Comp.	**Mol. Wt.**	**H-acceptor**	**H-donor**	**Rotatable bond**	**Log *p***	**Total polar surface area (TPSA)**	**Lipinski violations**	**Bioavailability Score**	**Synthetic Accessibility**
4a	472.37	3	2	5	3.97	57.51	01	0.55	3.63
4c	465.97	3	2	5	4.04	57.51	01	0.55	3.89
4g	447.53	4	2	6	4.04	66.74	00	0.55	3.96
5c	530.84	3	2	5	4.53	57.51	02	0.17	3.78
5d	465.97	3	2	5	4.37	57.51	01	0.55	3.85

3.2 Bioactivity Score:

Molinspiration software was employed to forecast the bioactivity of compounds. By evaluating bioactivity scores, a comparison was made between the isolated compounds and established drugs across protease inhibitors (PI), kinase inhibitors (KI), ion channel modulators (ICM), GPCR ligands (GPCRL), nuclear receptor ligands (NRL) and enzyme inhibitors (EI). **Table 3** presents the findings of the bioactivity assessment.

Table 3: Molinspiration bioactivity score

Comp.	GPCR ligand	Ion channel modulator	Kinase Inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
4a	-0.15	-0.25	-0.23	-0.23	-0.34	-0.15
4c	-0.18	-0.30	-0.26	-0.24	-0.37	-0.18
4g	-0.13	-0.23	-0.15	-0.18	-0.32	-0.12
5c	-0.27	-0.38	-0.28	-0.35	-0.47	-0.24
5d	-0.18	-0.29	-0.25	-0.24	-0.36	-0.18

3.3 In Silico Pharmacokinetic and Toxicity Prediction:

Pharmacokinetics prediction study like GI absorption, Caco absorption, p-gp, CYP2C19 Inhibitor, CYP2D6 Inhibitor mentioned in **Table 4** was done on admetSAR.

Table 4: Pharmacokinetic prediction using AdmetSAR.

Compound	GI Absorption	Caco absorption	p-gp
4a	High	No	No
4c	Low	No	No
4g	High	No	No
5c	Low	No	No
5d	High	No	No

Toxicity prediction study like ames mutagenesis, carcinogenicity, acute oral toxicity and acute toxicity LD 50 mentioned in **Table 5** was done on AdmetSAR software.

Table 5: Toxicity prediction using AdmetSAR software.

Compound	Ames Mutagenesis	Carcinogenicity	Acute Oral Toxicity	Acute Toxicity mol/Kg	LD50
4a	+0.6607	-0.5797	0.5021	2.235	
4c	+0.6857	-0.5414	III 0.5241	2.205	
4g	+0.5000	-0.5138	III 0.6001	2.3472	
5c	+0.6844	-0.5208	III 0.5319	2.239	
5d	+0.6964	-0.5159	III 0.5434	2.227	

3.4 Molecular Docking Results:
The docking study data suggests that the compound 4c forms stable interactions with the target protein, primarily through π-π stacking, π-σ, and π-alkyl interactions, with a significant binding affinity indicated by a binding energy of -8.7 kcal/mol **Figure 1.** These interactions are likely critical for the compound's binding to the target protein, with the listed residues playing a crucial role in this binding.[3-5]

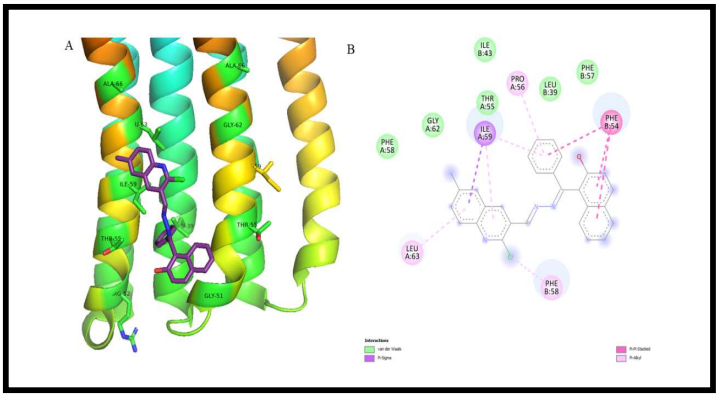


Figure 1: Binding mode of ATP synthase with 4c.

Here (A) shows the binding pocket of 4c and (B) shows the interaction network of 4c with ATP synthase residues using Discovery studio Visualizer.
To investigate the binding affinity and interaction of potentialnew *N*-substituted quinoline 3-carbaldehyde hydrazone derivatives, virtual screening was performed using Auto Dock Vina software. The docking analysis showed that the compound 4c among all having higher affinity with the ATP synthaze **Table 6**. These least binding energy new *N*-substituted quinoline 3-carbaldehyde hydrazone derivatives were further analyzed for binding mode and 2D interaction analysis using PyMoland Discovery studio Visualizer, respectively. [18-21].

Table 6: Hydrogen bonding interaction of *N*-substituted quinoline 3-carbaldehyde hydrazone derivatives with ATP synthaze using molecular docking.

Comp.	Binding energy in Kcal.mol	Atoms involved in the bonding	Distance	Angle	Interactions Type

		A:ILE59:CG2 - :UNK0	3.90061	Pi-Sigma
		B:PHE54 - :UNK0	4.51677	Pi-Pi Stacked
		B:PHE54 - :UNK0	4.0595	Pi-Pi Stacked
		B:PHE54 - :UNK0	4.65235	Pi-Pi Stacked
4c	-8.7	B:PHE58 - :UNK0:CL12	4.14736	Pi-Alkyl
		:UNK0 - A:ILE59	4.41697	Pi-Alkyl
		:UNK0 - A:LEU63	4.92239	Pi-Alkyl
		:UNK0 - A:PRO56	5.16757	Pi-Alkyl
		:UNK0 - A:ILE59	4.772	Pi-Alkyl

4. Conclusıon:

Above ADMET study suggest that all the drugs are safe and are not carcinogenic in nature. The utilization of molecular docking offers a cost-effective, safe, and user-friendly approach for exploring, interpreting, explaining, and uncovering molecular characteristics within three-dimensional structures. Docking is a method employed to predict the structural interactions between new *N*-Substituted Quinoline 3-Carbaldehyde hydrazone derivatives and ATP synthaze. Compounds **4d, 5a, 5b, 7b** and **7d** shown that they have good binding interaction with target ATP synthaze. These derivatives may turned out to be potential anti-tubercular drugs.

5. Acknowledgement:

Authors immensely thankful to Bharati Vidyapeeth College of Pharmacy, Palus and Government College of Pharmacy, Karad Maharashtra, India for providing facilities for research work and their constant support.

6. Competıng of Interest:

The Authors have stated that they have no competing interests.

7. References:

1. Kuntz ID, Blaney JM, Oatley SJ, Langridge R, Ferrin TE. A geometric approach to macromolecule-ligand interactions. J MolBiol 1982 Oct 25;161 (2):269–88. https://doi.org/10.1016/0022-2836(82)90153-X.
2. Diller DJ, MerzJr KM. High throughput docking for library design and library prioritization. Proteins 2001 May 1;43 (2):113–24.https://doi.org/10.1002/1097-0134(20010501)43:2<113::AID-PROT1023>3.0.CO;2-T.
3. Teodoro ML, Kavraki LE. Conformational flexibility models for the receptor in structure based drug design. CurrPharmaceut Des 2003;9(20):1635–48.http://doi.org/10.2174/1381612033454595.
4. Joshi SD, Tigadi N., Kumar D., Dixit SR, Jangade NM," Synthesis of some new Pyrrolyl hydrazine derivatives as an anti-tubercular agent", Indian Journal of Heterocyclic Chemistry, 2016, 26 (3 & 4), 237-241.https://connectjournals.com/achivestoc2.php?fulltext=2551803H_237-241.pdf&&bookmark=CJ-001644&&issue_id=03%20-%2004%20&&yaer=2016.
5. World Health Organization, Global Tuberculosis Report 2022, 1-49. https://iris.who.int/bitstream/handle/10665/363752/9789240061729-eng.pdf?sequence=1.
6. Joshi SD, Jangade NM, Dixit SR, Joshi AS, Kulkarni VH, "Quinoline: a promising and versatile scaffold for future" Indo American Journal of Pharmaceutical Research, 2016, 6 (4), 5033-5044.http://doi.org/10.1044/1980-iajpr.160324
7. Foley Michael, Leann Tilley, "Quinoline Antimalarials mechanism of action and resistance and prospects for new agents", Pharmacol. Ther. Elsevier incorp., 1998, 79(1), 55-87.https://doi.org/10.1016/S0163-7258(98)00012-6
8. Kumar Himank, JadhavManoj, DevarajiVinod, "Antihypertensive activity of a Quinoline appended chalcone derivative and its site specific binding interaction with relevant target carrier protein" RSC advances, 2015, https://doi.org/10.1039/C5RA08778C.
9. Nakamura T, Oka M, Aizawa K et al., Direct interaction between a quinolone derivative, MS-209 and multidrug resistance protein (MRP) in human gastric cancer cells, BiochemBiophys Res Commun. 1999; 255 (3): 618-624.https://doi.org/10.1006/bbrc.1999.0245.
10. Musiol R. Jampilek J., Buchta V et al., "Antifungal properties of new series of New 2-Substituted Quinoline 3-Carbaldehyde Betti Bases ", Bioorg. Med. Chem., 2006; 14 (10): 3592-3598.https://doi.org/10.1016/j.bmc.2006.01.016.

11. Mandewale MC, Patil UC, Shedge SV et al., "A review on Quinoline hydrazone derivatives as a new class of potent antitubercular and anticancer agents" Beni-Suef Univ. J. basic App. Sci., 2017, 6: 354-361. https://doi.org/10.1016/j.bjbas.2017.07.005.
12. Oleg Trott, Olson AJ, "AutoDock: Improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading" Journal of Computational Chemistry, Jan 2010, 31(2), 455-461.https://doi.org/10.1002/jcc.21334.
13. Kumbhar BV, Bhandare VV, "Exploring the interaction of Peloruside A with drug resistant αβII and αβIII tubulin isotypes in human ovarian carcinoma using a molecular modeling approach", Journal of Biomolecular Structure and Dynamics; http://doi.org/10.1080/07391102.2020.1745689.
14. Kumbhar BV, Borogaon A, Panda D, Kunwar A, "Exploring the origin of differential binding affinities of human tubulin iso types αβII & αβIII for DAMA colchicine using homology modeling molecular docking and molecular dynamics simulation", PLOS One, 2016;http://doi.org/10.1371/journal.pone.0156048.
15. Joshi, SD. &Chougula, BM. (2016). Synthesis, characterization, molecular docking studies of substituted 4-coumarinylpyrano[2,3-c]pyrazole derivatives as potent antibacterial and anti-inflammatory agents. Eur JMed Chem. Doi: 10.1016/j.ejmech.2016.09.021.https://doi.org/10.1016/j.ejmech.2016.09.021.
16. Sever B. Kaan K.,"In silico Molecular Docking and ADME Studies of 1,3,4-Thiadiazole Derivatives in Relation to in vitro PON1 Activity", Bentham Science, 15 (2), 2019; 136-144, doi.org 10.2174/1573409914666180518085908.
17. Daina, A. & Michielin, O.(2019). Swiss target prediction:updated data and new features for efficient prediction of proteintargets of small molecules. Nucleic Acids Res.;47: 357-366. Doi: 10.1093/nar/gkz382, https://doi.org/10.1093/nar/gkz382.
18. DeLano WL, "Unraveling hot spots in binding interfaces: progress and challenges", Current opinion in structural biology", 12(1), 14-20, http://doi.org/10.1016/S0959-440X(02)00283-X.
19. Patil Priyanka, Khulbe Preeti, Magdum Chandrakant, " Structure based virtual screening, molecular docking and brine shrimp bioassay of 1,3,4 Oxadiazole derivatives as potent VEGFR", Advances in Bioresearch; Vol. 14, Issue 1, Jan 2023, ISSN: 0976-4585, http://doi.org/ 10.2174/0929867330666230309143711.
20. Molinspiration cheminformatics, Bratislava, Slovak Republic, and Available from: http://www.molinspiration.com/services/properties.html ; [accessed 16.08.10].
21. Lipinski, CA. & Lomardo, F.,"Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings", Adv Drug Deliv Rev.64:4-17. DOI: 10.1016/j.addr.2012.09.019, https://doi.org/10.1016/S0169-409X(00)00129-0.