A Study of the New Imidazo Design and Synthesis [1, 2-A] The Anti-Bacterial Activity of Pyridine Devicatives

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***Abstract*—Antibacterial activity of new imidazo[1,2-a] pyridine derivatives is the primary subject of this work, which also involves their design, synthesis, and assessment. The synthesis of a series of chemicals (9a-l) began with 4-methyl acetophenone and proceeded through many steps. We used Fourier transform infrared (FT-IR), nuclear magnetic resonance (NMR), and mass spectroscopy to explore the newly produced chemicals. Their ability to inhibit the growth of four common bacteria was examined via disc diffusion testing, which included Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, and Bacillus subtilis. Molecular docking experiments were conducted to provide insight into the interactions between ligands and receptors in the active site of bacterial DNA gyrase. Compound 9a showed the maximum inhibition against Bacillus subtilis, whereas compounds 9c, 9e, and 9g showed potential antibacterial activity, according to the data. Experimental findings were in agreement with the docking investigations, demonstrating that these compounds had antibacterial potential.**

***Index Terms*—Imidazo[1,2-a] pyridine derivatives, Antibacterial activity, Molecular docking, DNA gyrase inhibition**

I. INTRODUCTION

The increasing prevalence of bacterial diseases and the emergence of resistance to conventional antibiotics highlight the critical need for novel antimicrobial medication design and production. Scientists have started looking at new chemical entities with better antibacterial properties in an effort to address the limitations of existing treatments. Because of their many biological activities, especially their robust antibacterial properties, imidazo[1,2-a] pyridine derivatives are being considered as a possible possibility. The unusual pharmacological properties shown by a unique class of heterocyclic compounds known as imidazole-pyridine rings make these molecules an attractive framework for drug development. Extensive study has been conducted on the antibacterial characteristics of imidazo[1,2-a] pyridines, which have a unique bicyclic structure and target both gram-positive and gram-negative bacteria. The imidazole ring, known for its basicity and hydrogen bonding capabilities, is an essential component in the interaction between these compounds and the membranes and enzymes of bacterial cells. The antibacterial activity of the molecule is enhanced by the pyridine group, which also guarantees its lipophilicity and stability. In the end, the growth of bacteria is halted by imidazo[1,2-a]pyridine derivatives because of their capacity to penetrate bacterial cells and interfere with important biological processes such DNA replication, protein synthesis, and cell wall building. One great thing about imidazo[1,2-a] pyridine derivatives is how well they react to different kinds of chemical alterations. Altering the substituents on the imidazole and pyridine rings allows scientists to customize these compounds' antibacterial characteristics. Substitutions with halogens, alkyl groups, or electron-donating or -removing groups might alter a molecule's antimicrobial activity, spectrum, and pharmacokinetic properties. One way to tackle problems like antibiotic resistance and narrow-spectrum activity is by developing medications with particular targets, which is made feasible by the capacity to adapt. (Kazemi et al., 2016) (V. M. Rao et al., 2018)

The battle against bacterial infections has seen encouraging outcomes in the creation of pyridine-based compounds, such as imidazo[1,2-a] pyridine analogs, in recent years. Merging imidazo[1,2-a] pyridine derivatives with the well-known heterocyclic molecule pyridine increases its antibacterial potency, among its many other

biological properties. These chemicals have shown promise in combating the notoriously resistant bacteria such as extended-spectrum beta-lactamase (ESBL) and multi-drug-resistant (MDR). It is thought that imidazo[1,2-a]pyridine derivatives block bacterial enzymes, damage bacterial cell membranes, and interfere with bacterial metabolism in their antibacterial effect. Several synthetic methods, including as cyclization processes, condensation reactions, and nucleophilic substitution reactions, are usually used in the synthesis of imidazo[1,2-a]pyridine derivatives. A wide variety of derivatives with different functional groups and substituents may be efficiently generated using these approaches. In order to optimize their antibacterial characteristics and study their structure-activity correlations (SAR), synthesis of these compounds is essential. Improved synthesis techniques made possible by developments in green chemistry have added to the growing interest in imidazo[1,2-a]pyridine derivatives as possible medicinal agents. Imidazo [1,2-a]pyridine derivatives are a new family of antibacterial medicines that show great promise in the fight against bacterial infections, especially those caused by bacteria that are resistant to antibiotics. These molecules provide a potent approach for the creation of new antimicrobial medicines via their design, production, and integration of pyridine derivatives. Developing effective therapies for infectious illnesses requires investigating new families of antibacterial drugs, such imidazo[1,2-a]pyridines, due to the increasing worldwide danger of antibiotic resistance. (Hanumantappa et al., 2021)(Bhatt et al., 2017) (Jiang et al., 2014)

II. LITERATURE REVIEW

(Budumuru et al., 2018) The goal of this study was to synthesize Imidazo [1,2-a]pyridine derivatives in order to produce novel antibacterial compounds. Applying 1H-nuclear magnetic resonance (NMR), 13C-NMR, Fourier transform infrared and mass spectral analysis, we screened a series of newly synthesized compounds for antibacterial activity using the disc diffusion technique. Molecular docking research was carried out utilizing Auto Dock 4.2.6 on the bacterial beta component of DNA gyrase. The docked conformations were analyzed using visual molecular dynamics. To investigate the relationship between structure and activity, we subjected the synthesized imidazo[1,2-a]pyridine derivatives to bacterial tests against both Gram-positive and Gram-negative strains. A compound called N-benzyl-4-((2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl) acetamido)methyl) benzamide was synthesized and possesses potent antibacterial effects against Bacillus subtilis (9a). Compared to the other compounds tested, compound 9a had a wider inhibitory zone. The antibacterial activity of the synthetic compounds was higher than that of streptomycin, the antibiotic often used as a benchmark. These findings point to the beta subunit of DNA gyrase as the target in bacteria that 9a and its analogues most likely inhibit.

(Nanda Kishore et al., 2017) The 2-aryl imidazo[1,2-a] pyridines (4a-4b) were prepared by combining 2-amino pyridine with a number of different phenacyl bromides. The resulting 2-aryl imidazo[1,2-a] pyridine carbaldehydes were then prepared. The Claisen-Schmidt condensation of 4a and 4b with different substituted acetophenones was used to generate chalcones (5a-5f). By treating chalcones with phenyl hydrazine, six new pyrazolyl imidazo[1,2-a]pyridine compounds (6a-6f) were effectively generated. The synthesized compounds were described by means of physical and spectroscopic data. The compounds were evaluated for their antibacterial and anti-inflammatory capabilities. Compounds 6a, 6b, and 6c showed a strong anti-inflammatory effect, and the results were comparable to those of the reference medication, ibuprofen. No antibacterial effect was seen against Gram +ve and Gram +ve pathogens, even at a dose of 1000 µg/ml, for any of the compounds.

(Reddyrajula & Dalimba, 2019) A commercial medicine called Ambien (zolpidem) is used to treat insomnia. It is an imidazo[1,2-a]pyridine derivative and it also has antitubercular action against Mycobacterium TB H37Rv. This study details the synthesis of three distinct series of imidazo[1,2-a]pyridine/pyrimidine-1,2,3-triazoles (IPTs) derived from zolpidem via targeted structural changes. With a MIC of 1.56 µg mL-1, this is twice as high as the MIC of zolpidem, the majority of the IPTs demonstrated impressive antitubercular efficacy in vitro. Additionally, the synthesized IPTs had moderate inhibitory effectiveness against many bacterial and fungal species, and their in vitro cytotoxicity evaluation against Vero cells confirmed

an acceptable safety profile. The strong IPTs also showed encouraging binding contacts with the InhA enzyme's active site. The binding manner was shown to be correlated with the inhibitory activity in vitro. The majority of the powerful compounds, with a MIC of 1.56 μg mL-1, interacted with the target enzyme via an H-bond with its Tyr 158 residue. These zolpidem structural modification initiatives may pave the way for future IPT core optimization and the creation of novel anti-TB medications.

(Megha et al., 2022) The use of ammonium acetate as a catalyst allows us to provide a practical and effective process for the production of 4-(substitutedphenyl)-1,2-dihydro-2-oxo-6-(2-oxo-2Hbenzo[g]chromen-3-yl)pyridine-3-carbonitrile chemicals. The structures of the compounds that were synthesized were verified by the use of spectroscopic methods such as FT-IR, 1H, 13C-NMR, and LC-MS. Using the disc diffusion technique at varying doses, the antibacterial activity of the produced compounds was assessed against bacterial strains. In addition, we used DPPH and MTT assays at varying doses to test all of the compounds for their antioxidant and anti-cancer properties, respectively. Anticancer and antioxidant properties were shown by compound 4b in a study using the MCF-7 cell line. By using molecular docking experiments with the human peroxiredoxin 5 (PDB ID: 1HD2) and P38 MAP kinase (PDB ID: 1OUK) proteins, the binding capabilities of the produced compounds (4a-j) were examined. Adsorption, distribution, metabolism, and excretion (ADME) experiments were used to assess the physicochemical parameters.

(N. S. Rao et al., 2012) Chalcone derivatives, also known as 1,3-diphenyl-2-propen-1- ones, have a number of anti-infective actions and may halt or postpone the inactivation, breakdown, and excretion of anti-infective medications. These chemicals have a broad range of pharmacological effects, including those against malaria, inflammation, cancer, cytotoxicity, and antioxidants. Many anti-infective effects, such as antibacterial, antiviral, antiprotozoal, and anthelmintic, are shown by the imidazopyridine nucleus and similar chalcone derivatives. Analgesic, anti-inflammatory, antifungal, calcium antagonist and anticancer properties are all shared by the imidazo pyrimidine nucleus. Using 2-aminopyrimidine and 2-aminopyridine, which are both commercially accessible, as starting materials, this work details the synthesis of novel chalcones containing this imidazopyridine/imidazopyrimidine heterocyclic core. The antibacterial activity against Escheria were assessed in the chalcones (4a-4f and 10a -10f) that were thus produced (Scheme 1 and Scheme 2).Using Ciprofloxacin as the reference medicine, we tested for the presence of Coli, Pseudomonas.aeruginosa, Staphylococcus aureus, and Streptococcus pyogenes (Table 1). Results for the investigated bacterial strains indicate that imidazo[1,2-a]pyrimidine chalcone (4a, 4b, 4c, 4e, and 4f) derivatives exhibit outstanding to good activity in comparison to imidazo[1,2-a] pyridine chalcone (10a - 10f).

III. METHODOLOGY

To convert your study into a secondary base study, you would focus on analyzing existing research and data related to the synthesis and applications of imidazo[1,2-a]pyridine derivatives. This involves conducting a comprehensive literature reviews, evaluating published synthesis methods, reaction conditions, and structural properties of similar compounds. Instead of generating new experimental data, your study would compare and interpret findings from previous studies, focusing on trends, discrepancies, and potential applications. By synthesizing existing knowledge, you can draw conclusions and propose new insights or research directions based on secondary data.

Purity Check**:** Analytical TLC (Merck60GF254) with chloroform:methanol (90:10) solvent system; spots visualized under UV light/iodine vapors.

Spectroscopy**:**

- FT-IR: Shimadzu FTIR 8300, KBr pellets.
- Mass Spectra: SHIMADZU QP 500.
- NMR: Bruker 300MHz, CDCl3/DMSO-d6, δ-scale (ppm) with TMS as standard.

Synthesis of Compounds

- Compound 3**:**

Reactants: 4-methyl acetophenone, $AlCl_3$, bromine, 2-amino-5-methyl pyridine.

Yield: 54.8%, MS: m/z 223.1 (M+1).

- Compound 4**:**

Reactants: Compound 3, acetic acid, dimethylamine, formalin.

Yield: 59.6%, MS: m/z 280.2 (M+1).

- Compound 5**:**

Reactants: Compound 4, methyl iodide, NaCN.
Yield: 68.8%, MS: m/z 262.1 (M+1).

- Compound 6**:**

Reactants: Compound 5, KOH.
Yield: 71%, MS: m/z 281.1 (M+1).

- Compound 7**:**

Reactants: Compound 6, TBTU, triethylamine, ethyl 4-(aminomethyl)benzoate.
Yield: 48.2%, MS: m/z 441.1 (M+1).

- Compound 8**:**

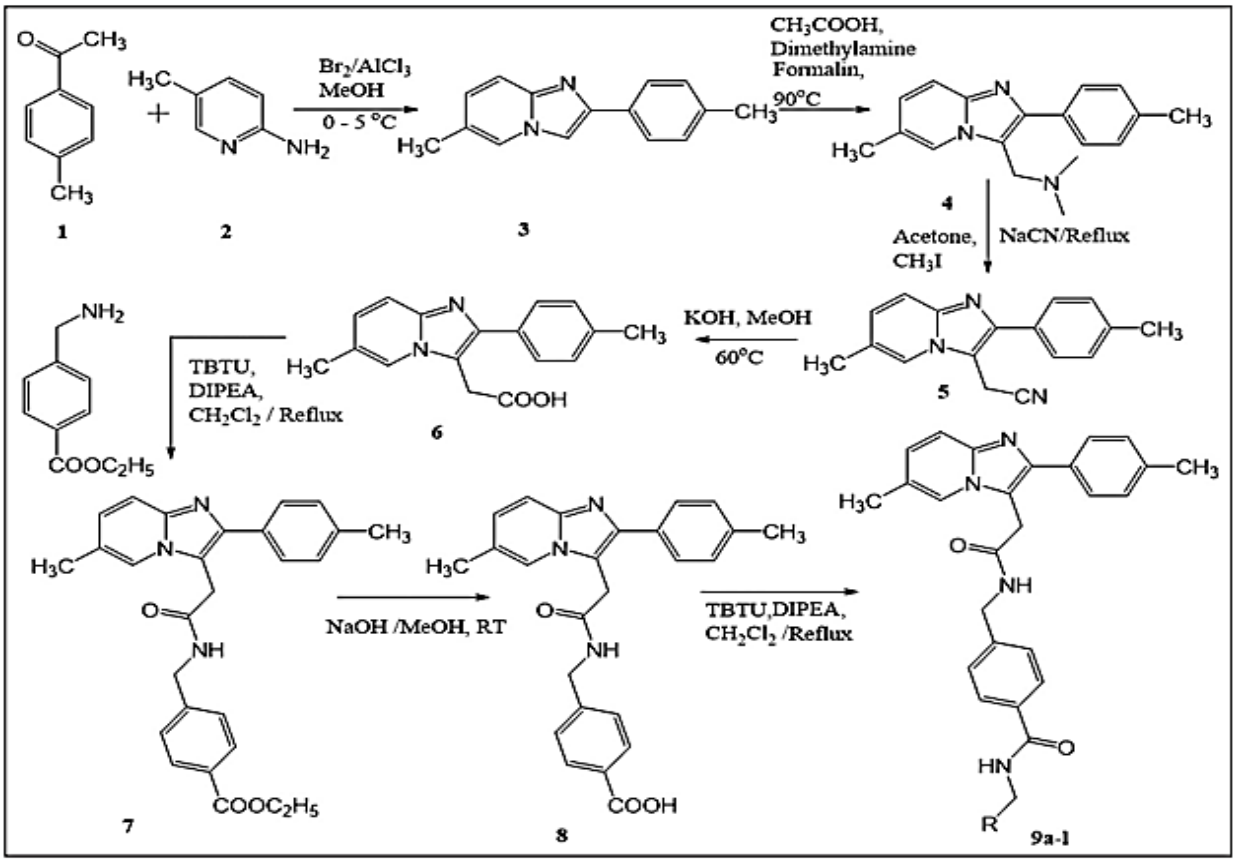
Reactants: Compound 7, NaOH.
Yield: 67.36%, MS: m/z 414.2 (M+1).

- Compounds (9a-l)**:**

Reactants: Compound 8, TBTU, diisopropylamine, substituted amines.
General Yield: 22.7–31.5%, characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR, and MS.

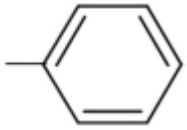
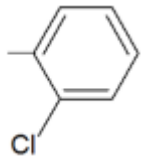
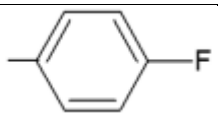
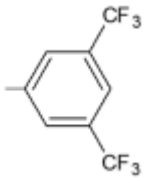
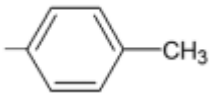
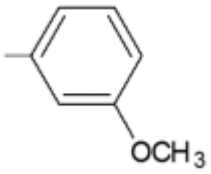
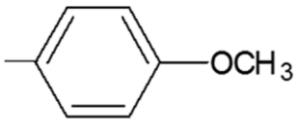
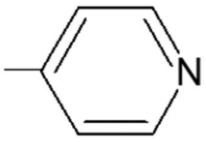
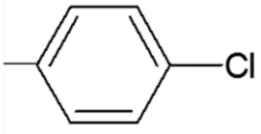
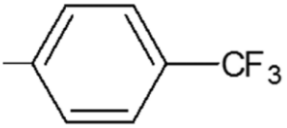
IV. RESULT

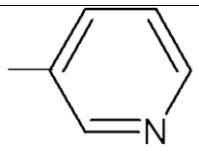
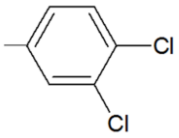
Following the steps outlined in Scheme 1, the desired compounds (9a-l) were created from 4-methyl acetophenone 1. The FTIR, NMR, and mass spectrum data of the suggested compounds were used to validate and describe them independently. Table 1 displayed the physicochemical characteristics of the substances that were produced. Presence of bromine and aluminum chloride allowed precursor 1 to react with 2-amino 5-methyl pyridine, resulting in 6-Methyl-2-p-tolyl-imidazo [1,2-a] pyridine. An excited protonated molecular ion was seen at m/z 223 in the mass spectrum of 3. Mass spectra at m/z 280 validated the structure, and the reaction between chemical 3, acetic acid, dimethylamine, and formalin at 90o C for 3 hours yields the dimethyl aminomethyl derivative of 4. Following its formation as a quaternary ammonium salt by reaction with methyl iodide, the related chemical 5 underwent further reactions with sodium cyanide to produce a cyano derivative.



Scheme 1: Synthetic route for compound 9a-l

Table 1: Physicochemical Properties of Synthesized Compounds

Compound	R	Molecular Formula	Molecular Weight	Yield (%)
9a		$C_{32}H_{30}N_4O_2$	502.6	31.5
9b		$C_{32}H_{29}ClN_4O_2$	537.05	22.7
9c		$C_{32}H_{29}FN_4O_2$	520.59	24.6
9d		$C_{34}H_{28}F_6N_4O_2$	638.6	22.5
9e		$C_{33}H_{32}N_4O_2$	516.63	38.5
9f		$C_{32}H_{30}N_4O_3$	532.63	19.9
9g		$C_{32}H_{30}N_4O_3$	532.63	24.6
9h		$C_{31}H_{29}N_5O_2$	503.59	32.3
9i		$C_{32}H_{29}ClN_4O_2$	537.05	39.3
9j		$C_{34}H_{28}F_3N_4O_2$	570.6	22.6

9k		$C_{31}H_{29}N_5O_2$	503.59	35.8
9l		$C_{33}H_{29}ClN_4O_2$	571.49	26.7

This compound was further hydrolyzed using potassium hydroxide and methanol to yield the acid derivative of compound 6. Compound 7 was quantitatively synthesized using compound 6 which reacts with TBTU, Ethyl 4-(aminomethyl) benzoate in the presence of triethylamine under reflux for 3 h. The high resolution-MS spectrum of 7 displayed a protonated molecular ion at m/z 442. Compound 7 was hydrolyzed using aqueous sodium hydroxide in methanol to form the corresponding acid derivative 8. The mass spectrum of 8 showed a molecular ion at m/z 414. The final compound of imidazo[1, 2-a] pyridine derivatives 9a-l was prepared by amide coupling with TBTU, triethylamine with corresponding benzylamines. The mass spectrum of the compound 9a showed a molecular ion peak at m/z 503 and a sharp band at 1634 cm-1 was observed in the IR spectrum which is recognized as amide C=O stretching. The FT-IR results contributed some additional information for functional groups such as NH and CH groups. In the 1 H-NMR spectrum, the two singlet signals at 2.30 ppm and 2.35ppm were observed and they were characterized for methyl groups. The amide NH groups were observed at 8.89 ppm and 9.03 ppm. Similarly, three CH2 units were appeared at 4.04 (d), 4.41(d), and 4.49(d). The aromatic protons also present at their corresponding regions.

Biology

Activity of imidazo[1,2-a]pyridine derivatives against microorganisms The global scientific and public health communities have been very worried about the rise of multidrug-resistant bacteria and viruses in hospitals and the general population. Antimicrobial drug discovery for the treatment of infectious illnesses is a major accomplishment of the last hundred years. Resistance to routinely used medications has emerged as a consequence of the growing usage of commercially accessible antimicrobial treatments, which has serious consequences for healthcare expenses, death rates, and morbidity. The disc diffusion technique was used to test all the imidazo[1,2-a]pyridine compounds that were produced for their antibacterial activity. For the purpose of calculating zones of inhibition, the compounds were tested in vitro against E. coli (ATCC-25922), S. aureus (ATCC-9144), K. pneumoniae (ATCC-13883), and B. subtilis (ATCC6051), in comparison to the gold standard antibiotic Streptomycin. At a dose of 1000 µg, all of the synthetic compounds inhibited the tested microbial pathogens in a promising way. The benzyl, 4-fluorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl-containing compounds 9a, 9c, 9e, and 9g showed the most promise among the produced compounds.

Table 2: Antibacterial Activity of Imidazo [1,2-a] Pyridine Derivatives

Zone of Inhibition (mm)								
Compound Code	S. aureus (500 µg)	S. aureus (1000 µg)	B. subtilis (500 µg)	B. subtilis (1000 µg)	E. coli (500 µg)	E. coli (1000 µg)	K. pneumoniae (500 µg)	K. pneumoniae (1000 µg)
9a	7	10	12	15	11	13	-	-
9b	-	8	9	13	9	12	-	-
9c	-	8	8	10	10	14	8	10
9d	-	-	7	9	10	13	8	10
9e	7	9	10	14	11	14	7	8
9f	-	9	9	10	11	14	7	8

9g	-	-	9	12	10	12	8	10
9h	-	-	9	11	12	13	-	-
9i	-	-	10	12	9	12	-	-
9j	-	10	9	13	9	12	-	-
9k	-	9	10	11	9	13	7	8
9l	-	-	9	10	9	11	7	8
Streptomycin	22	22	23	23	23	23	22	22

Note**:**

- *S. aureus*: Staphylococcus aureus
- *B. subtilis*: Bacillus subtilis
- *E. coli*: Escherichia coli
- *K. pneumoniae*: Klebsiella pneumoniae

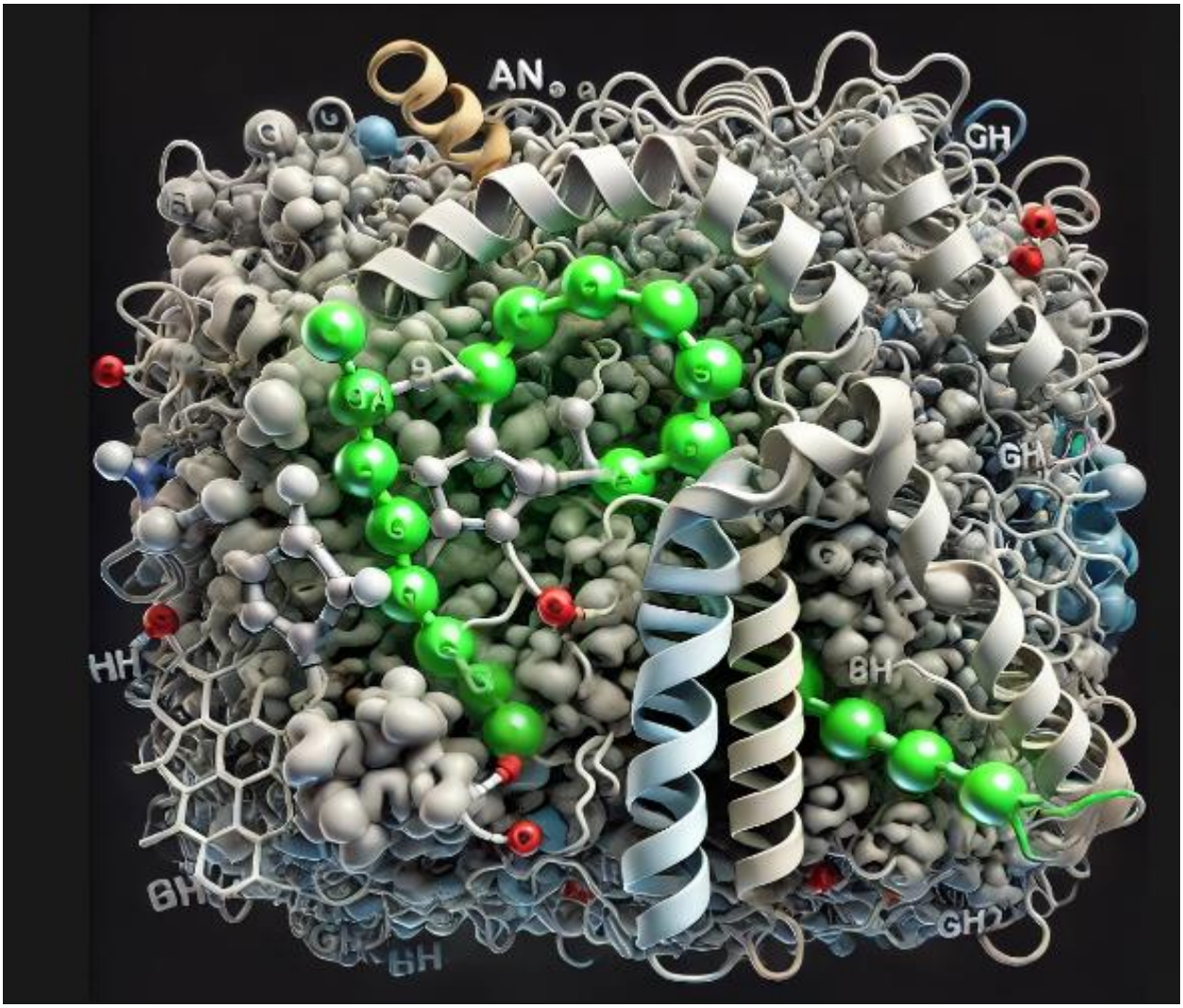


Fig. 1: 9a bound to the ATPase active site of bacterial DNA Gyrase (from Bacillus subtilis) showed an inhibition constant of 60 µM. The estimated binding free energy of this interaction is ~ - 6Kcal/mol. The hydrogen bond formed between 9a and side chain carboxyl group of Asp 61 and the hydrogen bond between 9a and backbone NH of Gly65 is shown as green spheres.

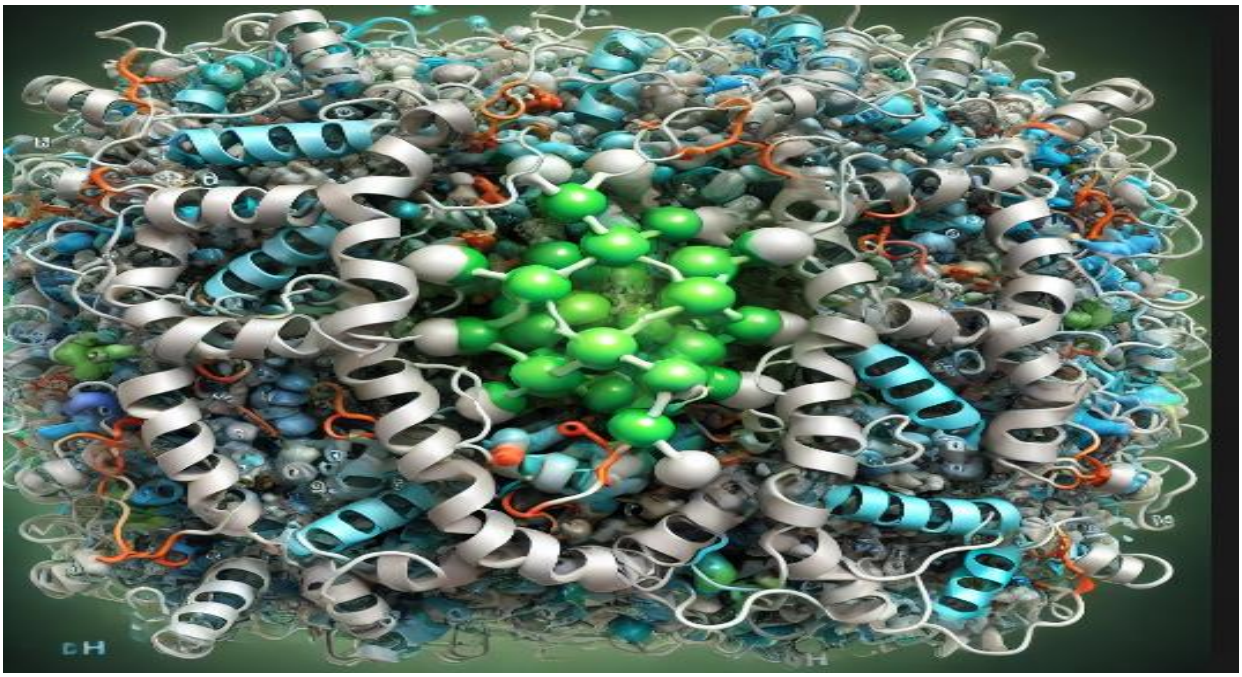


Fig. 2: 9e bound to the ATPase active site of bacterial DNA Gyrase (from Bacillus subtilis) showed an inhibition constant of 1mM. The estimated binding free energy of this interaction is ~ - 5Kcal/mol. The hydrogen bond formed between 9e and side chain carboxyl group of Glu 58 and the hydrogen bond between 9e and backbone NH of Gly85 is shown as green spheres

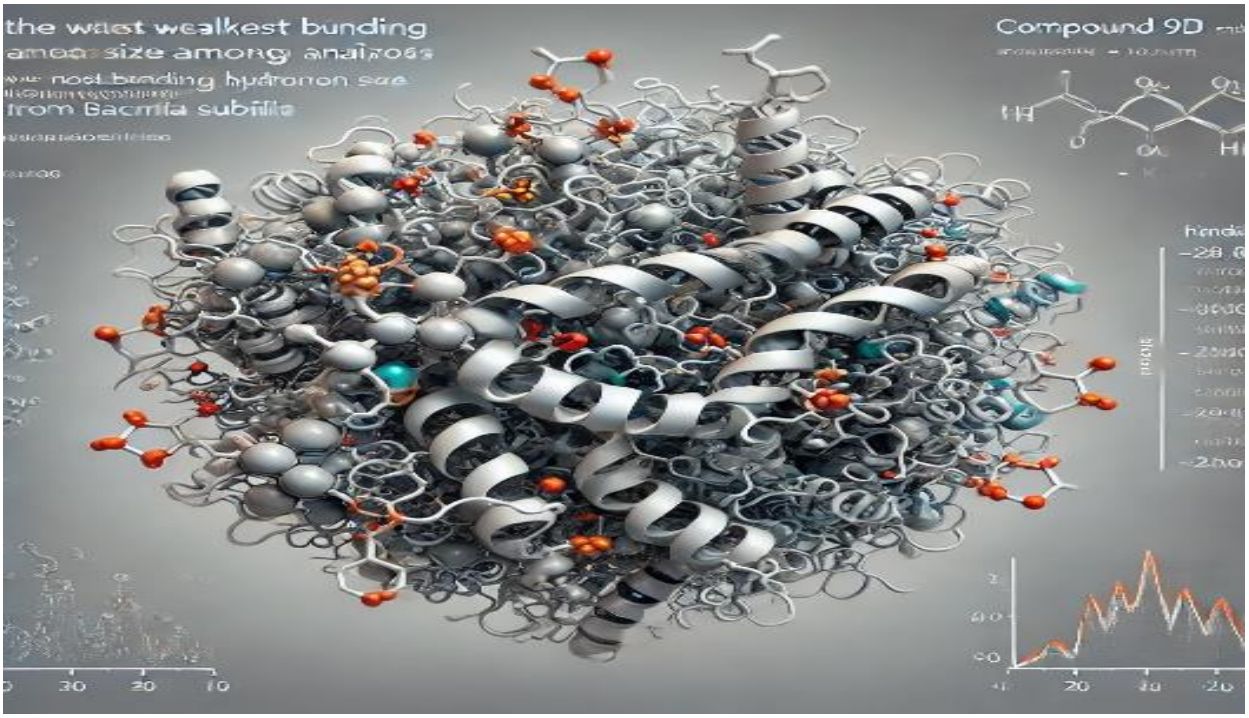


Fig. 3: 9d bound to the ATPase active site of bacterial DNA Gyrase (from Bacillus subtilis) showed the weakest binding among all the analogs with a predicted inhibition constant of 29.8mM. The estimated binding free energy of this interaction is ~ - 2Kcal/mol. No hydrogen bonds were formed between 9d and protein. The interaction was found to be predominantly hydrophobic in nature.

In addition, compounds 9e, 9g, and 9j exhibited anti-K. pneumonial activity due to the presence of 4-methylbenzyl, 4-methoxybenzyl, and 3,4,5-triflouromethyl benzyl substituents. The anti-S. aureus activity of all the synthetic drugs was low. At the lowest concentration tested (500 µg), none of the compounds 9a, 9b, 9d, 9g, 9h, 9i, and 9l showed any action against K. pneumoniae. Compound 9a, which is replaced with benzyl, exhibited the highest zone of inhibition against B. subtilis, which measured 15 mm. The results demonstrated that the synthetic compounds had antibacterial activity in comparison to the gold standard antibiotic. The microorganisms' zone of inhibition is shown in millimeters in Table. Consistent with the experimental findings, the docking results are shown in Figures. The binding score of compound 9a was shown to be higher than that of the other structural analogs tested. In comparison to the other chemicals tested, compound 9a produces much larger zones of inhibition. This data points to the notion that 9a and its analogues likely block the beta subunit of DNA gyrase in bacteria, which is how they exert their effect

V. CONCLUSION

The study effectively developed, produced, and tested a new class of antibacterial imidazo[1,2-a]pyridine derivatives (9a-l). Starting with 4-methyl acetophenone, these compounds were produced utilizing multi-step processes and characterized using FT-IR, NMR, and mass spectrometry. By optimizing molecular interactions with bacterial targets, the structural alterations included in the derivatives intended to enhance antibacterial activity. Several compounds showed substantial activity in antibacterial screening against Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, and Bacillus subtilis. Compounds 9a, 9c, 9e, and 9g stood out. In terms of inhibition zone against Bacillus subtilis, compound 9a stood out among the others, indicating that it has strong antibacterial capabilities. The structural characteristics that enhance cell permeability and target binding, such as hydrophobic groups and electron-donating substituents, coincide with the reported activity. Antibacterial activity was further substantiated by molecular docking experiments, which predicted significant ligand-receptor interactions with the key enzyme for bacterial DNA replication and cell division, DNA gyrase. The docking findings confirmed that compound 9a is a potential inhibitor of bacterial enzymes, because it established stable hydrogen bonds and had a favorable binding free energy. Evidence from this work suggests that imidazo[1,2-a]pyridine derivatives may be useful as antibacterial agents, particularly against bacteria that have developed resistance to other drugs. Opportunities for further optimization to enhance potency, selectivity, and pharmacokinetic features arise when the chemical structure may be fine-tuned. Investigating cytotoxicity profiles, doing in vivo testing, and studying synergistic effects with conventional antibiotics are all areas that will be the subject of future research. The compounds' potential for use in the creation of antimicrobial drugs may be further enhanced by broadening their reach to include additional types of bacteria and diseases that are resistant. To fight bacterial infections and new resistance problems, the produced compounds provide a potential framework for the development of next-generation antimicrobial drugs.

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