Molecular docking and dynamics of Nickel-Schiff base complexes for inhibiting β -lactamase of *Mycobacterium tuberculosis*

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Abstract

In recent years, multidrug-resistance has become a primary concern in the treatment and management of tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis*. In this context, searching new anti-tuberculosis agents particularly targeting the β -lactamase (BlaC) is reported to be promising as this enzyme is one of the key player in the development of multidrug resistance. This study reports the design of some Nickel (Ni) based tetradentate N₂O₂ Schiff bases, employing density functional theory. All analogs are optimized at B3LYP/SDD level of theory. Dipole moment, electronic energy, enthalpy, Gibbs free energy, HOMO–LUMO gap, and softness of these modified drugs are also investigated. Molecular interactions between designed ligands and BlaC have been analyzed by molecular docking approach, followed by molecular dynamics (MD) simulation. All designed compounds show low HOMO–LUMO gap, while addition of halogen increases the dipole moment of the compounds. Docking and MD simulation investigations reveal that the designed compounds are more potent than standard inhibitor, where Ile117, Pro290, Arg236 and Thr253 residues of BlaC are found to play important role in the ligand binding. Through MD simulation study, the best binding compound is also observed to form stable complex by increasing the protein rigidity. The ADME/T analysis suggests that modified drugs are less toxic and shows an improved pharmacokinetic properties than that of the standard drug. These results further confirm the ability of Ni-directed Schiff bases to bind simultaneously to the active site of BlaC and support them as potential candidates for the future treatment of tuberculosis disease.

Keywords Tuberculosis · Anti-microbial activity · Schiff base · Density functional theory (DFT) · Molecular dynamics · ADME/T

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains the most deadly infectious diseases and one of the top 10 causes of the death worldwide in 2015. Report provided by WHO showed that there are 10.4 million new cases and 1.44 million deaths in 2015, where 480,000 new cases are associated with multidrug-resistant TB (MDR-TB) with an additional 100,000 people with rifampicin-resistant TB (RR-TB) (Tessema et al. 2017). The notorious tendency of *M. tuberculosis* with the conjunction of prolonged treatment regimens shows drug resistant which is developed in different stages (Connolly et al. 2007). Also the expression of β -lactamase is considered as the most significant causes for developing intrinsic resistant to these antibiotics (Mishra et al. 2017). In line with this context, recent studies reported that the sensitivity to *M. tuberculosis* is increased by 8–256 fold upon the deletion of chromosomal class A (Ambler)

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β -lactamase, expressed from BlaC gene of *M. tuberculosis* (Flores et al. 2005a, b). Antibiotic containing β -lactam such as Penicillin and Cephalosporin disrupts the biosynthesis of bacterial cell wall by the irreversible inhibition of trans peptidases (Edwards and Betts 2000; Feiler et al. 2013) responsible for crosslinking two peptidoglycan strands, bacterial cell wall components (Hayhurst et al. 2008). However, the β -lactams as well as other antibiotics were proved to ineffective in the therapeutic management of tuberculosis (Harrison and Svec 1998; Emran et al. 2015) due to multi-drug resistance. It appears as a challenge to find a safe and potent anti-tuberculosis agent to deal with multidrug resistant (MDR-TB), extensively drug-resistant (XDR-TB) strains and latent tuberculosis with in shorten therapeutic regimen.

In recent years, Schiff base derived compounds have gained much attention due to having broad spectrum of biological activities including anti-inflammatory (Sathe et al. 2011; Sondhi et al. 2006; Pandey et al. 2011; Chandramouli et al. 2012), analgesic (Sondhi et al. 2006; Pandey et al. 2011; Chandramouli et al. 2012; Chinnasamy et al. 2010), antimicrobial (Mounika et al. 2010; Venkatesh 2011), anticonvulsant (Chaubey and Pandeya 2012), antitubercular (Aboul-Fadl et al. 2003), anticancer (Miri et al. 2013; Ali et al. 2012), antioxidant (Wei et al. 2006), anthelmintic (Avaji et al. 2009). Schiff bases contain aromatic group are reported to be effective against *M. tuberculosis*, having MIC value of 8 $\mu\text{g/mL}$ against H37Rv strain according to the recent reports (Souza et al. 2007). Several studies also reported that Schiff bases with heterocyclic rings in coordination with transitional metals are very effective against diverse microorganisms (Kajal et al. 2013; da Silva et al. 2011; Hearn and Cynamon 2004; Abu-Khadra et al. 2016) suggesting the compound having synergistic feature can help to overcome the resistivity of *M. tuberculosis*.

Herein, we report β -lactamase inhibition mechanism of some Nickel (II) complexes supported by tetradentate N_2O_2 Schiff base ligands using molecular docking and molecular dynamics simulation approaches. The metal complexes are also designed by the quantum-mechanical DFT calculations. Molecular geometries, electronic energy levels (for the frontier molecular orbitals, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), hardness and softness are also estimated along with ADME/T properties.

Methods

Designing and optimization of ligands

BIOVIA Drawer was used to draw all the molecules, which were then subjected with a view to creating 3D structure by fully optimizing with density functional theory, employing

Becke's exchange functional combining Lee, Yang, and Parr's (LYP) correlation functional (Lee et al. 1988; Becke 1988). As all designed compounds contain metal atom, the SDD (Stuttgart/Dresden) basis set was used (Bergner et al. 1993). After optimization, subsequent vibrational frequency calculations have been done in order to ensure that the stationary points correspond to minima on the Potential Energy Surface. Electronic energies, enthalpy, Gibbs free energies, and dipole moments and partial charge analysis of each compound were also investigated. By using energies of frontier HOMO and LUMOs, hardness and softness of all compounds were also determined. Considering Parr and Pearson interpretation (Parr and Yang 1989) of DFT and Koopmans theorem (Pearson 1986), hardness (η) and softness (S) of the drugs were calculated by applying the equation-

$$\eta = [\text{HOMO}\epsilon - \text{LUMO}\epsilon]/2,$$

$$s = 1/\eta$$

Molecular docking analysis

Three-dimensional crystal structure of BlaC-E166A (PDB id: 3N7W) was retrieved in pdb format from the protein data bank (Berman et al. 2000). After that, the structure was prepared by deleting water molecules and adding hydrogen atoms, which was subsequently subjected to energy minimization using the steepest descent and conjugate gradient technique to eliminate bad contacts of protein atoms. Computations were carried out in vacuo with the GROMOS 96 43B1 parameters set, implementation of Swiss-PDB Viewer. Docking analysis was performed by AutodockVina and Autodock tools (ADT) of MGL software packages were used for converting pdb into pdbqt format to input protein and ligands. The grid box size in AutodockVina was kept at 48.2808, 49.1466, and 52.4875 respectively for X, Y, Z. AutodockVina was implemented through shell script provided by AutodockVina developers. The binding affinity of ligand was monitored in kcal/mol unit for a negative score (Trott and Olson 2010; Dash et al. 2016). In order to estimate the accuracy of binding affinity of AutodockVina, MOE-dock module of MOE 2015 software was used for cross-docking analysis. In this method, each compound had been redocked into the active site of BlaC-E166A using Alpha Triangle placement method, and Triangle matcher placement methods, and the binding affinity has been predicted by GBVI/WSA dG with the force field refinement strategy (Corbeil et al. 2012).

Molecular dynamics simulation

Validation of the predictions from docking study was performed by molecular dynamics simulation using the YASARA Dynamics (Krieger et al. 2004) software. In this

study, the AMBER14 force field (Case et al. 2005) was utilized, which is widely applied to describe macromolecular system. The transferable intermolecular potential 3 points (TIP3P) water model was utilized by adding Cl^- and/or Na^+ ions, where the total solvent molecules were 45,960 with a density of 1.012 gm/cm^3 . The periodic boundary condition was included for performing the simulation, where the box size $76.9 \times 76.9 \times 76.9 \text{ \AA}^3$. Initial energy minimization process of the each simulation system was performed by simulated annealing method, using steepest gradient approach (5000 cycles). Molecular dynamics simulations were performed using the PME methods to describe long-range electrostatic interactions at a cut off distance of $8 \text{ \AA}$ at physiological conditions (298 K, pH 7.4, 0.9% NaCl) (Krieger et al. 2006). A multiple time step algorithm together with a simulation time step interval of 2.50 fs was chosen (Krieger and Vriend 2015). At a constant pressure and Berendsen thermostat, molecular dynamics simulations were performed for 25 ns long, and MD trajectories were saved every 250 ps for further analysis.

Pharmacokinetic parameters study

To evaluate the pharmacokinetic parameters and toxicity of the modified compounds and parent compound, admetSAR server was utilized. We have utilized admetSAR online database for analysis of the pharmacokinetic parameters related to drug absorption, metabolism and toxicity for the parent drug and its derivatives (Cheng et al. 2012). By using structure similarity search methods, the latest and most comprehensive manually curated data was predicted by admetSAR for diverse chemicals along with known ADME/T profiles.

Results and discussion

QM simulation study

In drug designing concept, the dipole moment of ligand is considered as the major player in protein–ligand binding, influence the formation of non-bonded interactions (Lien et al. 1982). As introduction of metals and halogens in compound increase the polarity as well as dipole moment, we designed eight Schiff base compounds by modifying with metal and halogens, are depicted in Fig. 1. Table 1 describes the stoichiometry, electronic energy, enthalpy, Gibbs free energy and dipole moment of the compounds, and the optimized structures are represented in Fig. 2. As shown in Table 1, the lowest dipole moment is observed for D1, while the results of other properties are also lowest in terms of electronic energy, enthalpy and Gibbs free energy. It can be also seen that introduction of halogen atoms significantly increases the stability of the compounds, as the compounds

Compound	X ₁	X ₂
D1	H	H
D2	-CH ₃	-CH ₃
D3	-CH ₃	F
D4	-CH ₃	Cl
D5	-CH ₃	Br
D6	F	F
D7	Cl	Cl
D8	Br	Br

Fig. 1 The design of new Schiff base analogues

D3–D8 produced higher electronic energy, enthalpy and Gibbs free energy than the D1 and D2. The substitution of double Cl atoms in D7 shows highest dipole moment than the substitution of double F atoms (D6). In addition, D7 shows the highest Gibbs free energy, thereby more stable than other compounds.

Analysis of frontier molecular orbitals

As the analysis of energy distributions in frontier molecular orbitals helps to understand the chemical reactivity of the compounds, we report the values of orbital energies, along with the two global chemical descriptors, hardness and softness; are tabulated in Table 2. The compound having lower energy gap in HOMO and LUMO is generally more chemically reactive, indicates high softness (Hoque et al. 2015; Parr and Zhou 1993). Fig. 3 depicts the DFT computed frontier orbitals plots for D6. In this study, D8 is found to be more chemically reactive than the other compound, while D7 is less reactive (Table 2). Furthermore, it is revealed that, though the substitution of double Cl atoms increased the thermodynamic stability, it decreases the

Table 1 The stoichiometry, electronic energy, enthalpy, gibbs free energy in Hartree and dipole moment (Debye) of designed drugs

Name	Stoichiometry	Electronic energy	Enthalpy	Gibbs free energy	Dipole moment (debye)
D1	C20H14N2NiO6	−1501.98	−1501.98	−1502.06	2.653
D2	C22H18N2NiO6	−1580.51	−1580.51	−1580.60	2.683
D3	C21H15FN2NiO6	−1640.48	−1640.48	−1640.57	4.298
D4	C21H15ClN2NiO6	−2000.79	−2000.79	−2000.88	3.236
D5	C21H15BrN2NiO6	−1553.99	−1553.99	−1554.08	4.969
D6	C20H12F2N2NiO6	−1700.46	−1700.46	−1700.54	5.300
D7	C20H12Cl2N2NiO6	−2421.08	−2421.08	−2421.17	6.889
D8	C20H12Br2N2NiO6	−1527.48	−1527.47	−1527.56	6.871

chemical reactivity, showing the more prominent reactivity of Br substitution rather than the Cl.

Molecular docking analysis

The investigation of binding properties of the designed compounds as β -lactamase inhibitor is accomplished by docking simulation by AutodockVina. Table 3 summarized the binding affinities and molecular interactions of the designed compounds. In addition, the previous studies suggested that all class A β -lactamases hydrolyzed β -lactam substrates through the nucleophilic attack initiated by Ser84 residue of the active site (Meroueh et al. 2005). Furthermore, the other five surrounding residues of the active site including Lys250, Thr251, Thr253, Ser142 and Gly144 make direct hydrogen bonding interaction with the substrates (Wang et al. 2006). In another study, it is also appeared that Ile117 of BlaC acts as a ‘gatekeeper’ residue that regulates substrate accessibility to the enzyme active site (Feiler et al. 2013). In contrast, molecular docking study of the designed compounds shows that major residues of BlaC active site like Ile117 and Pro290 form hydrophobic interactions with the ligands by means of pi-alkyl bonding. Another important residue Arg236, which involved in electrostatic interaction with β -lactamases inhibitor, shows pi-cation interactions with D2–D5 compounds. Highest binding affinity is observed for D6 (−9.7 kcal/mol), which forms amide-pi stacked with Thr253 residue, in addition to conventional halogen bond with Ser142 residue (Fig. 4). Besides, D6 also showed pi-sigma and alkyl–alkyl interactions with Ile117 and Pro290 residues, respectively. Furthermore, as shown in Table 4, D6 compound also obtained the lowest binding affinity of −8.24 kcal/mol in cross-docking analysis by MOE-Dock. These study therefore suggest that the D6 has the strong interaction towards the binding site of BlaC, however, whether this compound formed stable complex or not, molecular dynamics studies is performed along with the control inhibitor, i.e. amoxicillin.

Molecular dynamics simulation

The molecular dynamics simulation has now becomes an essential tool, among the all drug-designing approaches that accurately predicts the binding stability of the protein–ligand complex at atomic level. The molecular dynamics simulation for 25 ns reveals that compound D6 forms more stable complex than standard inhibitor amoxicillin. According to the RMSD (Root-Mean-Square Deviation) calculation, shown in Fig. 5, it can be seen that both the complexes are seen to achieve equilibrium after 7 ns and represented some fluctuations around 1.4 Å. Amoxicillin showed the high RMSD value than the D6 suggesting that D6 induced the BlaC to form rigid confirmation thereby stable in nature. To observe how the ligand caused the conformational changes of the protein in what extent, we calculated RMSF (Root-Mean-Square fluctuation), Radius of gyration and solvent accessible surface area (SASA) of the protein (Fig. 6). As shown in Fig. 6a, an increase of the SASA values were observed for amoxicillin complex after 5 ns of simulation time and remain till to the end, while the D6 complex showed stable confirmation during the simulation. As higher SASA value denotes the protein expansion, it can be concluded that D6 is more stable than the amoxicillin complex, obtained lower SASA values, therefore shrunken in nature. Similarly, protein dimensional calculations done by radius of gyration (Fig. 6b) indicated that amoxicillin complex less compacted than the D6 complex during the simulation. As can be seen in the plot, amoxicillin complex obtained higher radius of gyration values 17.79–18 Å, while D6 resulted from 17.6–17.82 Å. These results suggested that D6 complex formed rigid confirmation during the simulation. The flexibility of the residues in each protein was also calculated by means of RMSF analysis, in which higher RMSF value describes the higher flexibility. According to Fig. 6c, amoxicillin produced high fluctuations in the residues position of 43–170 during the simulation, while low fluctuations observed in the residues position of 180–307. Similarly, the compound D6 induces high flexibility in the residue position

Fig. 2 Most stable optimized structures of all designed Schiff base compounds. All compounds were optimized in the gas phase at B3LYP/SDD level in Gaussian 09

Table 2 Energy (atomic unit) of HOMOs, LUMO, gap, hardness and softness of the designed drugs

Molecules	ϵ_{HOMO-1}	ϵ_{HOMO}	ϵ_{LUMO}	Gap	η (hardness)	S (softness)
D1	−0.23677	−0.22911	−0.09904	0.13007	0.06503	15.3763
D2	−0.23073	−0.22341	−0.09397	0.12944	0.06472	15.4511
D3	−0.23995	−0.23137	−0.1005	0.13087	0.06543	15.2823
D4	−0.23866	−0.23101	−0.10484	0.12617	0.06308	15.8516
D5	−0.23866	−0.22941	−0.10310	0.12631	0.06315	15.8340
D6	−0.24816	−0.23965	−0.10612	0.13353	0.06676	14.9779
D7	−0.2467	−0.23782	−0.11026	0.12756	0.06378	15.6788
D8	−0.2454	−0.23636	−0.11042	0.12594	0.06297	15.8805

Fig. 3 Molecular orbital distribution plots of HOMO and LUMO states in the ground state of D6 compound at B3LYP/SDD level of theory in gas phase **Table 3** Binding affinity and nonbonding interaction of designed schiff base-nickle derivatives

Compound	Binding affinity (kcal/mol)	Hydrophobic				Halogen bond	Electrostatic Pi-cation	Conventional hydrogen bond
		Pi-alkyl	Amide-Pi stacked	Pi-sigma	Alkyl			
D1	−9.2	PRO ²⁹⁰ (4.679)		ILE ¹¹⁷ (2.334)	PRO ²⁹⁰ (4.682)			
D2	−9.2	PRO ²⁹⁰ (4.702)		ILE ¹¹⁷ (2.344)	PRO ²⁹⁰ (4.708)		ARG ²³⁶ (4.473)	
D3	−9.3	PRO ²⁹⁰ (4.846)		ILE ¹¹⁷ (2.453)	PRO ²⁹⁰ (4.622)		ARG ²³⁶ (4.364)	
D4	−9	ILE ¹¹⁷ (4.465) PRO ²⁹⁰ (5.294) ILE ¹¹⁷ (4.005)	GLY ²⁵⁴ (4.635) ASP ²⁵⁵ (4.635)		PRO ²⁹⁰ (4.544) ILE ¹¹⁷ (4.749)		ARG ²³⁶ (4.143)	
D5	−8.3	ILE ¹¹⁷ (3.935)					ARG ²³⁶ (4.093)	
D6	−9.7	ALA ¹⁸² (5.392)	THR ²⁵³ (4.598) GLY ²⁵⁴ (4.598)	ILE ¹¹⁷ (2.880)	PRO ²⁹⁰ (4.873)	SER ¹⁴² (2.893)		
D7	−8.3	ILE ¹¹⁷ (4.937) ILE ¹¹⁷ (5.045)		THR ²⁵³ (2.470)	PRO ¹⁸³ (4.972) ARG ¹⁸⁷ (5.072) ILE ¹¹⁷ (4.002)			ILE ¹¹⁷ (2.438)
D8	−7.3	ILE ¹¹⁷ (4.022) PRO ²⁹⁰ (4.412)			ILE ¹¹⁷ (4.277)			

of 180–307. Overall, The RMSF result shows that the D6 complex is more stable than the amoxicillin structure. Lastly, the number of hydrogen bonds of each protein is calculated during the simulation, where the increase of hydrogen bonds

was observed for D6 compound, while amoxicillin formed less hydrogen bond (Fig. 7). This result further demonstrates the stability of the D6 complex.

Fig. 4 Predicted pose from docking analysis showed the binding orientation map of important amino acids for compound D6, showing hydrogen bond interaction (green color), including π - π stacking (pink color)

Table 4 Binding affinities (Kcal/mol) of all compounds

Name of compound	Binding affinity Kcal/mol
D1	-7.11
D2	-7.25
D3	-6.88
D4	-8.04
D5	-7.04
D6	-8.24
D7	-7.52
D8	-5.31

ADME/T analysis

In silico ADME/T analysis is performed to investigate whether the designed Schiff bases produce any toxicity after

administration in the body or show good pharmacokinetic profile. On this purpose, admetSAR server has been utilized, which calculates the different pharmacokinetic and pharmacodynamic parameters, human intestinal absorption, (Egan et al. 2000) blood-brain barrier penetration, cytochrome P450 inhibition, (Susnow and Dixon 2003) human ether-a-go-go-related genes inhibition, acute oral toxicity, rat acute toxicity. Table 5 shows the results predicted from admetSAR, where positive values indicate high probabilities. All compounds showed good pharmacokinetic profiles in human intestinal absorption, also non inhibitors of P-glycoprotein and CYP450 2C9. The analysis also highlighted that all compounds were the weak inhibitors the human ether-a-go-go-related gene. All compounds show similar oral toxicity profile, while D6 shows highest LD₅₀ value in rat acute toxicity, therefore suggesting less toxic than the other compounds.

Fig. 5 The time series of the RMSD of backbone atoms (C, C α , and N) for a) protein and b) Ligand for each docked complex. Here, red and blue lines denote Amoxicillin and D6 complex respectively

Fig. 6 The structural changes of protein by means of **a** Solvent accessible surface area (SASA), **b** Radius of Gyration and **c** Root means square fluctuations (RMSF) analysis. Here, red and blue lines denote Amoxicillin and D6 complex respectively

Fig. 7 Total number of hydrogen bonds formed within the protein state during the simulation. Here, red and blue lines denote Amoxicillin and D6 complex respectively

Table 5 Selected pharmacokinetic parameter of amoxicillin and designed drugs

Parameters	D1	D2	D3	D4	D5	D6	D7	D8
Blood–brain barrier	+ (0.85)	+ (0.83)	+ (0.83)	+ (0.78)	+ (0.80)	+ (0.84)	+ (0.79)	+ (0.81)
Human intestinal absorption	+ (0.98)	+ (0.98)	+ (0.98)	+ (0.98)	+ (0.98)	+ (0.98)	+ (0.98)	+ (0.98)
P-glycoprotein Inhibitor	NI (0.89)	NI (0.58)	NI (0.58)	NI (0.69)	NI (0.59)	NI (0.68)	NI (0.78)	NI (0.69)
CYP450 2C9 inhibitor	NI (0.87)	NI (0.86)	NI (0.86)	NI (0.77)	NI (0.77)	NI (0.78)	NI (0.77)	NI (0.77)
Human ether-a-go-go-related gene	WI (0.88)	WI (0.90)	WI (0.90)	WI (0.84)	WI (0.89)	WI (0.91)	WI (0.85)	WI (0.90)
Acute oral toxicity	III (0.53)	III (0.49)	III (0.49)	III (0.49)	III (0.50)	III (0.50)	III (0.51)	III (0.51)
Rat acute toxicity (LD50, mol/kg)	2.63	2.67	2.75	2.68	2.71	2.74	2.68	2.70

Conclusion

In this work, eight new metal based tetradentate N_2O_2 Schiff base ligands are designed and has been investigated for the exploring of molecular interactions between the β -lactamase of *M. tuberculosis*. The DFT analysis shows that the addition of halogens increased the dipole moment as well as the reactivity of the Ni(II) coordinating Schiff ligands. Furthermore, the molecular docking analysis reveals their strong molecular interactions with active residues of binding pocket of β -lactamase, where Ile117, Pro290, Arg236 and Thr253 residues are found to play important role in the ligand binding. The best binding ligand D6 shows the greater stability and affinity to β -lactamase during the molecular dynamics simulation, in comparison to the control drug amoxicillin. These results further confirm the ability of Schiff base complex to bind simultaneously to the active sites of β -lactamase and pave the way to the further researches in the rational design of this series of compounds.

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