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Design, pharmacokinetic profiling, and assessment of kinetic and thermodynamic stability of novel anti-*Salmonella typhi* imidazole analogues

John Philip Ameji^{1*} , Adamu Uzairu², Gideon Adamu Shallangwa² and Sani Uba²

Abstract

Background Typhoid fever, a disease caused by a gram negative bacterial species known as *Salmonella typhi*, constitutes a significant cause of morbidity and mortality, especially in developing nations of the world. Antibiotic therapy is the major treatment option currently but the rising incidences of resistance to existing antibiotics has necessitated the search for newer ones. The aim of this study is to apply in silico techniques to design highly potent novel imidazole-based drug candidates that strongly antagonize a cell invasion protein (SipA) of *Salmonella typhi*.

Methods In this study, a set of anti-*Salmonella typhi* imidazole analogues were subjected to molecular docking against an important cell invasion protein of the bacterium known as SipA using PyRx graphical user interface of AutoDock Vina software. The best ligand was selected as template for designing more potent analogues. Drug-likeness, pharmacokinetic and toxicity profiles of the designed ligands were assessed through the use of Swiss ADME online tool and Osiris DataWarrior V5.5.0 chemo-informatics program. Kinetic and thermodynamic stabilities of the ligands were ascertained via Density Functional Theory's Becke-3-parameter Lee-Yang-Parr hybrid functional and 6-31G** basis set-based quantum chemical calculations.

Results The bioactive ligands were found to possess Gibb's free binding energy (ΔG) values ranging from -5.4 to -6.7 kcal/mol against the active sites of the protease. Ligand 13 with $\Delta G = -6.7$ kcal/mol was used as template to design more potent analogues; B-1 and B-2 with ΔG value of -7.8 kcal/mol and -7.6 kcal/mol, respectively, against the protein target. When compared with ciprofloxacin used as control with ΔG value of -6.8 kcal/mol, the designed ligands were found to be more potent. Furthermore, drug-likeness and ADMET profiling of the designed ligands revealed that they have excellent oral bioavailability and sound pharmacokinetic profiles. In addition, quantum chemical calculations revealed HOMO-LUMO energy gap of 3.58 eV and 3.45 eV; and global electrophilicity index of 4.95 eV and 4.79 eV for B-1 and B-2 ligands, respectively, indicative of their favorable kinetic and thermodynamic stabilities.

Conclusions It is envisaged that the findings of this study would provide an excellent blueprint for developing novel antibiotics against multidrug resistant *Salmonella typhi*.

Keywords Kinetic stability, Thermodynamic stability, *Salmonella typhi*, SipA, Imidazole

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Background

Typhoid fever is a systemic infection caused by *Salmonella typhi*, transmitted through the fecal–oral route (Klemm et al. 2018). The primary symptoms of this disease include prolonged high fever, headache, and malaise. If left untreated for a long time, the infection may degenerate to altered mental states, ileus, gastrointestinal bleeding, intestinal perforation, septic shock, and death (Basnyat et al. 2021; Birkhold et al. 2020). Typhoid fever is prevalent in South Asia, Southeast Asia, and sub-Saharan Africa where access to clean water, sanitation, and quality health care delivery is abysmally poor. It is a major cause of morbidity and mortality, especially among children and young adults globally with an estimated 14.3 million infections and over 135,000 deaths annually (GBD 2019; GBD 2016; Kim et al. 2019; Mogsale et al. 2014). Although, antibiotics such as chloramphenicol, ampicillin and cotrimoxazole, fluoroquinolones, third-generation cephalosporins and azithromycin have been currently recommended by the World Health Organization for the treatment of Typhoid fever infection, but the rising cases of resistance by *Salmonella typhi* to these drugs pose a serious threat to public health (Browne et al. 2020), necessitating the search for newer drug candidates in the antibiotic drug development pipeline.

In silico techniques such as structure-based drug design (SBDD), pharmacokinetic profiling, and quantum chemical calculations provide a safer, faster, and economical avenues in modern drug discovery. SBDD involves the use of molecular docking simulation to investigate the interaction of small molecules with the active sites of a protein target (macromolecule) whose 3D structure is known. Through the application of SBDD technique, the orientation of the therapeutic compound (pose) within the active sites of the macromolecule, its geometry conformation, and scoring, usually in form of Gibbs's free energy of binding (ΔG) are ascertained (Behl et al. 2021; Hussain et al. 2021). Also, In silico Pharmacokinetic profiling deals with the use computer aided techniques to determine the fate of a drug candidate in the biological system with respect to its absorption (A), distribution (D), metabolism (M), excretion (E), and toxicity (T) (Daina et al. 2017). This technique is used in modern pharmaceutical research to reduce attrition rates in drug development due to poor pharmacokinetics (Daoud et al. 2021). Furthermore, the safety and efficacy of a drug are grossly influenced by its ability to withstand degradation for a reasonable time within and outside biological system in order for it to optimally exert its therapeutic roles. Thus, ensuring the chemical and physical stability of therapeutic compounds is paramount to guarantee their safety and quality (Padmaja et al. 2009). The

kinetic and thermodynamic stability of molecules are influenced by the energies of their frontier orbitals, which could be determined via quantum chemical calculations (Khalid et al. 2017; Ruiz-Morales, 2002; Senosiain et al. 2005).

Imidazole heterocycle has found immense applications over the last decades owing to its wide range of pharmacological properties making them promising drug candidates. This class of chemical compounds has been reported to possess antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, and antidiabetic properties. Imidazole scaffolds are essential components of standard pharmaceuticals such as Miconazole, Econazole, Ketoconazole, Clotrimazole, Ornidazole, Azomycin, Oxiconazole, and Clonidine (Chen et al. 2018a, b; Hu et al. 2018; Rossi and Ciofalo 2020; Serdaliyeva et al. 2022; Wang et al. 2019). The antibacterial properties of nitroimidazole scaffold is based on its ability to penetrate the cell of the organisms via passive diffusion where it experiences reduction reaction leading to the formation of nitro radical anion which eventually oxidizes the bacteria's DNA leading to breakage of DNA strand and cell death (Edwards et al. 1993). Also, imidazoles inhibit flavohemoglobin, a protein in bacteria that metabolizes nitric oxide (NO) to nitrates and prevent NO-mediated damage, growth inhibition, and death (Helmick et al. 2005). In another study, imidazole scaffold was found to inhibit enoyl acyl carrier protein reductase (FabI), an enzyme involved in the synthesis of bacterial fatty acids (Heerding et al. 2001).

In search of novel antibiotic drug candidates that could curb the threat to public health posed by rising incidences of multidrug resistant *Salmonella typhi*, some in silico investigations targeting different enzymes of the bacterium has been conducted recently (Akter et al. 2022; Anebi et al. 2021; Arunkumar et al. 2022; Bakthavatchalam et al. 2017; Qadir et al. 2018; Verma et al. 2020). In this study, we are aiming at the application of in silico techniques to design highly potent, non-toxic, kinetic and thermodynamically stable novel imidazole-based inhibitors of SipA protease of *Salmonella typhi*, an effector protein of the bacterium crucial to its virulence and pathogenicity. SipA is type-3 secretion protein that enables the bacterium to survive the harsh conditions of the extracellular milieu of the small intestine of the host, due to factors such as low pH, shear stress due to mucosal secretions or blood and host defense mechanisms and subsequently invade the intestines of its host and gains entry into the tissues where it replicates rapidly and manifest varying degree of virulence (Birhanu et al. 2021, 2018; Khan and Shamim 2022). Despite the enormous antibacterial properties of imidazole-based compounds, no in silico investigation of its antibacterial properties

against *Salmonella typhi* has been carried out to the best of our knowledge.

Methods

Collection of data set

A set of thirty anti-*Salmonella typhi* imidazole derivatives was gotten from reported work (Ganguly et al. 2011). The biological activity of the ligands were expressed as Minimum Inhibitory Concentration (MIC). The 2D chemical structure and experimentally determined MIC values for each member of the data set are presented in Table 1.

Many methods abound in literature for one-pot synthesis of imidazole derivatives but are faced with drawbacks such as toxic and expensive catalysts that requires harsh reaction conditions. However, the use of green lactic acid as solvent presents an inexpensive, biodegradable, environmentally friendly approach. The green solvent (lactic acid) is easily obtainable from fermentation of carbohydrates, easy to handle, readily available, and has been reported to be used as organocatalyst in many organic reactions (Sonar et al. 2019). The reaction scheme involving the use of lactic acid as solvent for synthesis of some substituted imidazole derivative is presented in Fig. 1.

Energy minimization of the ligands

In order to obtain the most stable conformations of the ligands, their 2D chemical structures were drawn with ChemDraw Ultra 12.0 and exported unto Spartan 14 work space (www.wavefun.com) where they were subsequently optimized using Semi-empirical (pm3) method. The optimized molecules were then saved in pdb and sdf formats for further in silico analysis (Ameji et al. 2022).

Molecular Docking evaluation

Molecular Docking simulation is an in silico technique that allows accurate prediction of the strength of association between a ligand and a target macromolecule. The optimized ligands were prepared using the AutoDock Vina interface and saved as pdbqt files. The 3D crystal structure of SipA protein was retrieved from protein data bank at www.rcsb.org/pdb (PDB Code: 1Q5Z). The protein was firstly prepared on Discovery Studio

software interface where attached water molecules and heteroatoms were removed. It was further exported unto the AutoDock Vina platform where missing atoms were checked, repaired, and polar hydrogen and Kollman charges were added to the macromolecule. The prepared protein was then saved as pdbqt file formats. As a way of ascertaining the binding affinity values of the investigated imidazole analogues against SipA enzyme of *Salmonella typhi*, the bioactive ligands were docked against the active sites of the protease using the PyRx graphical user interface of AutoDock Vina software (Ameji et al. 2022).

Design of novel derivatives

In line with a major objective of this study, which is the design of highly potent imidazole-based drug candidates, the ligand with the best binding affinity (highest negative ΔG value) was selected as template molecule and subsequently subjected to pharmacophoric modifications giving rise to some new derivatives. The new derivatives were then docked against the SipA target and the analogues with better ΔG values than the template molecule were selected as the novel drug candidates to be subjected to more analysis. As a quality control measure, an approved antibiotic, ciprofloxacin was docked against SipA macromolecule and the computed binding affinity value was compared with those of the novel ligands (Ameji et al. 2022).

Drug-likeness assessment

Drug-likeness is primarily concerned with the evaluation of the oral bioavailability of therapeutic compounds. This important parameter was evaluated for the designed ligands using the Lipinski's rule of five and the Veber's rule. The former rule states that a drug-like compound must not violate any of the following indices; molecular weight ($M_w \leq 500$), number of hydrogen bond donors ($HBD \leq 5$, octanol/ water partition coefficient ($\log P \leq 5$) and number of hydrogen bond acceptors ($HBA \leq 10$). The latter rule on the other hand, states that a drug-like molecule must have number of rotatable bonds (NRB) and topological polar surface area (TPSA) that is not greater than 10 and 140 \AA^2 , respectively

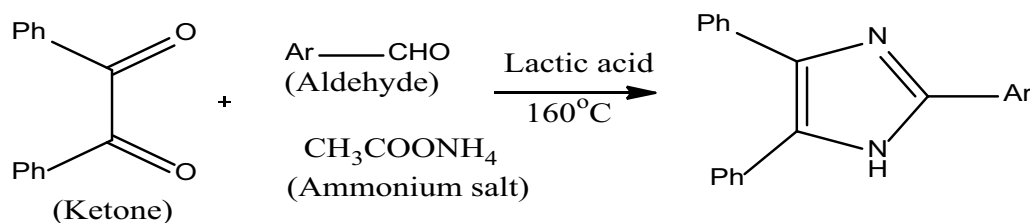
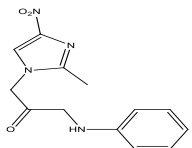
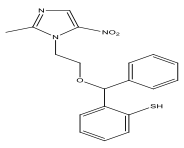
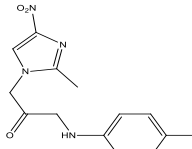
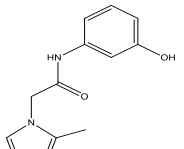
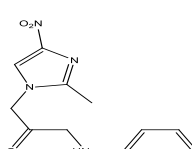
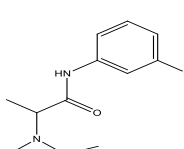
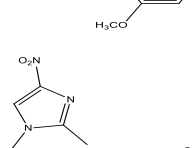
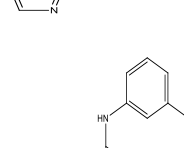
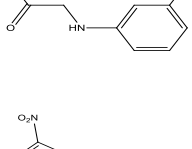
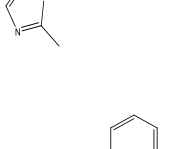
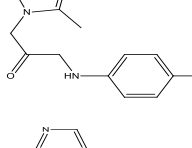
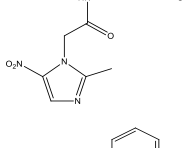
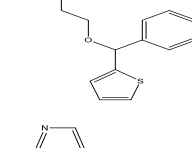
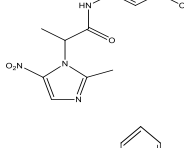
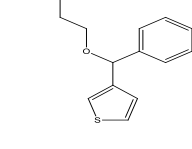


Fig. 1 General reaction scheme for the synthesis of 2,4,5-trisubstituted imidazole

Table 1 Chemical structure and experimental MIC values of the investigated compounds

S/n	Structure	MIC (µg/mL)	S/n	Structure	MIC (µg/mL)
1		400	9		100
2		200	10		100
3		400	11		100
4		200	12		200
5		200	13		50
6		200	14		100
7		200	15		50
8		400		Metronidazole	>400

(Ameji et al. 2022). The drug-likeness of the novel ligands were evaluated with the aid of SwissADME online tool at www.swissadme.ch/.

Pharmacokinetic profiling

Pharmacokinetics describes the time course of drugs and their effects in the body. It include absorption (A), distribution (D), metabolism (M), excretion (E), and toxicity (T) of drugs. The SwissADME (www.swissadme.ch/) online resource and Osiris DataWarrior V5.5.0 cheminformatics program were used to assess the ADMET profiles of the designed ligands.

Assessment of kinetic and thermodynamic stabilities

Thermodynamic stability is the stability of the lowest energy state of a system while kinetic stability is the stability of the highest energy state of a system. Ensuring the chemical and physical stability of therapeutic compounds is paramount to guarantee their safety and quality. The knowledge of the energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) give idea on stabilities of molecules (Khalid et al. 2017). The LUMO serves as electron acceptor with an associated energy expressed as electron affinity (EA), while the HOMO plays the role of electron donors and its energy is linked to ionization potential (IP). The charge transfer interaction within a molecule is explained by the HOMO–LUMO energy gap defined in Eq. 1. High HOMO–LUMO energy gap in a molecule connote low chemical reactivity and high kinetic stability. This is because, it is not energetically feasible to add electron to the high-lying LUMO by removing electrons from the low-lying HOMO (Ruiz-Morales, 2002; Senosiain et al. 2005). Molecules with HOMO–LUMO energy gap > 1.30 are generally considered to be kinetically stable (Aihara 1999).

$$\Delta E (\text{Energy gap}) = E_{\text{LUMO}} - E_{\text{HOMO}} \quad (1)$$

where E_{LUMO} and E_{HOMO} denote energy of LUMO and energy of HOMO, respectively.

An important quantum chemical descriptor of thermodynamic stability of a molecule is the global electrophilicity index (ω). ω is defined as the energy decrease that accompanies the flow of electron from HOMO to LUMO in molecules. ω is defined in Eq. 2.

$$\omega = \frac{\mu^2}{2\eta}, \quad (2)$$

where η is the global chemical hardness and μ the electronic chemical potential which describes the charge

Table 2 Binding affinity values of the imidazole analogues and R with SipA target

Molecule ID	ΔG (kcal/mol)	Molecule ID	ΔG (kcal/mol)
1	−5.5	10	−6.4
2	−5.7	11	−6.3
3	−5.4	12	−6.1
4	−5.9	13	−6.7
5	−5.5	14	−5.7
6	−6.3	15	−5.9
7	−6.2	B-1	−7.8
8	−6.4	B-2	−7.6
9	−5.8	R	−6.8

transfer within a system in the ground state. Equations 3 and 4, defines η and μ , respectively.

$$\eta = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \quad (3)$$

$$\mu = \frac{E_{\text{LUMO}} + E_{\text{HOMO}}}{2} \quad (4)$$

The higher the value of ω in a molecule, the higher its reactivity and vice versa (Senosiain et al. 2005).

The Spartan'14 software (www.wavefun.com) was used to perform quantum chemical calculations on the designed ligands and the standard antibiotics. Geometry optimization and frequency calculations were carried out using DFT alongside the B3LYP standard principle in conjunction with the split-valence 6-31G** basis function. The choice of this method is anchored on its computational efficiency and high accuracy in obtaining geometries, zero-point energy and frequencies (Halls et al. 2001; Miar et al. 2021).

Results

Identification of template molecule

Antibiotics such as quinolones and beta lactams function by binding to a target enzyme of the bacterium, disrupting its enzymatic functions leading to inactivation or death of the microbe. The result of the molecular docking investigation of the studied bioactive imidazole-based ligands and Ciprofloxacin (R) against SipA protease of *Salmonella typhi* is presented in Table 2. Potency of the ligands varies directly with the negative value of Binding affinity (ΔG). Thus, ligand 13 with ΔG value of −6.7 kcal/mol was selected as the template molecule to be used to design more potent analogues. The 3D and 2D diagrams of interaction of the ligand within the binding pocket of SipA protease are shown in Fig. 2.

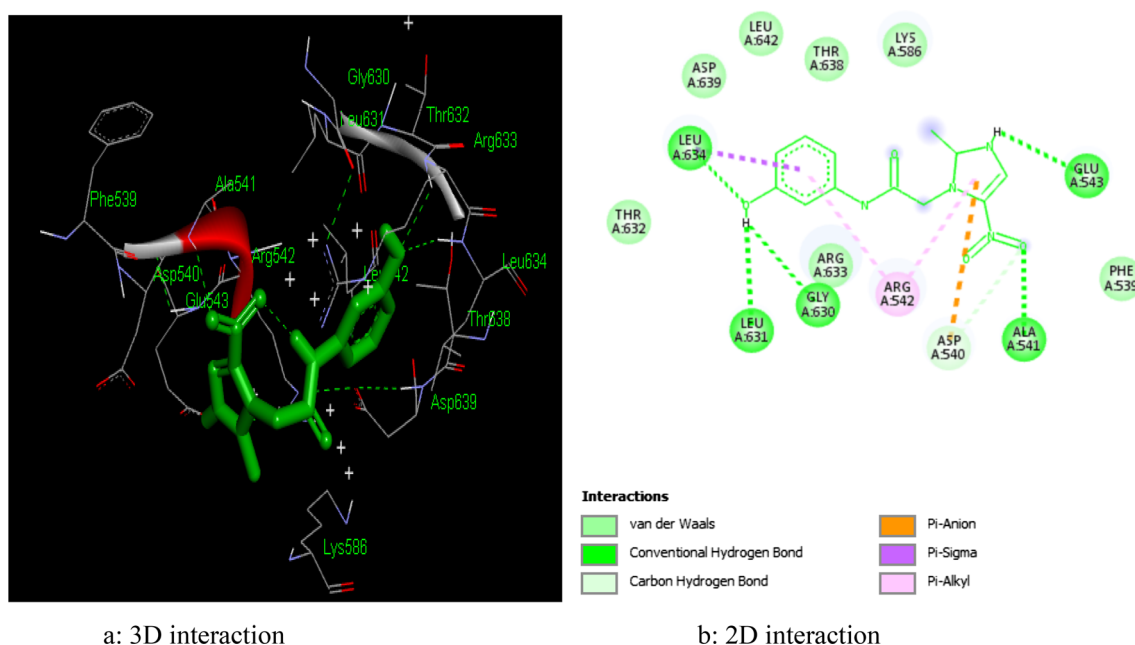


Fig. 2 3D and 2D diagram of interaction of the template molecule with SipA

Newly designed ligands

Potency of a bioactive molecule against any macromolecular target is a function of certain features within its moiety called pharmacophores. In order to obtain more potent derivatives of the template, it was subjected to pharmacophoric modifications leading to the design of ligand B-1 and B-2 with ΔG value of -7.8 kcal/mol and -7.6 kcal/mol, respectively. Figure 3 gives the 2D chemical structures of B-1, B-2 and R, while their 2D diagram of interactions with the amino acid residues of the target are presented in Fig. 4.

Drug-likeness and ADMET properties of B-1, B-2 and R

Drug-likeness and ADMET properties of a bioactive ligand are functions of certain physicochemical features of the molecule. The computed values of molecular descriptors of drug-likeness and ADMET properties of the novel ligands and R are presented in Tables 3 and 4, respectively.

Quantum chemical descriptors of B-1, B-2 and R

Electronic features of B-1, B-2 and R derived from quantum mechanical calculations are presented in Table 5. The shapes and energies of the LUMO and HOMO for the ligands are shown in Fig. 5

Discussion

SipA protein in *Salmonella typhi* plays unique roles in pathogenicity and virulence in the organism. It aids the survival of the pathogen in the intestine of the host and

enhances its penetration into relevant tissues where it create a niche for itself and unleash varying degree of virulence. Binding of bioactive ligands to this macromolecular target inhibits its enzymatic roles and consequently predisposes the bacterial species to the harsh conditions of the extracellular milieu of the small intestine of the host leading to its inactivation or death. The result of molecular docking simulation study on the bioactive imidazole analogues against the SipA target of *Salmonella typhi* is presented in Table 2. The binding affinity (ΔG) values of the ligands range from -5.4 to -6.7 kcal/mol. However, ligand 13 with the best ΔG value of -6.7 kcal/mol was selected as template molecule for designing more potent analogues. Ligand 13 whose 2D and 3D diagram of interactions with the active sites of SipA protease is shown in Fig. 2, was found to interact with the amino acid residues of the target via pi-alkyl interactions with ARG542; a pi-sigma interaction with LEU 634; a pi-anion and a Van der waals interaction with ASP 540; and five conventional hydrogen bonds with LEU 631, LEU 640, GLY 630, GLU 543, and ALA 541 amino acid residues.

Two novel ligands; B-1 and B-2 (Fig. 3) with ΔG value of -7.8 kcal/mol and -7.6 kcal/mol, respectively, against the SipA target, were designed through structural modification of the template ligand. The novel ligands were found to more potent when compared with the standard ligand, ciprofloxacin (R) with ΔG value of -6.8 kcal/mol against the target. Ligands B-1 and B-2 were found to interact with the active sites of the SipA target via similar mechanism. They both bind to the target via; pi-alkyl

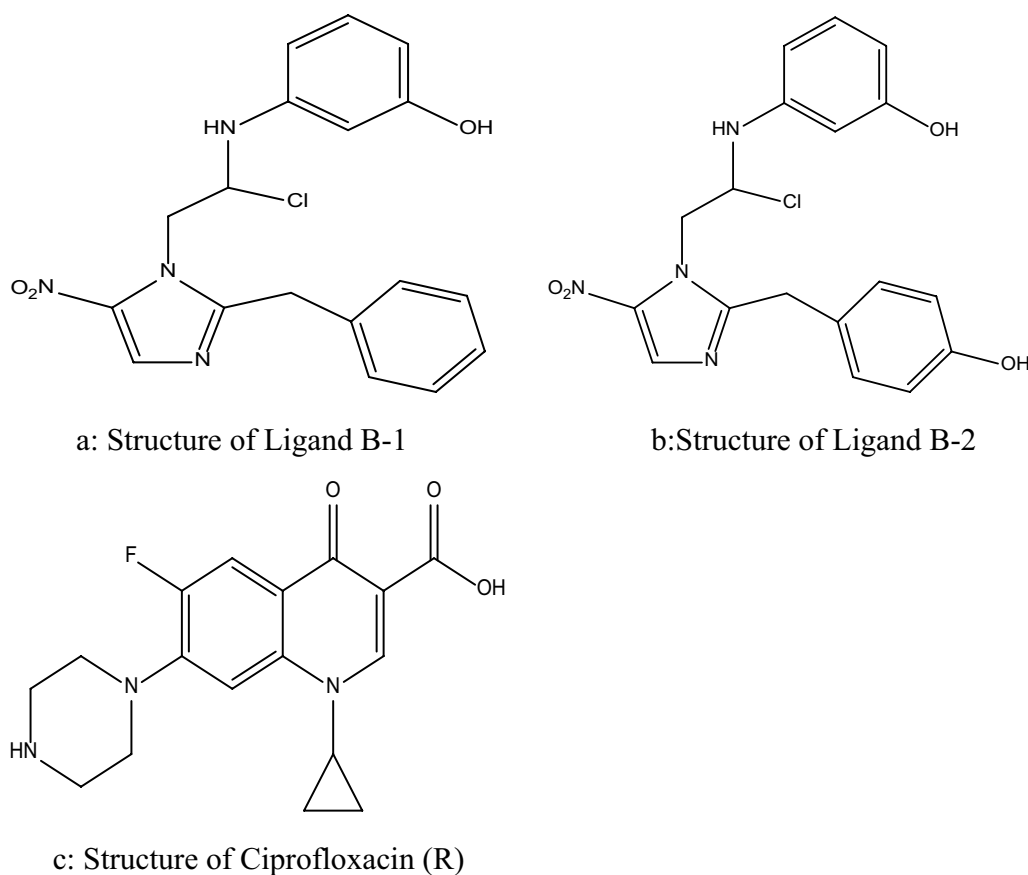


Fig. 3 2D chemical structures of the novel ligands and R. **a:** 3-((2-(2-benzyl-5-nitro-1H-imidazol-1-yl)-1-chloroethyl)amino)phenol. **b:** 3-((1-chloro-2-(2-(4-hydroxybenzyl)-5-nitro-1H-imidazol-1-yl)ethyl)amino)phenol. **c:** 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid

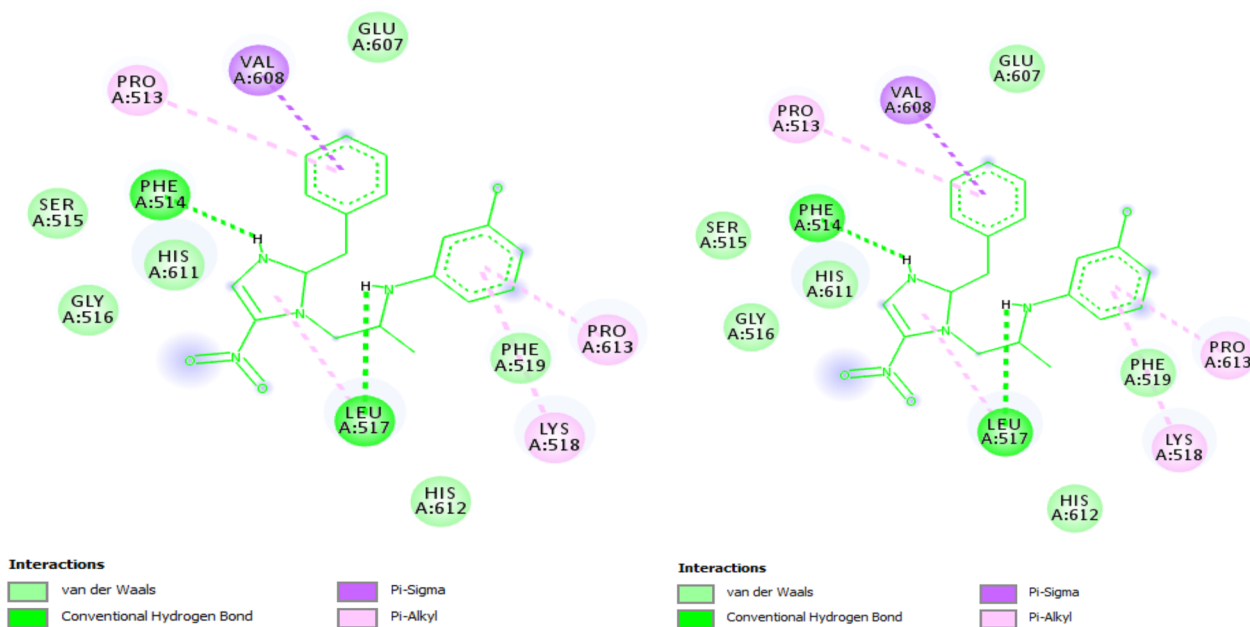
interactions with LYS 518, PRO 613 and PRO 513 amino acid side chains, a pi-sigma interaction with VAL 608, and two conventional hydrogen bonds with LEU 517 and PHE 514 (Fig. 4a,b). Also, the standard ligand (R) binds to the target protease (Fig. 3c) through; a pi-alkyl interaction with LYS 551; a pi-sigma with THR 544; and a conventional hydrogen bond with SER 526.

Drug-likeness defines the oral bioavailability of bioactive compounds. This parameter plays a significant role in drug discovery and development because substantial number of drugs are administered through the oral route. The physicochemical properties of B-1 and B-2 ligands that could be used to describe their drug-likeness are presented in Table 3. The result shows that the ligands, like R obey both the Lipinski's and Veber's rules, an indication of their excellent oral bioavailability.

Pharmacokinetic and toxicity profiling of therapeutic molecules with reference to their absorption, distribution, metabolism, excretion, and toxicity (ADMET) at early stage of drug discovery is a crucial component of modern drug design owing to the facts that these

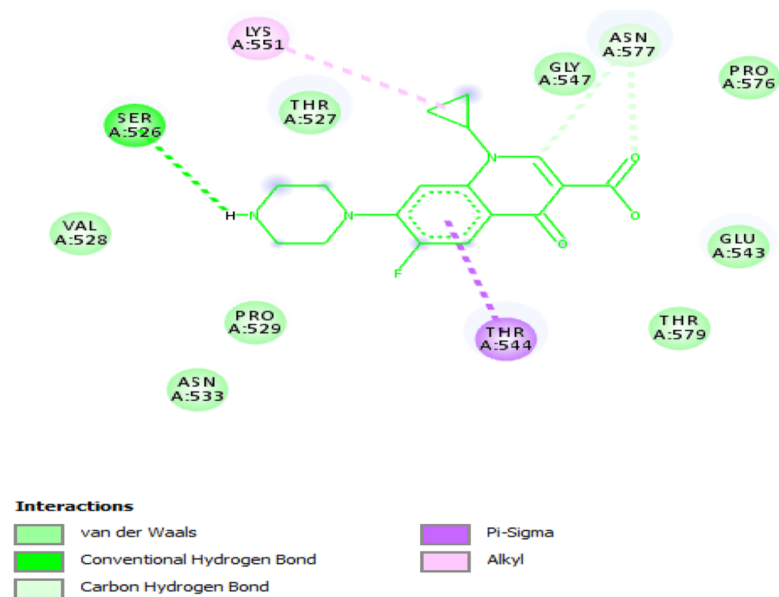
properties play pivotal roles in the success or failure rates of drug candidates. Pharmacokinetic profiles of B-1 and B-2 ligands presented in Table 4 show that they possess good gastrointestinal absorption just like the standard ligand, R.

Also, aqueous solubility deals with the maximum amount of a substance that dissolves completely in water at a given temperature and pressure. It is an essential parameter for consideration in modern drug design since drugs must be reasonably soluble in order to exert significant pharmacological response (Birch et al. 2019; Oja et al. 2022). Poor aqueous solubility has been pointed out to be responsible for slow absorption of drugs, leading to poor bioavailability and gastrointestinal mucosal toxicity (Shah et al. 2017). Ligands R, B-1, B-2, with estimated solubility (ESOL) value of 15.7 mg/ml, 0.006 mg/ml, and 0.009 mg/ml, respectively, were found to exhibit moderate to high solubility (Table 4). Likewise, Blood Brain Barrier (BBB) is an endothelial cell layer of the brain that restrict entry of toxins and xenobiotic into the brain (Alsenan et al. 2021; Tong et al. 2022; Wang et al. 2019).



a: ligand B-1 in the binding pocket of the target

b: ligand B-2 in the binding pocket of the target



c: R in the binding pocket of the target

Fig. 4 2D diagram of interaction of the designed ligands and R with amino acid residues of SipA target

The result in Table 4 shows that all the ligands possess no BBB permeating potentials.

Furthermore, P-glycoprotein (P-gp) are membrane transporters that protects the body from harmful substances by extruding via efflux action, substrate

xenobiotic absorbed in the intestines back to the lumen, removing drugs from the kidneys and liver into the urine and bile, respectively, and maintaining integrity of BBB by limiting cellular uptake of its substrates from blood circulation into the brain (Chen et al. 2018a, b; Miyake

Table 3 Drug-likeness Properties of B-1, B-2 and R

Ligand Rule	B-1	B-2	R
Lipinski's	yes	yes	yes
HBA	4	5	5
HBD	2	3	2
MW (g mol ⁻¹)	372.8	388.8	331.34
cLogP _(o/w)	2.45	2.04	1.10
Veber's	Yes	yes	yes
NRB	7	7	3
TPSA (Å ²)	95.9	116.13	74.54

HBA hydrogen bond acceptor, HBD hydrogen bond donor, Mw molecular weight, cLogP consensus octanol water partition coefficient, NRB number of rotatable bond, TPSA topological polar surface area

et al. 2021). The designed ligands, unlike R were found to be non-substrate of P-gp and are such could be unperturbed by the efflux action of P-gp.

Additionally, the ligands were screened against cytochrome P450 (CYP45) which performs the role of metabolism and biotransformation of drugs in the biological system. The result (Table 4) revealed that ligands B-1 and B-2, unlike R are inhibitors of all the five isoforms of CYP45 namely; CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 and as such may not be easily metabolized by these proteins. Toxicity evaluation of the ligands revealed that B-1 and B-2 are neither tumorigenic nor possess irritating effect. However, the two ligands could be mutagenic and pose threat to the reproductive system.

Stability of therapeutic compounds is necessary in order to guarantee their safety and efficacy. Drugs must exhibit reasonable level of stability for it to withstand unwanted physical and chemical degradation that affects its safety and pharmacological response. The stability of

molecules is governed by the energies of their frontier orbitals (HOMO and LUMO energies). Thermodynamic stability refers to the stability of the lowest energy state of a system while kinetic stability is the stability of the highest energy state of a system. The former is governed by the quantum chemical descriptor known as global electrophilicity index (ω) while the latter is governed by the HOMO/LUMO energy gap. Figure 5 presents the HOMO and LUMO regions of the designed ligands and R. The energy gap value of 3.58 eV, 3.45 eV, and 4.38 eV computed for B-1, B-2, and R, respectively (Table 5) are > 1.30 eV. Thus, the novel ligands, like R are kinetically stable. Likewise, the ω value of 4.95 eV, 4.75 eV, and 2.70 eV were computed for ligands B-1, B-2, and R, respectively (Table 5). The low values of this descriptor is an indication of high thermodynamic stability of the ligands.

Summarily, this study is an in silico research and as such the aforementioned research findings will require further in vitro and in vivo validations.

Conclusions

The rising cases of drug resistant strains of *Salmonella typhi* has necessitated the search for newer drug candidates in the drug development pipeline. In search for novel antibiotic drugs against this bacterium, a set of bioactive imidazole analogues were subjected to molecular docking-based virtual screening against a cell invasion protein, SipA of the organism using the PyRx graphical user interface of AutoDock Vina software. The ligands were found to bind to the target sites of the macromolecular target with binding affinity (ΔG) values that ranges from -5.4 to -6.7 kcal/mol. Ligand 13 with the best dock score of -6.7 kcal/mol was used as template to design more potent analogues; B-1 and B-2 with ΔG

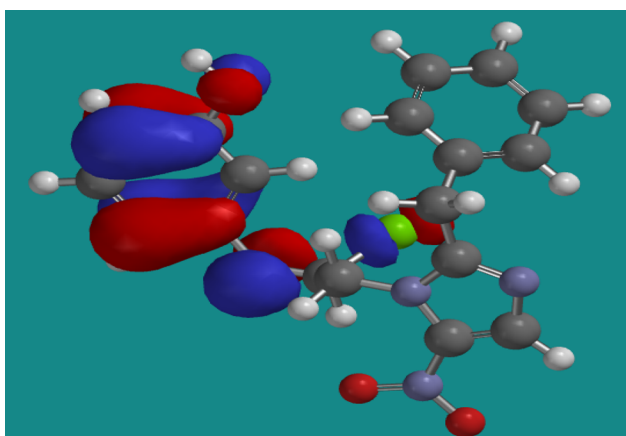
Table 4 ADMET profiles of B-1, B-2 and R

Ligand	CYP45 inhibitor	ESOL (mg/ml)	GIA	P-gp ⁺	BBB	MUT	TUM	IR	RE
B-1	Yes	0.006	High	No	No	Yes	None	None	Yes
B-2	Yes	0.009	High	No	No	Yes	None	None	Yes
R	No	15.7	High	Yes	No	None	None	None	None

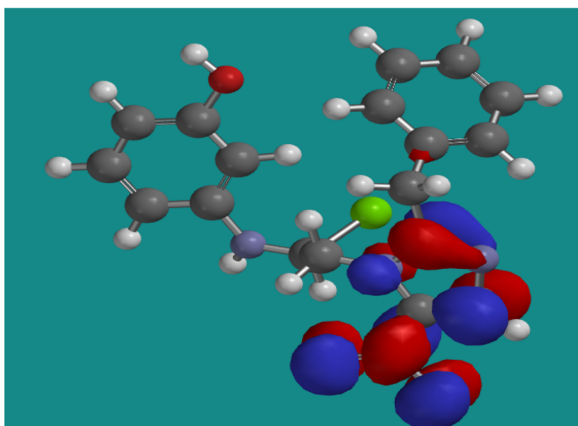
ESOL estimated solubility, GIA gastrointestinal absorption, BBB blood brain barrier penetration, P-gp⁺ P-glycoprotein substrate, MU mutagenicity, TUM tumorigenic, IR irritating effect, RE reproductive effect

Table 5 Electronic properties of B-1, B-2, and R

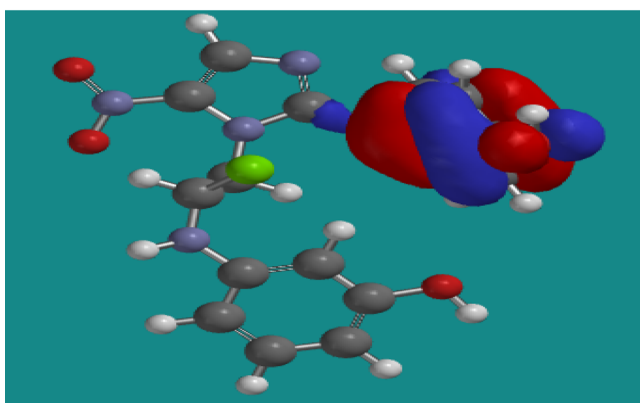
Ligand	HOMO (eV)	LUMO (eV)	ΔE (eV)	μ (eV)	η (eV)	ω (eV)
B-1	-6.00	-2.42	3.58	-4.21	1.79	4.95
B-2	-5.86	-2.41	3.45	-4.14	1.73	4.79
R	-5.63	-1.25	4.38	-3.44	2.19	2.70



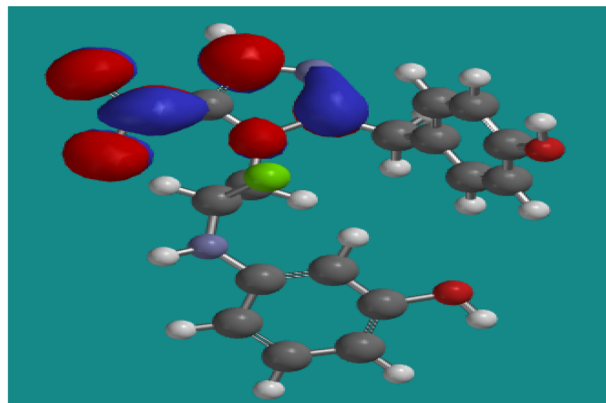
Ligand B-1: HOMO (-6.00 eV)



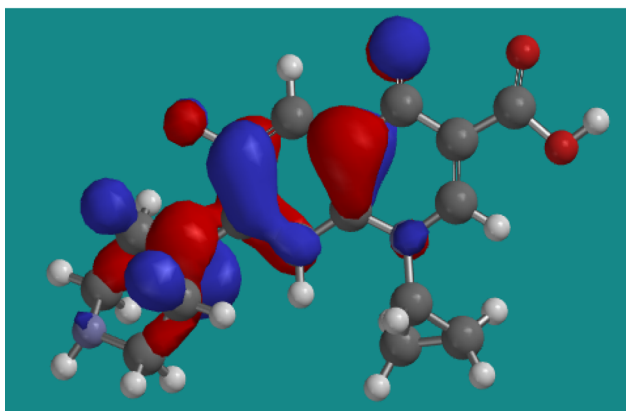
LUMO (-2.42 eV)



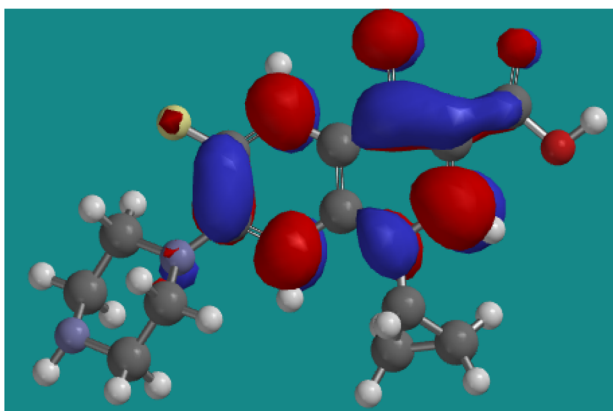
Ligand B-2: HOMO (-5.86 eV)



LUMO (-2.41 eV)



Ligand R: HOMO (-5.63 eV)



LUMO (E= -1.25 eV)

Fig. 5 The shapes and energy of the Frontier orbitals of the designed ligands and R

value of -7.8 and -7.6 kcal/mol, respectively. When compared with a standard drug, ciprofloxacin (ΔG value of -6.8 kcal/mol) used as control, the designed ligands were found to be more potent. Ligands B-1 and B-2

were found to obey both the Lipinski's rule of five and Veber's rule, an indication of their positive drug-likeness. Also, ADMET profiling of the designed ligands reveals their excellent pharmacokinetic and toxicity profiles.

Furthermore, DFT-based quantum chemical calculation revealed an appreciable kinetic and thermodynamic stability of the ligands. Further in vivo and in vitro investigations of these newly designed ligands may lead to discovery of novel antibiotics that could curb the rising cases of drug resistance in *Salmonella typhi*.

Abbreviations

SipA	Salmonella invasion protein A
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
ADMET	Absorption, distribution, metabolism, excretion, toxicity
SBDD	Structure-based drug design
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
Mw	Molecular weight
cLogP	Consensus octanol water partition coefficient
NRB	Number of rotatable bond
TPSA	Topological polar surface area
ESOL	Estimated solubility
GIA	Gastrointestinal absorption
BBB	Blood brain barrier penetration
P-gp ⁺	P-glycoprotein substrate

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Author contributions

AU outlined and designed the research work. GAS and SU analyzed and supervised the study. APJ handled the computational chemistry software and drafted the manuscript. In addition, all authors read and approved the manuscript.

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Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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