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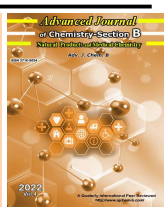

Original Research Article

Molecular Docking Study and Insilico Design of Novel Drug Candidates against Salmonella typhi

John Philip Ameji[1]*, Adamu Uzairu[2], Adamu Gideon Shallangwa[2], Sani Uba[2]
[1]*Department of Chemistry, Federal University Lokoja, P.M.B., 1154, Lokoja, Kogi State, Nigeria*
[2]*Department of Chemistry, Ahmadu Bello University, P.M.B. 1044, Zaria, Kaduna State Nigeria*

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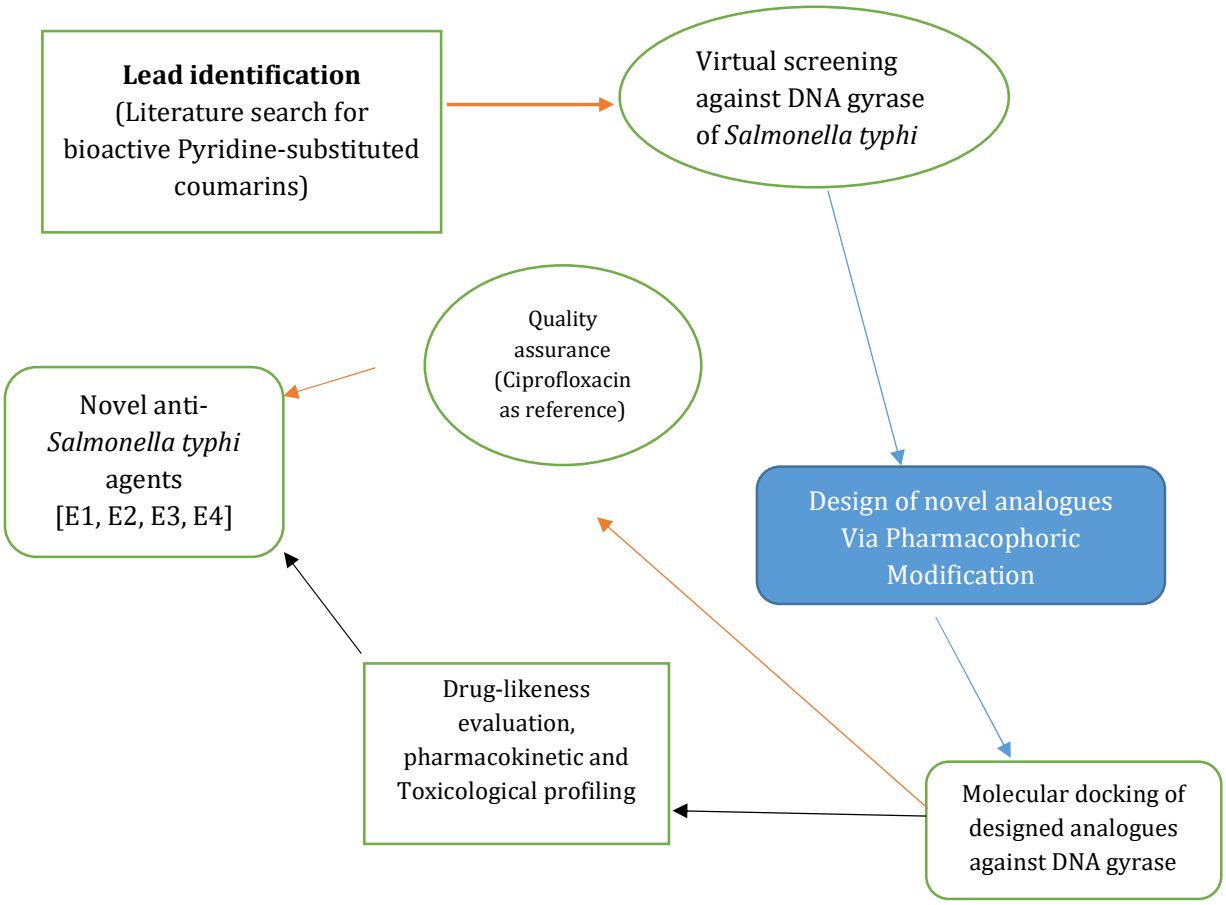
ABSTRACT

Typhoid fever, a disease caused by a Gram-negative bacterium known as Salmonella typhi constitutes a significant cause of morbidity and mortality, especially in developing nations. The rising cases of resistance to existing antibiotics by this bacterium have necessitated the search for the novel drug candidates. In this study, a data set of some anti-Salmonella typhi pyridine-substituted coumarins were subjected to Molecular Docking-based Virtual Screening against the active sites of DNA gyrase of the bacterium using EasyDock Vina 2.0 of AutoDock Vina software. Prior to the molecular docking calculation, the structures of the compounds were optimized using the DFT method of Spartan 14 software to obtain their minimum energy conformations. The outcome of the Virtual Screening led to the selection of compounds 12, 13, and 15 as template molecules for the design of more potent analogues because they bind better to the active sites of DNA gyrase target with binding affinity values (ΔG) of -9.6 kcal/mol, -9.5 kcal/mol and -9.6 kcal/mol, respectively. Subsequently, the template molecules were subjected to structural modifications leading to the design of more potent analogues with ΔG values ranging from -9.9 kcal/mol to -10.6 kcal/mol against DNA gyrase target. Furthermore, insilico drug-likeness and ADMET evaluation of the designed ligands revealed that they possess good oral bioavailability and positive pharmacokinetic profiles. It is hoped that the findings of this research would provide an excellent template for the development of novel drugs that could curb the alarming rate of resistance to existing antibiotics by Salmonella typhi.

* Corresponding author: John Philip Ameji
✉ E-mail: ameji4real55@gmail.com

GRAPHICAL ABSTRACT



1. Introduction

Typhoid fever is an infectious disease caused by *Salmonella typhi*. Some of the clinical manifestations of this disease include high body temperature, headache, body pains, lethargy, cough, and indigestion [1]. Prevalent in developing nations, the global annual mortality, and morbidity rates of typhoid fever was estimated at 128 000–161 000 and 11–21 million, respectively [2, 3]. Major predisposing factors to this contagion include poor sanitation and lack of access to portable water supply [4,5]. Although treatment of typhoid fever is via the use of antibiotics by the infested host, but the rising incidences of resistance to the existing antibiotics therapies portends great danger to public health [6,7]. Thus, the need for novel antibiotic drug candidates in the drug development pipeline is more urgent than ever. Conventional drug development is confronted with the bottle necks of lengthy time and huge financial resources. However, the application of Insilico techniques in modern drug design has remedied these twin challenges tremendously thanks to the advances in computing technologies.

Insilico drug design techniques are modern drug design strategies involving the use of computational methods to discover and design novel drugs as against the trial and error approaches that characterizes the traditional methods [8]. The major aim of Insilico methods is to complement experimental methods by

bringing the best drug-like compounds to the experimental testing thereby reducing costs and late stage attrition [9,10]. The Insilico techniques adopted in this work are the Structure-Based Drug Design (SBDD), pharmacokinetic, and toxicity profiling.

In SBDD, the three-dimensional configuration of the target macromolecule is known, and following molecular docking simulation studies, the binding affinities of tested compounds to the active sites of the target are calculated, paving way for the design of the novel therapeutic molecules with better binding to the target protein [11-13].

Molecular docking involves the use of automated computer algorithm to ascertain the binding interaction of a small molecule (ligand) within the active site of a protein target (macromolecule). Through this technique, the orientation of the compound (pose), its geometry conformation, and scoring usually in form of free energy of binding are determined [14,15]. This simulation technique largely utilizes an enlarged equation that input entropic factors into the molecular mechanics models. The binding affinities between the ligands and target protein are measured as free energy of binding (ΔG). The energy variables that constitutes ΔG scoring function is shown in Equation 1.

$$\Delta G = \Delta G_V + \beta 1 \Delta G_H + \beta 2 \Delta G_E + \beta 3 \Delta G_C + \beta 4 \Delta G_T + \beta 5 \Delta G_S + \beta 6 T \Delta S_T \quad (1)$$

Where, $\beta 3\Delta G_C$, ΔG_V , $\beta 1\Delta G_H$, and $\beta 2\Delta G_E$ are ΔG terms for conformational strain penalty, Van der Waals, hydrogen bonding, and electrostatic interactions, respectively. The restriction of internal rotors, global rotation, and translation are depicted by the $\beta 4\Delta G_T$ term, while $\beta 5\Delta G_S$ represents the desolvation penalty associated with binding. The entropic term, ΔST added to the equation is based on the rotatable torsion count which is a constant when poses of the same ligand are considered. Likewise, T is the temperature in Kelvin, while β1- β6 are ligands and biomolecules parameter coefficients [16]. The docking of the ligands to the active sites of the receptor using Autodock Vina enables allocation of scores to the molecules through the Autodock Vina scoring algorithm. Furthermore, the fate of therapeutic compounds in the biological system with respect to their absorption (A), distribution (D), metabolism (M), excretion (E), and toxicity (T) is ascertained through the evaluation of their ADMET or Pharmacokinetic and Toxicity profiles [17]. The application of insilico ADMET profiling at earlier stages of drug discovery programs help to lower possible attrition rates due to the poor pharmacokinetic and toxicity profiles of drug candidates [18].

An essential macromolecular target in *Salmonella typhi* by antibiotics such as the quinolones is its DNA gyrase. This macromolecule plays a vital role during replication in *Salmonella typhi* because it introduces the negative super helical twists into the bacterium's chromosomes and maintains a particular level of supercoiling [19,20]. Antibiotics such as quinolones that target DNA gyrase of *Salmonella typhi* bind to the protein target and inhibit the DNA synthesis in the organism leading to rapid cell death [21,22]. The fact that this enzyme is crucial to bacteria existence but absent in higher eukaryotes makes it an attractive target of antibacterial drugs [23].

In a bid to discover the novel drug candidates for the treatment of typhoid fever, some *insilico* investigations have been reported on ligands targeting DNA gyrase of *Salmonella typhi* [24-27]. Despite the significant antibacterial activities of Pyridine-substituted coumarins against Salmonella typhi, no attempt has been made to improve its structures for enhanced pharmacological properties. In this research, it is aimed to Insilico design of pyridine-substituted coumarins based on the novel inhibitors of DNA gyrase of *Salmonella typhi* with excellent potencies, outstanding pharmacokinetic profiles, and unique mechanisms of actions. The choice of pyridine-substituted coumarins as scaffold in this study is anchored on the fact that it forms an

important category of heterocyclic molecules with profound biological activities against *Salmonella typhi* [28].

Materials and Methods

Materials

The materials used for this research work include Dell computer system (Intel ® Core i3-6100U CPU Dual with 2.30 GHz processor and a RAM size of 12 GB) operated on Microsoft windows 8.1 Ultimate Operating System, ChemDraw Ultra 12, Spartan 14 V 1.1.2 software, Discovery Studio Visualizer V. 16.1.0, EasyDock Vina 2.0 graphical user interface of AutoDock 4.3 program, DataWarrior v.4.2.2 chemo-informatics tool, and SwissADME online tools.

Methods

Data Collection and Geometry optimization

A data set of twenty-five pyridine-substituted coumarins with established activities against *Salmonella typhi* were obtained from reported work of Lad *et al*. [28]. The molecules were then subjected to energy minimization using DFT (B3LYP/6-31G** basis set) method of Spartan 14 computational chemistry software (www. wavef un. com) to obtain their minimum energy conformations. The geometry-optimized structures of the compounds were then saved in PDB and Sdf file formats for the subsequent analysis. The 2D chemical structures and experimentally determined anti-*Salmonella typhi* properties of the investigated bioactive compounds are presented in Table 1.

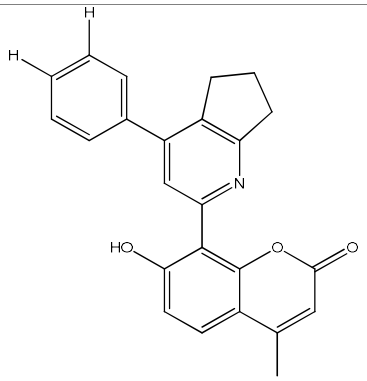
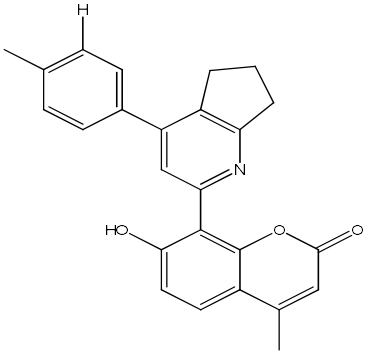
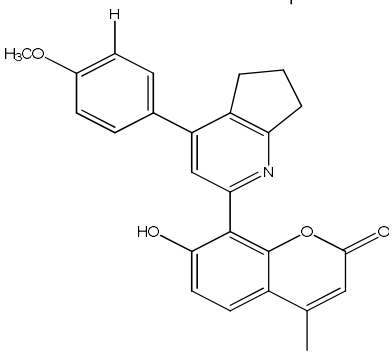
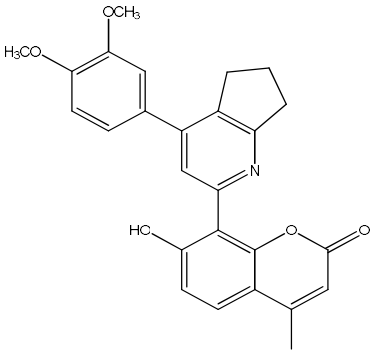
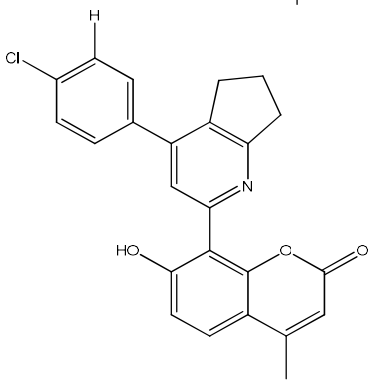
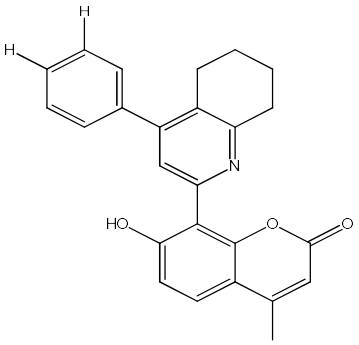
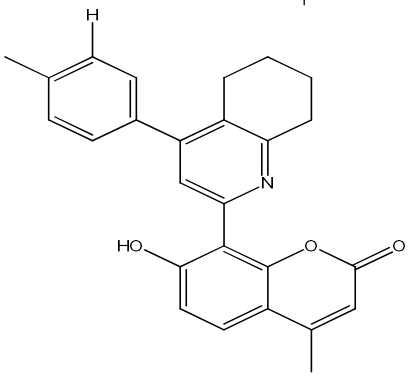
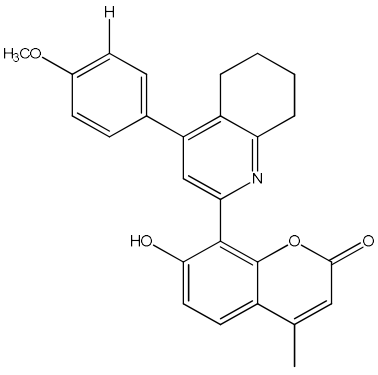
Virtual Screening Using Molecular Docking Technique

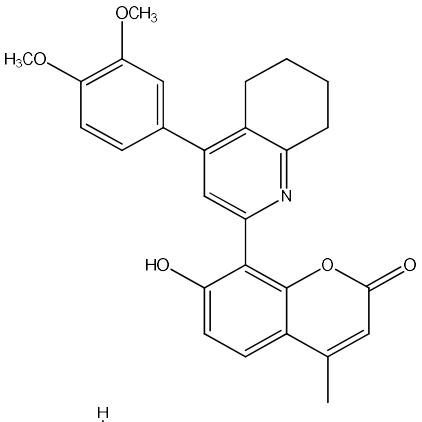
A crucial indicator of a potent molecule is its ability to bind effectively to a target macromolecule (protein target). In this study, the binding affinities of the pyridine-substituted coumarins (ligands) to the active sites of DNA gyrase target were investigated using Molecular Docking technique. Prior to the molecular docking calculation, the optimized ligands were prepared on AutoDock Vina interface and saved in pdbqt file formats. The crystal structure of DNA gyrase (macromolecule) was obtained from protein data bank (www. rcsb. org/pdb) with PDB code of 5ztj and exported unto the Discovery Studio 2016 interface where attached ligands, water molecules, and heteroatoms were removed. The macromolecule was subsequently exported unto the AutoDock Vina interface, where it was further processed via the addition of polar hydrogens and Kollman charges in addition to check and repair its missing atoms. Docking calculations were performed on the prepared protein target and the ligands using the EasyDock Vina 2.0, a graphical user interface of AutoDock Vina software. The 3D and 2D interactions of the ligands and the target macromolecule were visualized using the Discovery Studio 2016 [29-31].

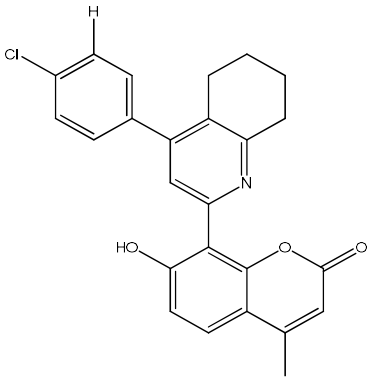
Design of New Ligands

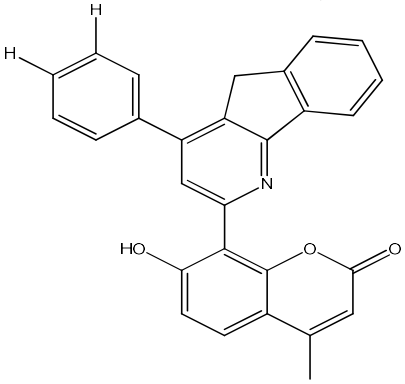
In view of the crucial roles DNA gyrase plays in *Salmonella typhi*, its inhibition disrupts DNA synthesis in bacterial species leading to cell death [32,33]. A major objective of this study is to design the novel analogues of the studied compounds with enhanced potencies. In pursuant of this, members of the lead compounds with the best dock scores were selected as templates for designing more potent analogues taking into cognizance their pharmacophores. The templates molecules were structurally modified leading to the design of more potent derivatives. The designed compounds were further docked against the active sites of DNA gyrase using the aforementioned procedures. The compounds with better binding efficacies (lower free energy of binding) than the templates were chosen as the best ligands for further *insilico* evaluations.

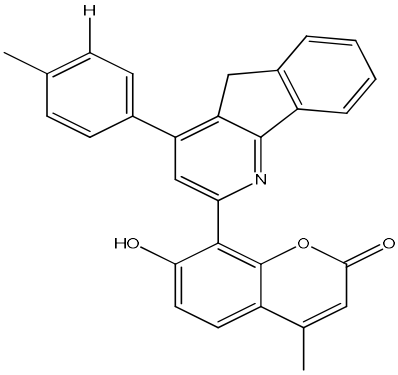
Table 1. Molecular structures and antibacterial properties of the lead compounds

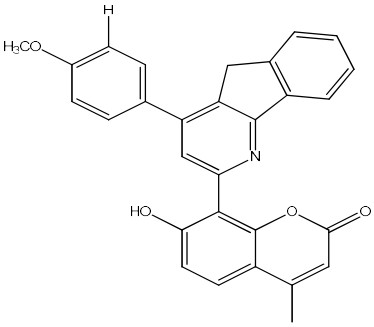
S/n	2D Structure	MIC (µg/mL)	S/n	2D Structure	MIC (µg/mL)
1.		200	2.		500
3.		250	4.		200
5.		500	6.		200
7.		63	8.		500

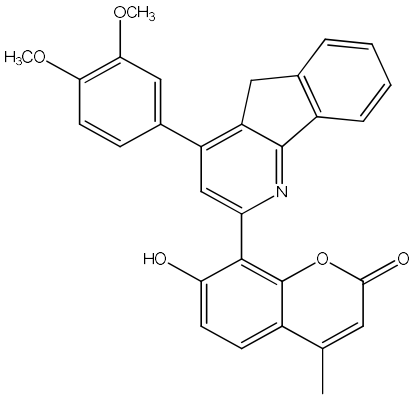
9.  100

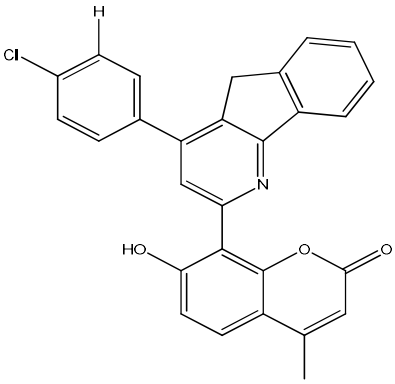
10.  500

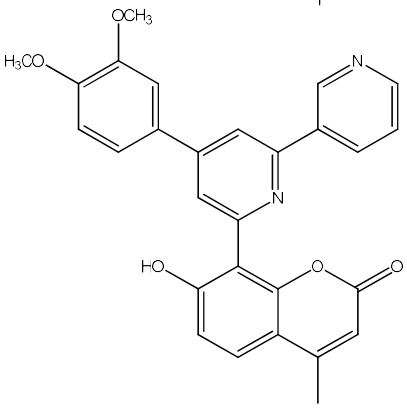
11.  200

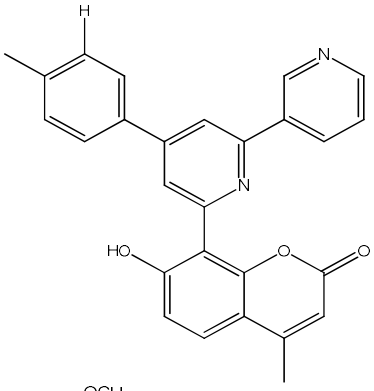
12.  250

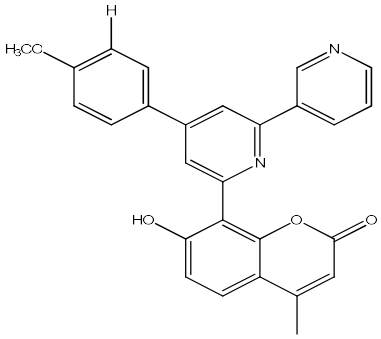
13.  100

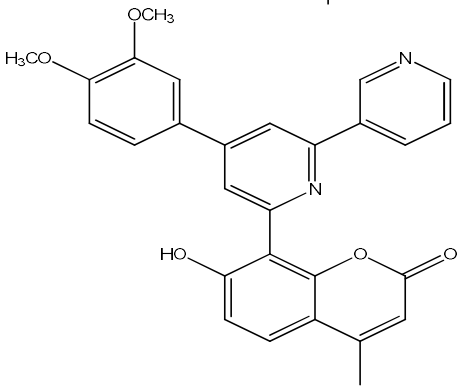
14.  250

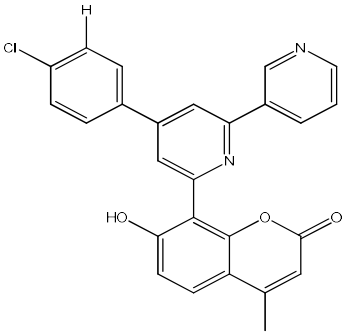
15.  500

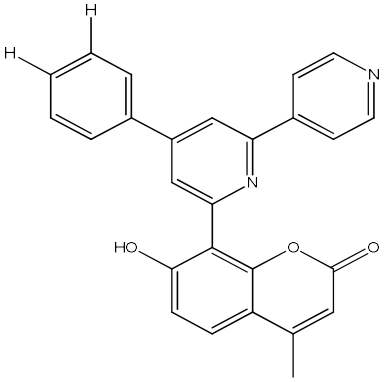
16.  200

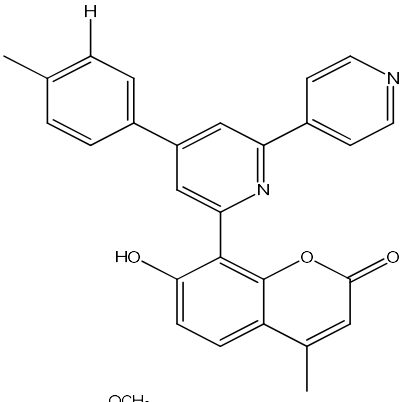
17.  250

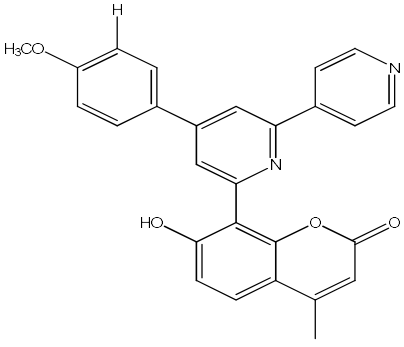
18.  50

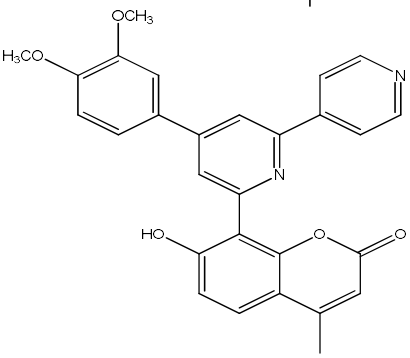
19.  100

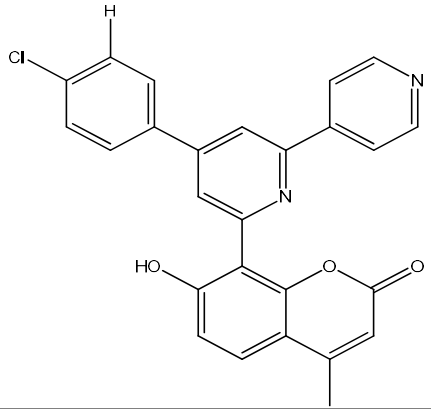
20.  200

21.  200

22.  250

23.  500

24.  100

25.  100

Drug-likeness Assessment of the Designed Compounds

Drug-likeness is the quantitative description of the oral bioavailability of a therapeutic compound. This important parameter was evaluated for the designed compounds using the well-known Veber's rule. According to this rule, for a drug to be orally bioavailable, the number of its rotatable bonds (NRB) must be < 10 and its topological polar surface area (TPSA) should be < 140 $Å^2$ [34]. The aforementioned physicochemical properties of the molecules were calculated with the aid of SwissADME (www.swissadme.ch/) online tool and DataWarrior Chemoinformatics program.

ADME/T Profiling of Designed Compounds

ADME/T defines the Absorption, Distribution, Metabolism, Excretion, and Toxicity of a therapeutic compound. The accomplishment of a drug in clinical trials is largely dependent on these properties. Computer aided ADME/T profiling of drug candidates is therefore an essential component of modern drug design [35,36]. ADME/T profile of the designed compounds were computed using SwissADME (www.swissadme.ch/ accessed on 21 September, 2022) and DataWarrior V5.5.0 Chemoinformatics program.

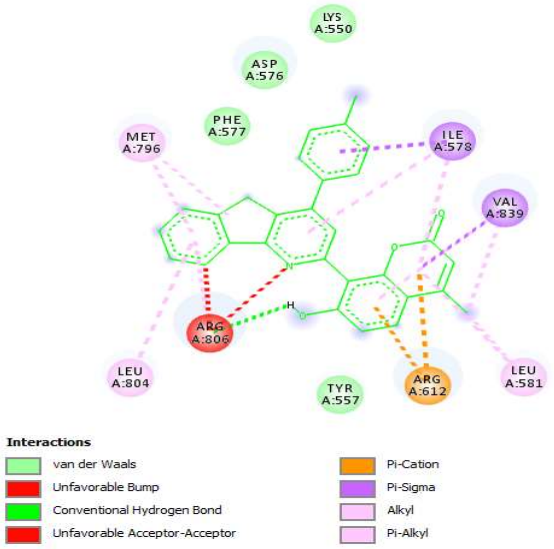
Results

Molecular docking evaluation

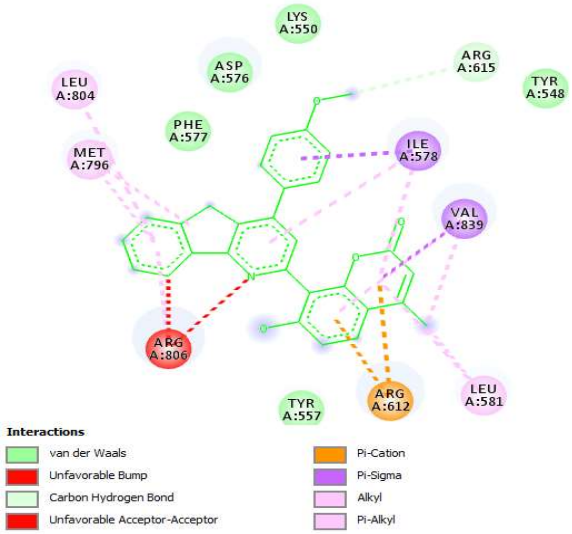
Table 2 lists the result of molecular docking simulation performed on the investigated bioactive compounds to determine their binding affinities with ATP binding pocket of DNA gyrase enzyme. The magnitude of binding interaction between the compounds and the target enzyme was expressed as change in Gibb's free energy (ΔG). The more negative the ΔG value, the higher the binding affinity. However, compounds 12, 13, and 15 displayed the best dock scores and were selected as templates for designing more potent derivatives of pyridine-substituted coumarin. The 2D diagram of interactions of the compounds with the active sites of the target is displayed in Figure 1.

Table 2. Binding affinity values of the compounds with DNA Gyrase target protein

S/n	ΔG (kcal/mol)	S/n	ΔG (kcal/mol)	S/n	ΔG (kcal/mol)
1	-8.2	10	-8.6	19	-8.4
2	-8.5	11	-9.2	20	-8.6
3	-8.4	12	-9.6	21	-8.5
4	-8.0	13	-9.5	22	-8.9
5	-8.4	14	-9.0	23	-8.5
6	-8.3	15	-9.6	24	-8.3
7	-8.7	16	-8.4	25	-8.7
8	-8.7	17	-8.8		
9	-8.2	18	-8.4		



Compound 12



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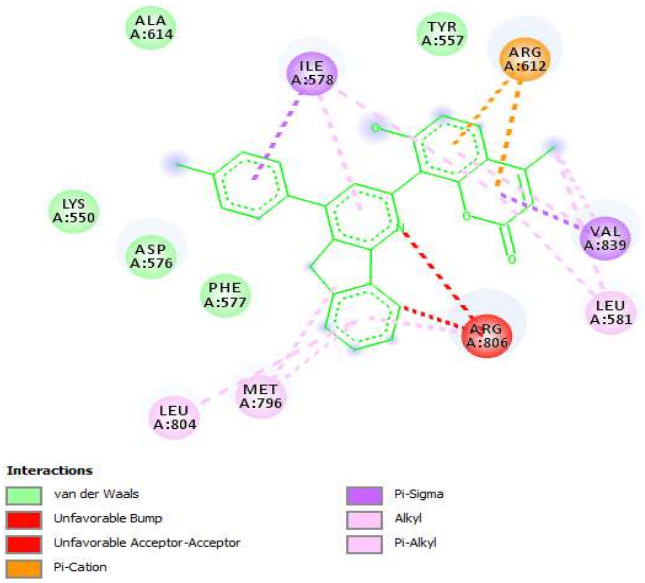
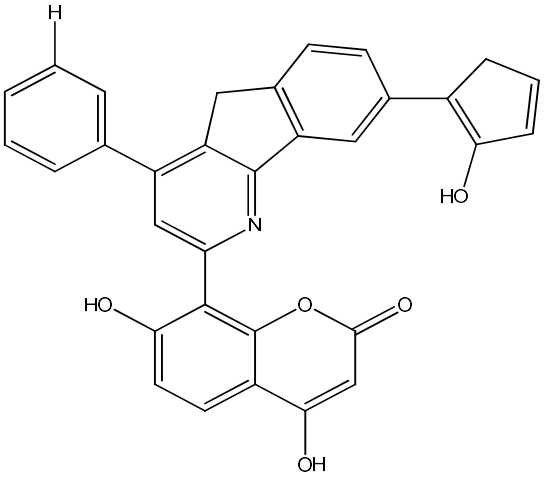


Compound 15

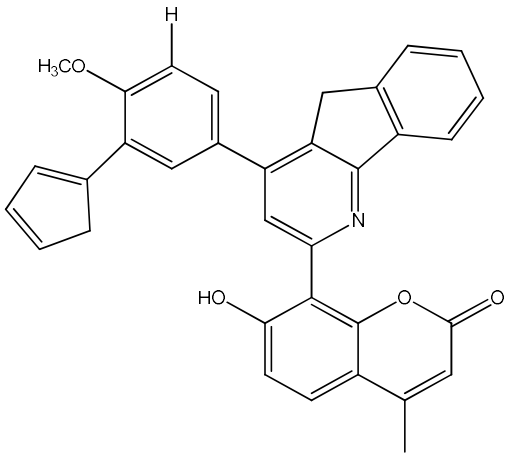
Figure 1. Binding interactions of the template molecules with active sites of DNA gyrase protein

Design of new analogues

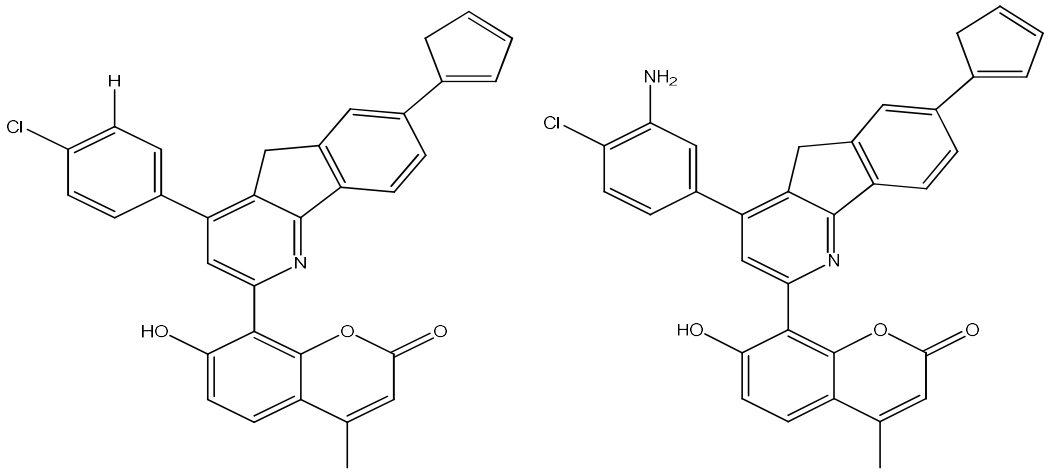
To design more potent derivatives of pyridine-substituted coumarine against *Salmonella typhi*, the selected templates were subjected to the structural modifications leading to the design of novel analogues; E1, E2, E3, and E4 (Figure 2). The designed compounds and ciprofloxacin (CiproF), a standard antibiotics used for quality control were further subjected to molecular docking simulation against DNA gyrase protein to ascertain their binding affinities. Their 2D diagram of interactions with the with ATP binding pocket of DNA gyrase enzyme are depicted in Figure 3, while Table 3 presents their binding affinity values, IUPAC names, and binding modes with the amino acid residues of the macromolecule.



E1



E2

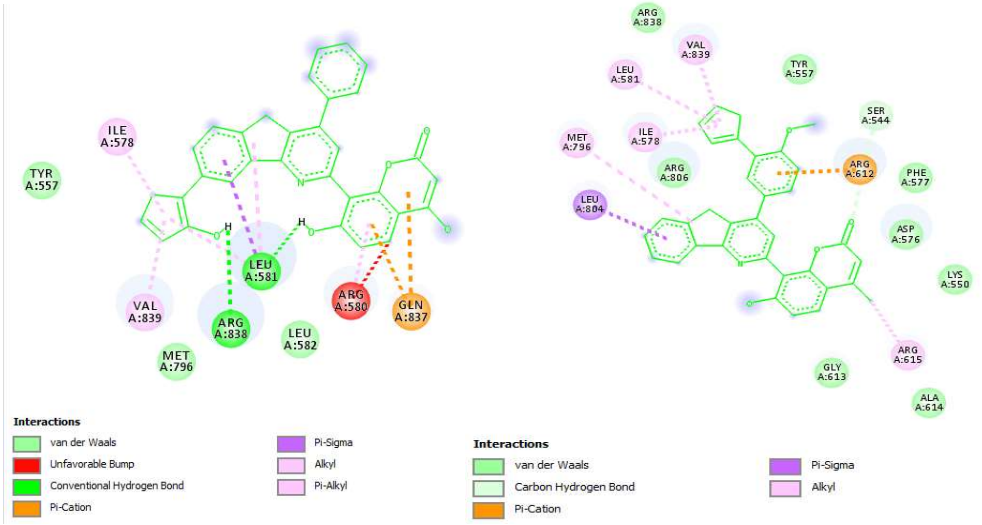


E3 E4

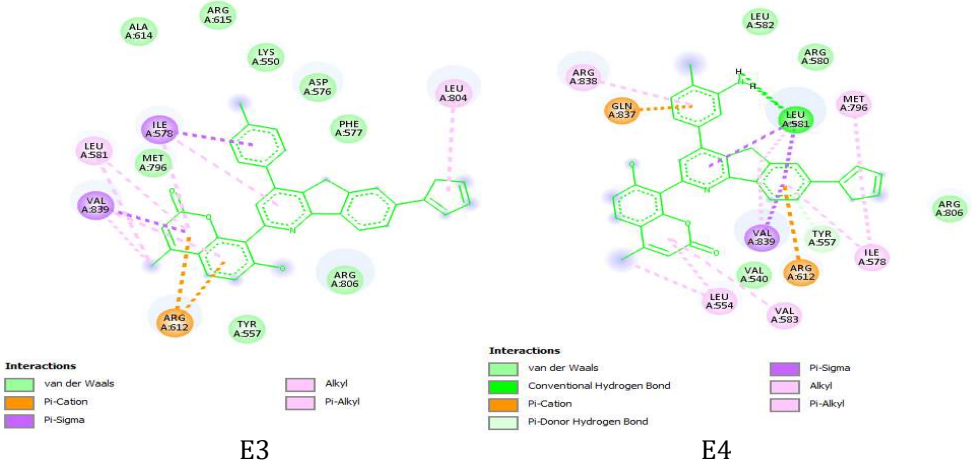
Figure 2. The 2D chemical structures of the newly designed compounds

Table 3. Binding affinity values, IUPAC names, and binding modes of the designed compounds

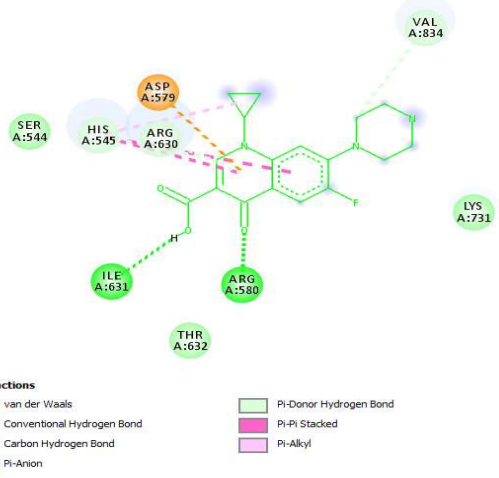
Compound ID	ΔG (kcal/mol)	IUPAC Name	Interacting residues
E1	-10.3	4,7-dihydroxy-8-(8-(2-hydroxycyclopenta-1,3-dien-1-yl)-4-phenyl-5H-indeno[1,2-b]pyridin-2-yl)-2H-chromen-2-one	ILE578, VAL839, ARG838, LEU581, ARG580, GLN837
E2	-10.2	8-(4-(3-(cyclopenta-1,3-dien-1-yl)-4-methoxyphenyl)-5H-indeno[1,2-b]pyridin-2-yl)-7-hydroxy-4-methyl-2H-chromen-2-one	VAL839, LEU581, ILE578, MET796, LEU804, ARG615, ARG612
E3	-9.9	8-(4-(4-chlorophenyl)-7-(cyclopenta-1,3-dien-1-yl)-5H-indeno[1,2-b]pyridin-2-yl)-7-hydroxy-4-methyl-2H-chromen-2-one	ILE578, LEU581, MET796, VAL839, ARG612, LEU804
E4	-10.6	8-(4-(3-amino-4-chlorophenyl)-7-(cyclopenta-1,3-dien-1-yl)-5H-indeno[1,2-b]pyridin-2-yl)-7-hydroxy-4-methyl-2H-chromen-2-one	ARG838, GLN837, LEU554, VAL583, VAL839, ARG612, ILE578, MET796, LEU581
CiproF	-6.6	1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid	ASP578, HIS545, ILE681, ARG580, VAL834



E1 E2



E3 E4



CiproF

Figure 3. Binding interactions of the designed ligands and ciprofloxacin with the active sites of DNA gyrase

Drug-likeness and ADMET profiles of designed ligands

The physicochemical descriptors that define the oral bioavailability potentials of the novel ligands, their insilico pharmacokinetic, and toxicological assays are provided in Table 4.

Table 4. Drug-likeness and ADMET profiles of the designed ligands

Ligand	TPSA (Å²)	NRB	Toxicity	Pharmacokinetic
E1	103.79	3	Mutagenic: **NO** Tumorigenic: **NO**	Solubility; **YES** CYP45 Substrate; **YES** GIA: **YES** PG-P substrate: **YES**
E2	72.56	4	Mutagenic: **High** Tumorigenic: **low**	Solubility; **YES** CYP45 Substrate; **YES** GIA: **YES** PG-P substrate: **YES**
E3	63.33	3	Mutagenic: **High** Tumorigenic: **Low**	Solubility; **YES** CYP45 Substrate; **YES** GIA: **YES** PG-P substrate: **YES**
E4	89.35	3	Mutagenic: **High** Tumorigenic: **High**	Solubility; **YES** CYP45 Substrate; **YES** GIA: **YES** PG-P substrate: **YES**

GIA: gastrointestinal absorption, Pg-P: P-glycoprotein, TPSA: topological polar surface area, and NRB: number of rotatable bond

Discussion

In Silico Molecular Docking Assessment.

DNA gyrase, a topoisomerase enzyme plays an essential role in bacteria by controlling the topology of DNA during transcription, replication, and recombination [37-39]. This it does through the introduction of transient breaks to the two strands of DNA. In this regard, this enzyme is indispensable for the bacterial survival and therefore crucial to be exploited as an antibacterial drug target [40]. Thus, in this research, molecular docking simulation was performed on the studied compounds to examine their binding affinity values with DNA gyrase. The result of the investigation presented in Table 2 reveals that compounds 12, 13, and 15 with ΔG value of -9.6, -9.5, and -9.6 kcal/mol, respectively, exhibit the best dock scores with the active sites of the protease and were selected as template molecules for the design of more potent analogues. Investigation of their 2D diagram of interaction (Figure 1) reveals that the conjugated cyclic rings are the major pharmacophores of the compounds.

The Designed Analogues

The potencies of the template molecules were optimized through the attachment of cyclopentadienyl ring to different locations of the template molecules. The different analogues generated via these structural modifications were subjected to molecular docking to investigate their binding pattern with DNA gyrase and compare them with standard inhibitor (ciprofloxacin) and the templates. Eventually, molecules, E1, E2, E3, and E4 (Figure 2) with binding affinity values of -10.3, -10.2, -9.9, and -10.6 kcal/mol (Table 3), respectively, were selected as the best among the designed molecules because they display excellent binding affinities to the active sites of the target protease. These newly designed bioactive compounds display better potencies when compared with the templates and Ciprofloxacin. The binding of the standard antibiotic, Ciprofloxacin, to the active sites of DNA gyrase with ΔG = -6.6 kcal/mol is similar to the finding of Kumar *et al.* [25], where the authors reported that the antibiotic binds to the macromolecule with a binding affinity value of -6.092 kcal/mol.

The residual interaction of the novel compounds and ciprofloxacin are summarized in Table 3 and their 2D diagrams of interaction with the protein target are shown in Figure 3. Compared with ciprofloxacin, the designed compounds (E1, E2, E3, and E4) displayed better and different residual interaction profiles with amino acid residues of DNA gyrase, an indication that they might have different mechanisms of action against the bacterium. Compounds E1 and E4 have additional hydrogen bonding interaction with ARG838 and LEU581 amino acid residues of DNA gyrase, respectively. The hydrogen bonding interactions in ciprofloxacin are with ILE631 and ARG580 amino acid side chains.

Generally, the designed compounds bind better to the active site of DNA gyrase when compared with the standard inhibitor, ciprofloxacin. Thus, they could be better alternatives to this widely used antibiotics in the face of the current trend of multidrug resistance by *Salmonella typhi*. The higher binding affinities of the templates and designed molecules against DNA gyrase when compared with Ciprofloxacin agrees with the findings of Anebi *et al.* [24] where the authors performed some molecular docking calculations on some thiophene derivatives against DNA gyrase of *Salmonella typhi*. Furthermore, the amino acids; isoleucine (ILE), valine (VAL), arginine (ARG), and leucine (LEU) contributed significantly to the binding affinity of the designed ligands to DNA gyrase. The results of molecular docking studies on benzoxazine acetamides against the active sites of DNA gyrase by Elseginy and Mannal [27] also revealed similar findings.

Drug-likeness and ADME/T Projection

Insilico drug-likeness assessment and ADMET profiling are cost-effective and time-saving drug design strategies that help scientifically establish a bioactive compound as a promising drug candidate prior to *in vitro* experiments [41,42]. Drug-likeness assessment is very necessary since oral delivery remains the most common path of drug delivery into the systemic circulation. This important parameter was assessed for the designed ligands using the Veber's rule. The results (Table 4) showed that all the compounds have TPSA values < 140 $Å^2$ and NRB values < 10, an indication that they are most likely going to be orally bioavailable.

Likewise, pharmacokinetic data (Table 4) of the designed ligands showed that they have good aqueous solubility and could permeate through the intestinal lining of humans. Furthermore, they were found to bind to P-glycoproteins, a cell membrane protein that enhances the movement of many drugs through the cell membrane. Moreover, Cytochrome P450 refers to group of enzymes that regulates drug biotransformation, drug interaction, and their elimination from the biological system. Inhibition of these enzymes by any therapeutic molecule could result to delayed removal, severe toxicity, and failure of the drug in

the human body [43-45]. Interestingly, all the designed ligands were found to be substrate of one or more of these enzymes.

In addition, toxicity evaluation was performed on the designed ligands to ascertain their mutagenicity and/or tumorigenic tendencies. The insilico toxicity assay (Table 4) revealed that E1 has the best profile as it has no mutagenic or tumorigenic tendencies. E2 and E3 possess high mutagenicity but low tumorigenic inclinations. However, E4 has high values of these two toxicity endpoints.

Conclusion

The use of *in silico* techniques in modern drug discovery strategies is growing speedily and has found immense applications in academia and pharmaceutical industries. In this study, *insilico* molecular docking technique was used to virtually screen a set of bioactive pyridine-substituted coumarins against the DNA gyrase of *Salmonella typhi*, a Gram-negative bacterium responsible for typhoid fever. The compounds with the best binding affinity values to the active sites of the target macromolecule were selected as templates and subsequently subjected to the structural modifications leading to the design of more potent analogues. As an *insilico* quality assurance strategy, ciprofloxacin, an approved antibiotic for treating typhoid fever was also docked to DNA grase of the bacterium and its binding affinity was compared with those of the designed ligands. The novel ligands were found to be more potent than the template molecules and the Ciprofloxacin antibiotic. Furthermore, *insilico* drug-likeness assessment and ADMET evaluation of the designed ligands revealed that they possess positive drug-likeness, the excellent pharmacokinetic, and toxicity profiles. It is envisaged that the wealth of information enshrined in the findings of this research work will provide a roadmap towards the development of novel antibiotics that could curb the increasing cases of resistance to existing antibiotics by *Salmonella typhi*.

Competing interests

There is no competing interest to declare by the authors.

Authors' contribution

The research was designed by AU and supervised by AGS and SU. JPA carried out the computational analysis and drafted the manuscript.

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