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Molecular Docking, ADMET, Synthesis and Characterisation of Isoxazoline Derivatives as Potential Antibacterial Agents

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Abstract
The rising problem of antimicrobial resistance (AMR) underscores the pressing necessity for novel antibacterial agents, especially to address Mycobacterium tuberculosis. This work involved the synthesis and evaluation of four isoxazoline derivatives as prospective antibacterial medication candidates. Molecular docking was conducted utilizing the crystal structure of M. tuberculosis protein tyrosine phosphatase (PDB ID: 2OZ5) to predict binding affinities and inhibition constants (Ki). Among the synthesized derivatives, compound 3-(pyridin-2-yl)-5-(p-tolyl)-4,5-dihydroisoxazoline **(4a)** demonstrated the lowest binding energy with Chain A (−6.75 kcal/mol; Ki = 11.34 μM), whereas 3-(pyridin-3-yl)-5-(*p*-tolyl)-4,5-dihydroisoxazoline **(4b)** displayed the most favorable interaction with Chain B (−7.28 kcal/mol; Ki = 4.60 μM). ADMET analyses conducted with SwissADME, ADMETLab, and Molsoft verified that all compounds adhered to principal drug-likeness criteria and exhibited satisfactory pharmacokinetic profiles, with Molsoft scores varying from −2.0 to 2.0. The structures of isoxazolines were confirmed using FTIR and ^{1}H NMR analysis. The compounds were synthesized through chalcone production followed by cyclization with hydroxylamine hydrochloride, resulting in chalcones (54.50–72.80%) and isoxazolines (10.62–30.10%). The results suggest that the synthesized isoxazoline derivatives, especially)**4a(** and)**4b(**, are promising candidates for the development of future antibacterial medicines aimed against *M. tuberculosis.*
Keywords: Isoxazoline; Molecular docking; ADMET; Antibacterial

Introduction

Antimicrobial resistance (AMR) has emerged as a pressing global health crisis, threatening the effectiveness of current treatments against infectious diseases, especially *Mycobacterium tuberculosis.* Both Gram-positive and Gram-negative bacterial strains have developed significant resistance to commonly used antibiotics, rendering many therapies ineffective and directly increasing the mortality rates. According to the World Health Organisation (WHO), bacterial AMR was directly responsible for 1.27 million deaths in 2019 and contributed to nearly 5 million deaths in 2020, underscoring its devastating impact on healthcare systems. The rise of AMR is primarily driven by the improper use of antibiotics and spontaneous genetic mutations in bacteria [1]. The situation is worsened by the critically underdeveloped pipeline of new antibiotics, where the WHO has reported a scarcity in antimicrobial candidates, signalling an urgent need for novel and effective antibacterial agents to combat drug-resistant strains.

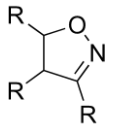
Isoxazolines are heterocyclic compounds that have been reported to be potent antimicrobial agents [2]. Isoxazoline is very important when it comes to modern drug discovery as an essential pharmacophore. It can address the current gap in the antibiotic pipeline through different isoxazoline derivatives.

Drug development is a lengthy, complex, and costly process, entrenched with a high degree

of uncertainty that a drug will succeed [3]. Hence, to streamline the drug discovery and development process, molecular docking is often employed to evaluate potential antibacterial agents, such as isoxazoline derivatives, which serve as a form of screening prior to *in vitro* cell culture-based assays or chemical modifications [4].

In addition to molecular docking, ADMET was also employed in this study for evaluating the pharmacokinetics and safety aspects of potential drug candidates. ADMET, which stands for Absorption, Distribution, Metabolism, Excretion and Toxicity, is able to predict how the human body process and react to the compound, in terms of the drug absorption into the body as well as drug-drug interactions. This approach gave numerous advantages, which reduced the time, effort, and financial expenditure considerably [5].

Isoxazolines are heterocyclic chemical compounds with a five-membered ring, which has one atom each of oxygen and nitrogen, located adjacent to one another at positions 1 and 2. Isoxazolines are considered to be valuable intermediates as a moiety for many chemicals because of the presence of the isoxazoline ring system, which provides a particular convenience to modify the substituents in their ring structures [6]. It has gained importance in the pharmaceutical field due to its broad use as an active hypoglycemic, anti-diabetic, anti-pyretic, analgesic, anti-inflammatory, antiviral, antiallergic, anticancer, antidepressant, and antimicrobial agent. Figure 1 represents the chemical structure of isoxazoline.



R: alkyl/aryl/H

Figure 1 Chemical structure of isooxazoline

Studies have shown the potential of isoxazoline derivatives as effective antibacterial agents against both Gram-positive and Gram-negative bacteria. The structural features of isoxazoline compounds suggest that the isoxazoline scaffold plays a critical role in their antibacterial activity. Notably, some derivatives show significant inhibitory effects, highlighting their potential as alternatives to conventional antibiotics, particularly in the face of rising antimicrobial resistance. Further optimisation of these compounds could enhance their potency and pharmacokinetic properties, offering promising candidates for future antibacterial drug development.

Docking is regarded as highly beneficial and has revolutionised the process of drug discovery, design, and optimisation. This is because drug discovery has always been a very time-consuming and challenging process. Typically, it takes 10–15 years and requires an investment of over $ 2.5 billion to bring a novel medication to the market [7]. This is because drugs are typically found by accident through a process of trial and error, utilising high-throughput screening techniques that test the activity of several compounds against a target *in vitro* [8]. Hence, molecular docking is said to be essential in drug discovery, as it allows for the identification of promising therapeutic candidates to be faster, cheaper, and more effective [9]. Molecular docking achieves that by screening large numbers of small molecules in an effort to predict and identify potential hits.

ADMET, an acronym for Absorption, Distribution, Metabolism, Elimination and Toxicity, is very significant in the early stages of drug discovery and development because a high-quality potential drug should not be evaluated solely on the efficiency against the therapeutic target but must also show appropriate ADMET properties at a therapeutic dose. Undesirable pharmacokinetics and toxicity are major contributors to drug development failures and may pose potential health risks to humans. Hence, online tools such as SwissADME, Molsoft and ADMETLab are instrumental in this assessment. These online tools have several predictive models for assessing the pharmacokinetic properties and drug-likeness of potential drugs, such as BOILED-Egg, iLOGP and Bioavailability Radar.

Materials and methods

Molecular docking

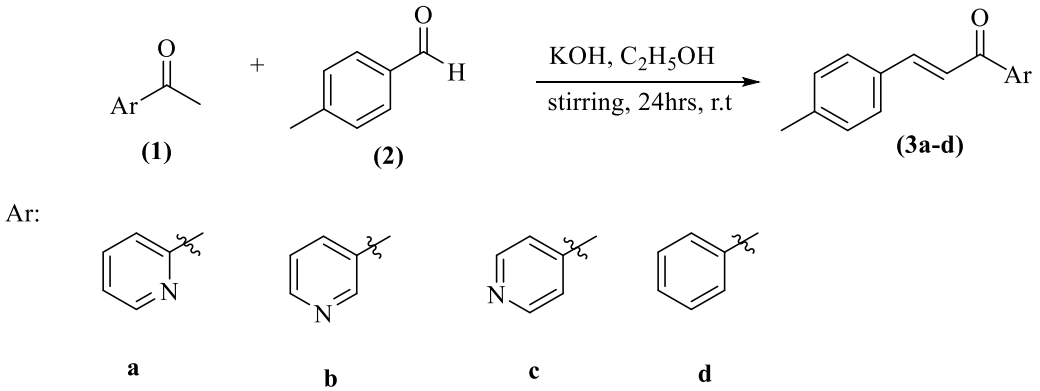
The crystal structure was retrieved from PDB in .pdb format. Then, solvent molecules were removed from the protein, which were subsequently validated through the use of PyMOL. The ligand structures were drawn in ChemDraw, converted to 3D in Avogadro, and structure-optimised to obtain optimal conformations. The optimised structures were saved as PDB files and converted to PDBQT format for docking studies. Isoxazoline derivatives and the pure protein were loaded into the AutoDock software)Auto Dock 4.2 program and dock tools 1.5.4(. Population size and the number of runs were set at 100 and 20, respectively, in order to get more accurate results. After the run, the results for both the lowest free binding energy and the inhibition constant were also obtained, corresponding to each of the ligand conformation. The results were then visualised in both 2D and 3D using the Discovery Studio 2020 Client program.

ADMET Analysis

The computational input of the four isoxazoline derivatives was loaded into SwissADME as SMILES at the input zone, where these inputs were obtained through a molecular sketcher, ChemDraw. The drug likeness of each isoxazoline was evaluated by assessing the output panels. Several computational parameters were assessed, including Physicochemical Properties, Lipophilicity, Pharmacokinetics, Drug-likeness and Medicinal Chemistry. Molsoft were also used to evaluate the drug-likeness score of the four isoxazoline derivatives. Upon computing the input, Molsoft generated a drug-likeness score for the input using Molsoft's chemical fingerprints and the isoxazoline derivatives were evaluated based on the drug-likeness model score.

General procedure for synthesis of chalcones (***3a-d***)

Acetyl-substituted pyridine derivatives (0.01 mol) **(1)** or acetophenone and 4-methylbenzaldehyde (0.01 mol) **(2)** were each dissolved in ethanol, respectively, in separate beakers. Each beaker containing the respective reagents was added to the round-bottomed flask before adding 10% KOH to the resulting mixture as a catalyst. The resulting mixture was stirred on an electromagnetic stirrer for 24 hours at room temperature. The resulting mixture was then filtered by vacuum filtration, washed, dried in an oven and recrystallised from ethanol to give crystals of chalcone (**3a-d**). Scheme 1 illustrates the synthetic pathway for chalcone (**3a-d**).



Scheme 1 Synthetic pathway for chalcone **(3a-d)**

*Synthesis of (E)-1-(Pyridin-2-yl)-3-(p-tolyl)prop-2-en-1-one **(3a)***

Compound **(3a)** was obtained from 2-acetylpyridine and 4-methylbenzaldehyde, using procedure mentioned in section 3.3.2 to give a white crystalline powder; Yield: 72.8 %; FT-IR (cm^{-1}); 3051 (aromatic C-H), 3008 (C-H sp^2 alkene), 2905 (C-H sp^3 alkane), 1685 (C=O), 1586 , 1512 (C=C aromatic), 1568 (C=C alkene), 1433 (C-H sp^3 bending), 1398 (C=N), 1355 (C-H sp^3 bending). ^{1}H-NMR (400 MHz, DMSO): δ 2.04 (s, 3H), 5.51 (d, 1H), 6.07 (s,1H), 6.60 (d, 1H), 6.83 (d, 1H), 7.50 (m, 3H), 8.16 (dd, 1H), 8.33 (dd, 1H), 8.44 (dd, 1H).

*Synthesis of (E)-1-(Pyridin-3-yl)-3-(p-tolyl)prop-2-en-1-one **(3b)***

Compound **(3b)** was obtained from 3-acetylpyridine and 4-methylbenzaldehyde, using procedure mentioned in section 3.3.2 to give a white crystalline powder; Yield: 54.87 %; FT-IR (cm^{-1}); 3044 (aromatic C-H), 3001 (C-H

sp^2 alkene), 2910 (C-H sp^3 alkane), 1673 (C=O), 1585, 1476 (C=C aromatic), 1568 (C=C alkene), 1398 (C=N). ^{1}H-NMR (400 MHz, DMSO): δ 2.04 (s, 3H), 5.51 (d,1H), 6.07 (s,1H), 6.60 (d, 1H), 6.83 (d, 1H), 7.50 (m, 3H), 8.16 (dd, 1H), 8.33 (dd, 1H), 8.44 (dd, 1H).

*Synthesis of (E)-1-(Pyridin-4-yl)-3-(p-tolyl)prop-2-en-1-one **(3c)***

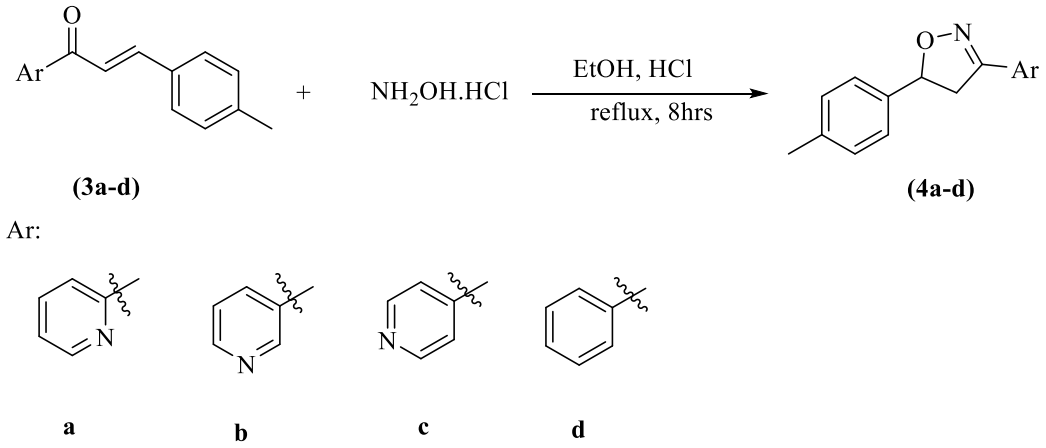
Compound **(3c)** was obtained from 4-acetylpyridine and 4-methylbenzaldehyde, using procedure mentioned in section 3.3.2 to give a white crystalline powder; Yield: 54.50 %; FT-IR (cm^{-1}); 3044 (aromatic C-H), 2949 (C-H sp^2 alkene), 2925 (C-H sp^3 alkane), 1684 (C=O), 1556, 1492 (C=C aromatic), 1556 (C=C alkene),1409 (C=N). ^{1}H-NMR (400 MHz, DMSO): δ 2.09 (s, 3H), 4.90 (d, 1H), 6.75 (d, 2H), 6.95 (d, 2H), 7.21 (d, 1H), 8.45 (d, 2H), 8.25 (d, 2H).

*Synthesis of (E)-1-phenyl-3-(p-tolyl)prop-2-en-1-one **(3d)***

Compound **(3d)** was obtained from acetophenone and 4-methylbenzaldehyde, using procedure mentioned in section 3.3.2 to give a pale-yellow powder; Yield: 68.20 %; FT-IR (cm^{-1}); 3062, 3028 (aromatic C-H), 2917 (C-H sp^2 alkene), 2856 (C-H sp^3 alkane), 1655 (C=O), 1591 (C=C aromatic), 1567 (C=C alkene). ^{1}H-NMR (400 MHz, DMSO): δ 2.36 (s, 3H), 7.29 (d, 2H), 7.67 (t, 1H), 7.70 (d, 1H), 7.79 (d, 2H), 7.88 (d, 1H), 8.14 (d, 2H), 7.57 (t, 2H).

*General procedure for synthesis of isoxazoline (**4a-d**)*

The chalcone derivatives were dissolved in a minimum amount of ethanol before four drops of 1M HCl were added to the stirring solution. Then, hydroxylamine hydrochloride (1 equiv) was dissolved in 5 mL of ethanol and was added dropwise to the stirring solution. The reaction mixture was refluxed in an oil bath for a duration of 24 hours until completion of the reaction. The reaction mixture was then poured into crushed ice and left in the refrigerator for further crystallisation. The solid formed was filtered, washed with water, dried in an oven and recrystallised from n-hexane. TLC identified completion of the reaction. Scheme 2 displays the synthetic pathway for isoxazoline (**4a-4d**).



Scheme 2 Synthetic pathway for isoxazoline **(4a-d)**

*Synthesis of 3-(Pyridin-2-yl)-5-(p-tolyl)-4,5-dihydroisoxazoline **(4a)***

Compound **(4a)** was obtained from reflux with hydroxylamine hydrochloride and 1M HCl in a minimum amount of ethanol for 24 hours to give a pale-purple powder; Yield: 18.87 %; FT-IR (cm^{-1}): 3053 (C-H sp^2 aromatic), 2918 (C-H sp^3), 1218 (C-O).

*Synthesis of 3-(Pyridin-3-yl)-5-(p-tolyl)-4,5-dihydroisoxazoline **(4b)***

Compound **(4b)** was obtained from reflux with hydroxylamine hydrochloride and 1M HCl in a minimum amount of ethanol for 24 hours to give a pale-purple powder; Yield: 10.62 %; FT-IR (cm^{-1}): 3062 (C-H sp^2 aromatic), 2952 (C-H sp^3), 1259 (C-O).

*Synthesis of 3-(Pyridin-4-yl)-5-(p-tolyl)-4,5-dihydroisoxazoline **(4c)***
Compound **(4c)** was obtained from reflux with hydroxylamine hydrochloride and 1M HCl in a minimum amount of ethanol for 24 hours to give a white powder; Yield: 17.63 %; FT-IR (cm^{-1}): 3092 (C-H sp^2 aromatic), 2971 (C-H sp^3), 1256 (C-O).
*Synthesis of 3-phenyl-5-(p-tolyl)-4,5-dihydroisoxazoline **(4d)***
Compound **(4d)** was obtained from reflux with hydroxylamine hydrochloride and 1M HCl in a minimum amount of ethanol for 24 hours to give a white powder; Yield: 30.10 %; FT-IR (cm^{-1}): 3019 (C-H sp^2 aromatic), 2916 (C-H sp^3), 1334 (C-O).

Results and discussion

Molecular docking
The binding site on chain A (x = 4.145 Å, y = 56.206 Å, z = 5.688 Å) and chain B (x = 42.872 Å, y = 74.061 Å, z = 5.257 Å) of protein 2OZ5 are located on the grid map in x, y and z coordinates. By using the binding site grid coordinates, the free binding energies and minimum inhibition constants are summarised in Tables 1 and 2.

Table 1: Binding energy and inhibition constant of compounds against chain A of the protein 2OZ5

Compounds	Run	Binding Energy (kcal/mol)	Inhibition Constant, K_i (μM)
Control	17	-8.12	1.11
(4a)	16	-6.75	11.34
(4b)	5	-6.35	22.06
(4c)	5	-6.30	24.05
(4d)	15	-6.62	13.93

Table 2: Binding energy and inhibition constant of compounds against chain B of the protein 2OZ5

Compounds	Run	Binding Energy (kcal/mol)	Inhibition Constant, K_i (μM)
Control	2	-7.39	3.84
(4a)	18	-7.12	6.03
(4b)	6	-7.28	4.60
(4c)	10	-7.00	6.50
(4d)	1	-7.21	5.17

All isoxazoline compounds showed negative free binding energies against both chain A and B of the protein 2OZ5. This negative value of free binding energies signifies the spontaneity of the binding reaction of the isoxazoline compounds towards the protein 2OZ5, and they will bind on their own without external energy input. Compounds with K_i values lower than 100 μM are still considered to pose as potential inhibitors; hence, the isoxazoline derivatives still have biological relevance. By comparison, compounds **(4a)** and **(4b)** showed the most negative free binding energy among the four isoxazoline compounds at -6.75 kcal/mol and -7.28 kcal/mol when docked against chain A and B of protein 2OZ5, respectively. Both compounds **(4a)** and **(4b)** also showed the lowest K_i value at 11.34 μM and 4.60 μM. Both showed good potency as antibacterial agents to inhibit the activity of the enzyme of protein 2OZ5.

The purpose resides in the intention for understanding the interaction of the isoxazoline compounds with the active sites in the target protein 2OZ5, along with the type of interaction and bond distances, as these interactions have a very significant influence on the stability and free binding energy

of the complex. The best conformation of each isoxazoline compound within the binding site of chains A and B of protein 2OZ5 was illustrated using Discovery Studio Visualiser in 2D with information on the interaction within the protein-ligand complex **(Figure 4** and **Figure 5)**.

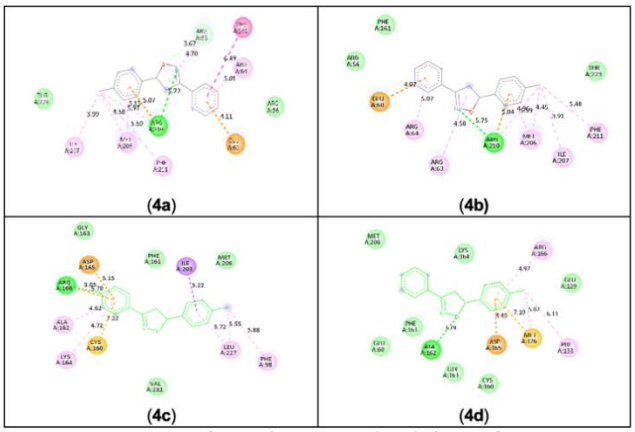


Figure 4 Interactions of isoxazoline compounds (**4a-d**) with chain A of protein 2OZ5

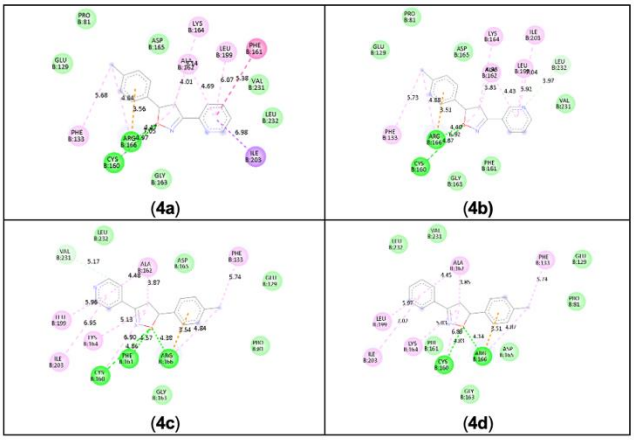


Figure 5 Interactions of isoxazoline compounds (**4a-d**) with chain B of protein 2OZ5

In the 2D diagram, green dotted lines represent the conventional hydrogen bond interactions, while the light green dotted line represents weak van der Waals interactions. Additionally, dotted lines in violet display the π-σ interactions, and alkyl and π-alkyl interactions are shown as pink dotted lines. π-sulfur is visualised as a yellow dotted line while a pink dotted line represents π-π Ti-shaped.

ADMET Analysis

The pharmacokinetics of these isoxazoline compounds and the control were scored based on the predicted 18 ADMET properties, and the predicted results gave a comprehensive insight into the drug-likeness of the compound. The bioavailability radar of control and compounds **(4a)**, **(4b)**, **(4c)** and **(4d)** is generated and shown in Figures 6 and 7, respectively. The drug-likeness properties of the compounds were represented by the red distorted hexagon within the pink region, and the radar plot falls within the pink region, which makes the compounds (**4a-d**) considered drug-like.
considered drug-like.

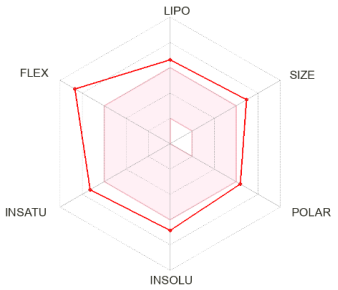


Figure 6 Bioavailability of control (ID: 7XY)

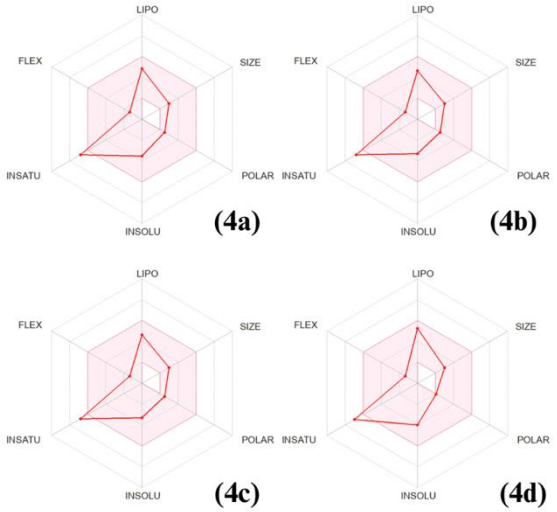


Figure 7 Bioavailability radar for isoxazoline compounds (4a-d)

Notably, all isoxazoline compounds' drug-likeness falls within the optimal parameters to be considered a bioavailable drug, with slightly higher unsaturation indicated by the saturation vertex. Compared to the control drug (ID: 7XY), the control did not fall within the optimal range for all six parameters. From a quick glance at the bioavailability radar, it can be concluded that the isoxazoline compounds generally have sufficient oral bioavailability. In contrast, the control drug, on the other hand, may face issues like poor solubility or low permeability.

Table 3: Comparison of Drug-Likeness Rule Violations and Bioavailability Scores

	Drug-likeness Rules					Bioavailability
	Lipinski	**Ghose**	**Veber**	**Egan**	**Muegge**	**Score**
Control drug (ID: 7XY)	Yes; 1 violation	No; 3 violation	No; 2 violation	No; 2 violation	No 1 violation	0.56
(4a)	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
(4b)	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
(4c)	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
(4d)	Yes;	Yes	Yes	Yes	Yes	0.55

0 violation	

Five commonly used rules for evaluating drug-likeness are Lipinski's Rule, Ghose Rule, Veber Rule, Egan Rule and Muegge Rule. Based on Table 3, all target isoxazoline compounds were observed to adhere to all the drug-likeness rules compared to the control drug (ID: 7XY), which violates at least one criterion on each rule with a total of 9 violations. The bioavailability score of the isoxazoline compounds is very similar at 0.55 and comparable to the control drug, with minimal difference. In conclusion, the four targeted compounds have comparable drug-likeness scores to the control drug, while exhibiting superior drug-likeness and pharmacokinetic properties with no violations.

Molsoft

The overall drug-likeness score and MolLogP of the four targeted isoxazoline derivatives (**4a-d**) and the control were predicted using Molsoft's chemical fingerprints and summarised in Table 4.

Table 4: Drug-likeness and MolLogP of Compounds and Control (ID: 7XY)

Compounds	Drug-likeness Score	MolLogP
Control drug (ID: 7XY)	1.20	5.80
4a	-0.23	3.16
4b	0.14	2.95
4c	-0.24	2.97
4d	-0.65	4.15

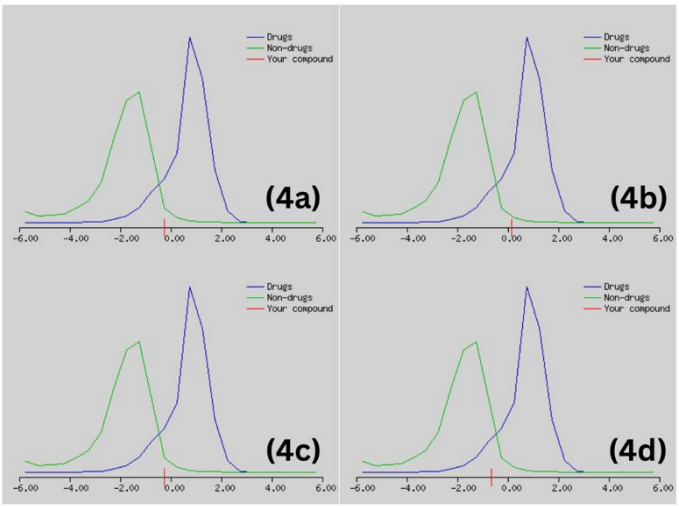


Figure 8 MOLSOFT Drug-likeness Model of Isoxazoline Compounds

Based on the drug-likeness score, all four isoxazoline compounds were considered as potential therapeutic drugs as the scores fall within the region of -2.00 to 2.00. Based on predicted MolLogP, isoxazoline compounds **(4a)**, **(4b)**, **(4c)**, and **(4d)** were expected to have MolLogP values of 3.16, 2.95, 2.97 and 4.15, which are well within the recommended limit of less than 5.0 and hence, did not show any violations towards the Lipinski Rule of Five (RO5).

Characterisation

The IR spectrum of the isoxazoline derivatives typically has an absorption band corresponding to the C-H aromatic stretching ranging from 3000 to 3100 cm^{-1}. Not only that, but there is also the C-H stretching of sp^3 carbon of the methyl group, ranging from 2900 to 3000 cm^{-1}. Most importantly, there is the C=N stretching of the isoxazoline ring, which ranges around 1700 cm^{-1}.

Conclusion

This study successfully synthesised and characterised four isoxazoline derivatives (**4a**–**d**), which showed promising antibacterial potential based on molecular docking, ADMET, and drug-likeness evaluations. Compounds **(4a)** and **(4b)** demonstrated the strongest binding affinities and lowest inhibition constants against the target protein 2OZ5, indicating their potential as lead candidates. All isoxazoline compounds displayed favourable ADMET profiles, better drug-likeness, and improved safety compared to the control drug (ID: 7XY). However, the synthesis methods used were not environmentally friendly, and future work should explore greener alternatives such as microwave-assisted or solvent-free approaches. Further structural analysis and biological validation through antibacterial assays are recommended to confirm the therapeutic potential of these compounds.

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