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Role of 4-Phenylbutyric Acid in DNA and Protein Binding and its Functional Analysis

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Abstract: 4-Phenylbutyric acid (4-PBA) is a small molecule known for its protein folding capacity to reduce endoplasmic reticulum (ER)-stress. This study aimed to explore the potential of 4-PBA by studying its interactions with DNA and protein and examining its effects on cellular toxicity and antibacterial activity. UV-VIS absorption spectroscopy demonstrated that 4-PBA effectively binds to calf thymus DNA (CT-DNA), as indicated by an evident hyperchromic shift, suggesting stable intercalating interactions. Similarly, the fluorescence quenching assay demonstrated that 4-PBA also interacts with bovine serum albumin (BSA), reducing fluorescence intensity by occupying specific binding sites on the protein. The cytotoxicity analysis using cell counting kit-8 further showed no significant reduction in cell viability of normal human lung epithelial cell line (L132). Subsequently, 4-PBA also exhibited minimal growth inhibition of *Escherichia coli* and *Staphylococcus aureus* bacterial strains, indicating limited antibacterial activity under the tested conditions. Additionally, this study provides a basis for future research towards the molecular mechanisms and therapeutic applications of 4-PBA.

Introduction

In recent years, there has been a growing interest in the therapeutic potential of 4-phenylbutyric acid (4-PBA). 4-PBA, known clinically as Buphenyl, is primarily used to treat urea cycle disorders (Villani et al., 2023; Cao et al., 2016). Originally, it appeared in the scientific literature through the work of Franz Knoop (Knoop, 1968). 4-PBA was used to describe β-oxidation in phenyl-substituted fatty acids (Klob et al.,2015). Recent studies (Klob et al., 2015) have expanded the therapeutic landscape of 4-PBA, highlighting its potential pharmacological activities. It has been identified as an ammonia scavenger, a weak histone deacetylase inhibitor (HDACi), and an inhibitor of endoplasmic reticulum (ER) stress (Klob et al., 2015). Multiple studies have shown 4-PBA as a molecular chaperone that can assist in the folding of proteins (Luo et al., 2015; de Almeida et al., 2007; Wang et al., 2003; Chen et al., 2013; Deka et al., 2022) and prevent protein aggregation within the ER (Chamcheu et al., 2011; Valastyan and Lindquist, 2014). Therefore, by analyzing the binding capabilities between 4-PBA and its target proteins or DNA, researchers can understand how the chaperone modulates the dynamics and function of these biomolecules. For instance, chemical chaperones may bind to specific regions of a protein, stabilizing it in its specific conformation and protecting it from denaturation under ER stress conditions (Saibil, 2013; Deka et al., 2022). Similarly, binding to DNA can affect gene expression by regulating the activity of DNA-binding proteins or by directly interacting with the DNA to influence its conformation and accessibility (Mazaira et al., 2018). These interactions can provide insights into the chaperone's mode of action, including its specificity, binding affinity, and the conformational changes it induces in target molecules. Understanding these mechanisms is essential

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for developing therapeutic approaches to treat diseases in combination with the conventional approaches associated with protein misfolding and aggregation, such as neurodegenerative disorders, inflammatory bowel disease, and cancers (Kolb et al., 2015). Further, its interaction with DNA and proteins must be carefully studied to avoid unintended toxic effects, such as mutagenesis or disruption of essential protein functions (Liebler et al., 2005). Toxicity analysis helps determine whether 4-PBA binds to DNA or proteins in a way that could cause damage or interfere with normal cellular processes. For instance, if 4-PBA binds to DNA in a manner that causes structural alterations, it could lead to mutations or interfere with gene expression, contributing to carcinogenesis. Similarly, if 4-PBA binds to proteins in a way that disrupts their function rather than stabilizes them, it could lead to adverse cellular outcomes, including apoptosis or impaired cell signaling pathways (Kusaczuk et al., 2015). Therefore, the present study investigates the binding affinity of 4-PBA with DNA and protein to understand its molecular interactions and potential mechanisms of action, particularly how it might influence cellular processes. Subsequently, the cytotoxicity effect in a normal human cell line (L132) was also studied to ensure the therapeutic potential of 4-PBA. Additionally, evaluating its anti-bacterial effect is crucial to determine whether 4-PBA can selectively inhibit bacterial growth.

Materials and methods

DNA binding analysis

Studying the interactions between 4-PBA (Cat No: 1821-12-1; Sigma-Aldrich) and CT-DNA (calf thymus DNA) (Cat No: 73049-39-5; Sigma-Aldrich) is essential for understanding the binding affinity of 4-PBA. The absorbance ratio of CT-DNA at 260/280 nm was observed to be about 1.8:1, proving that the CT–DNA was devoid of protein contamination. Initially, various concentrations of CT-DNA ranging from 10 µM to 100 µM (10 µM, 20 µM, 40 µM, 60 µM, 80 µM, 100 µM) and 4-PBA (10 µM, 20 µM, 30 µM, 40 µM, 50 µM) are taken and the absorption spectra are recorded using a UV-visible spectrophotometer (Model No.: UV-1800 240V) for reference.

50 µM concentration was selected for 4-PBA and incubated separately with varying concentrations of CT-DNA (10 µM, 20 µM, 40 µM, 60 µM, 80 µM, 100 µM) and the absorption spectra were recorded using a UV-visible spectrophotometer. The 50 µM concentration of 4-PBA was selected for the DNA binding assay due to its effective interaction with CT-DNA, providing stronger absorption spectra compared to lower concentrations. The concentrations of the compound affect various aspects of the interaction, including binding affinity, saturation, mode of interaction, and potential biological relevance (Cox et al., 2009).

Protein binding analysis

BSA (bovine serum albumin) binding studies are usually carried out as a parameter of biophysical characterization. The present study analysed the emission spectra of the BSA with the compound (4-PBA). Due to the existence of trp-212 and trp-134 residues in their molecular makeup, BSA exhibits an emission band at 350 nm upon excitation at 295 nm (Balakrishnan et al., 2019). Initially, the emission spectra of BSA and 4-PBA with varying concentrations of 1 µM, 2 µM, 3 µM, 4 µM, and 5 µM for BSA and 10 µM, 20 µM, 30 µM, 40 µM, and 50 µM for 4-PBA were recorded for reference using Jasco Spectrofluorometer FP-8300. Finally, 4-PBA in various concentrations viz., 10 µM, 20 µM, 30 µM, 40 µM, and 50 µM are incubated separately for 2 hours at 37°C with 3 µM concentrations of BSA (Cox et al., 2009; Balakrishnan et al., 2019) and the emission spectra are recorded. Studying the concentration-dependent behavior of 4-PBA in protein binding studies provides valuable insights into the interactions' nature, potential mechanisms, and relevance in a biological context.

Effect of 4-PBA on L132, normal lung cell line

LI32, a human lung epithelial cell line, was purchased from NCCS-Pune, India. Cells were culture expanded in Dulbecco's Modified Eagles Medium (DMEM) containing 20% fetal bovine serum (FBS) and 1X penicillin/Streptomycin antibiotic and maintained at 37°C with 5% CO_2.

Cell viability analysis

The cell counting kit-8 (CCK-8) (Sigma-Aldrich Cat No:96992) was used to determine the viability of L132 cells. 2×10^3 cells per well were seeded in a 96-well plate. After 24 h of seeding the cells, they were treated with various concentrations of 4-PBA (10 µM, 50 µM, 100 µM, 250 µM, 500 µM, 750 µM, 1 mM) and incubated for 72 h. Subsequently, the absorbance was measured at 450 nm with a microplate reader (Robonik, readwell TOUCH ELISA Plate Analyser).

Anti-bacterial activity of 4-PBA

The antibacterial activity of 4-PBA was evaluated using the disc diffusion method (Krishnan et al., 2019). The bacterial culture (*Escherichia coli* (MTCC 739), and *Staphylococcus aureus* (MTCC 737) were uniformly spread on the surface of the Mueller Hinton agar plates using sterile cotton swabs. A stock solution of 1 mM 4-PBA was prepared; further, the working standards of 4-

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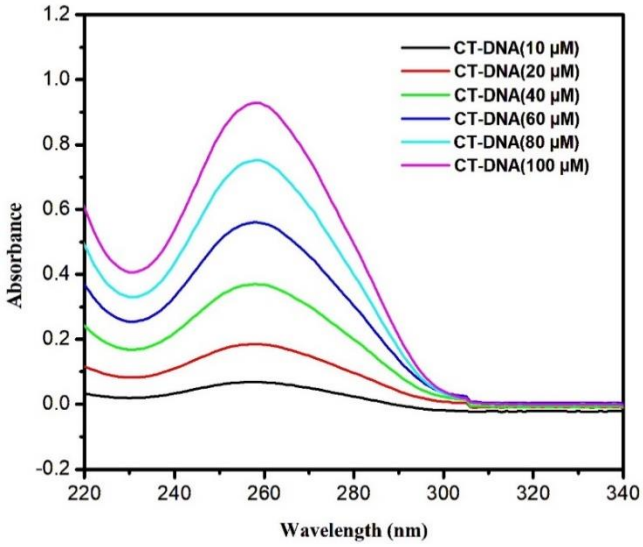

Figure 1(a). Graph illustrating the absorption spectra of CT-DNA with varying concentrations ranging from 10 µM-100 µM (10 µM, 20 µM, 40 µM, 60 µM, 80 µM, and 100 µM).

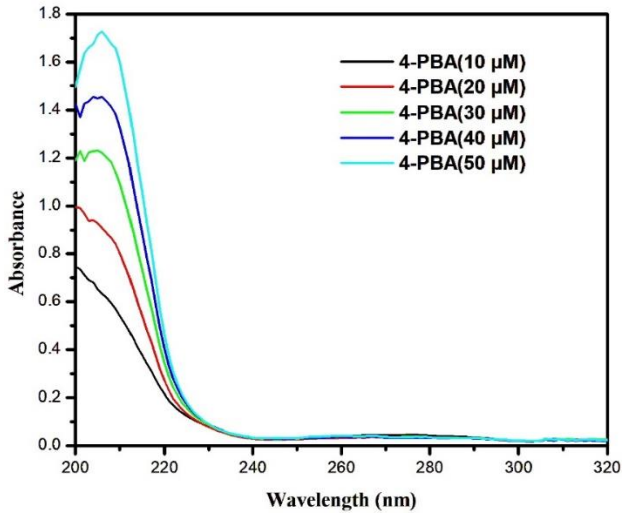

Figure 1(b). Graph illustrating the absorption spectra of 4-PBA with varying concentrations ranging from 10 µM, 20 µM, 30 µM, 40 µM and 50 µM.

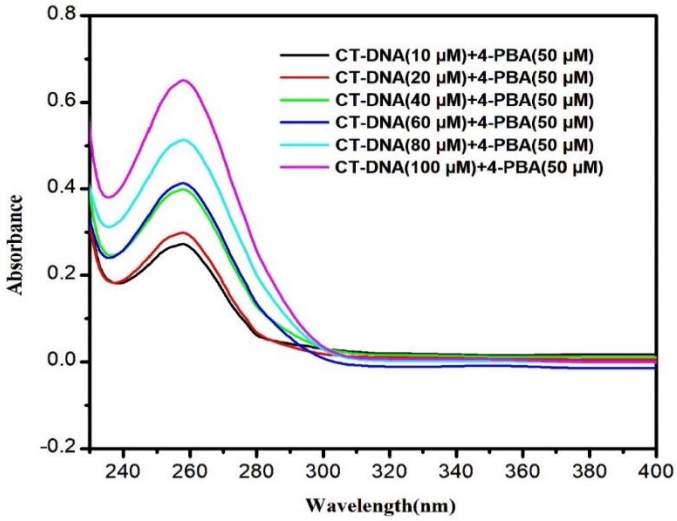

Figure 1(c). Graph illustrating UV-VIS absorption spectra of 4-PBA at a constant concentration of 50 µM with varying concentrations of CT-DNA (10 µM, 20 µM, 40 µM, 60 µM, 80 µM, and 100 µM). The pronounced hyperchromic shift at 260 nm indicates stable intercalating interactions between 4-PBA and DNA base pairs, demonstrating the binding capacity of 4-PBA with CT-DNA.

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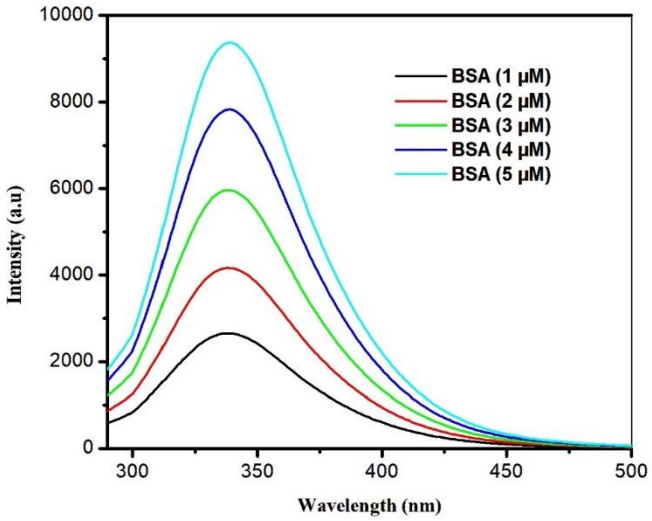

Figure 2(a). Graph illustrating the emission spectra of BSA with increasing concentrations of 1 µM, 2 µM, 3 µM, 4 µM and 5 µM.

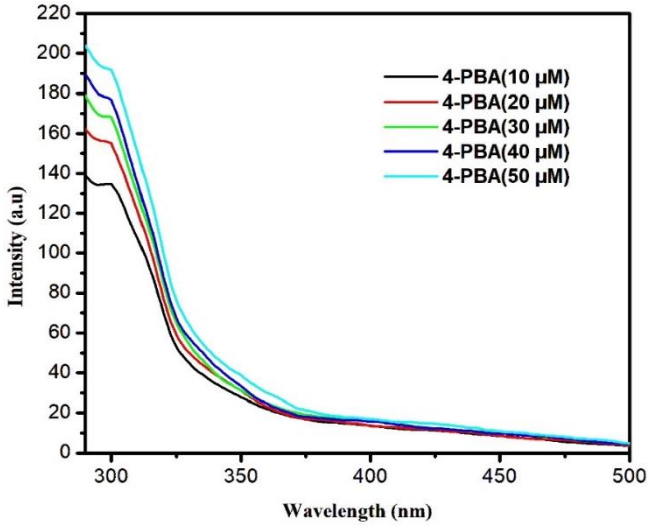

Figure 2(b). Emission spectra of 4-PBA with incremental concentrations of 10 µM, 20 µM, 30 µM, 40 µM and 50 µM.

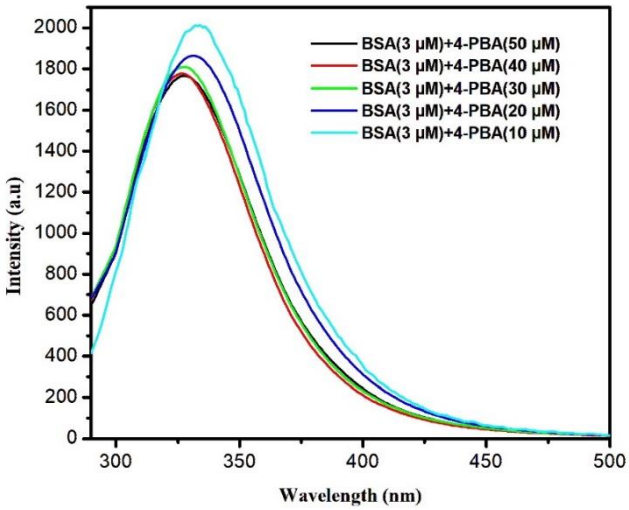

Figure 2(c). Fluorescence quenching spectra of BSA (3µM) in the presence of increasing concentrations of 4-PBA (10-50 µM). The decrease in fluorescence intensity suggests that 4-PBA binds to BSA, occupying binding sites and causing quenching without significant changes in the protein's conformation.

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PBA were prepared in varying concentrations (10 µM, 15 µM, 20 µM, 25 µM). The selected concentrations of 4-PBA were applied to each 6 mm sterilized paper disc, and the plates were incubated at 37ºC for 24 h. Further, gentamicin (1 mg/mL) was used as a control in the present study. Following 24 h of incubation, the zone of inhibition was measured using a metric ruler.

Statistics

Statistical analysis was performed by using GraphPad V8.4.2 software (Online version). The student's t-test evaluated the significant difference between the treatment and control groups. The results are presented as mean ± standard error. The asterisk (*) indicated the *p*-value < 0.05.

Results

UV-VIS absorption spectroscopy of 4-PBA with CT-DNA

The current study focuses on the interaction between 4-PBA and CT-DNA. The experiment involves conducting an absorption titration, where the concentration of 4-PBA is kept constant at 50 µM, while variable concentrations of CT-DNA (10 µM, 20 µM, 40 µM, 60 µM, 80 µM, and 100 µM) were used. The absorption spectra of the compound 4-PBA with various concentrations of CT-DNA are depicted in Figure 1(c). Notably, visible peaks at 260 nm within the spectra indicate the binding interaction between CT-DNA and 4-PBA. An evident hyperchromic shift is distinctly observed. This hyperchromic effect demonstrates intercalating and stable binding interactions between 4-PBA and CT-DNA. Further, the peaks for CT-DNA and 4-PBA alone that are used as references are shown in Figure 1(a-b).

Fluorescence quenching studies of 4-PBA with bovine serum albumin

The graph in Figure 2(c) shows a decrease in fluorescence intensity with increasing concentrations of 4-PBA. This phenomenon is known as fluorescence quenching. It suggests that 4-PBA binds to BSA in a way that either physically shields the tryptophan residues from being excited or facilitates non-radiative energy transfer, thereby reducing the fluorescence emission. The quenching effect is more significant as the concentration of 4-PBA increases from 10 µM to 50 µM as shown in Figure 2(c). This implies that more binding sites on BSA are occupied by 4-PBA at higher concentrations, leading to a greater reduction in fluorescence intensity. The saturation or significant quenching at higher concentrations might indicate that the binding sites on BSA are becoming saturated with 4-PBA. The emission peak remains relatively constant regarding wavelength, with no significant red or blue shift observed. This suggests that the binding of 4-PBA to BSA does not cause a major conformational change in the protein's structure, which would typically result in a shift in the Em (emission maximum). Subsequently, the fluorescence intensity of BSA and 4-PBA individually is also represented in Figure 2(a-b).

Cytotoxicity analysis

The results revealed that the 4-PBA treatment to normal lung epithelial cell line (L132) did not significantly reduce cell viability, as shown in Figure 3. The results further suggest that while 4-PBA, when present at concentrations ranging from 10 to 50 µM, can interact with biological macromolecules like DNA and proteins, it does not exert cytotoxic effects on normal cells when treated with doses as stated above.

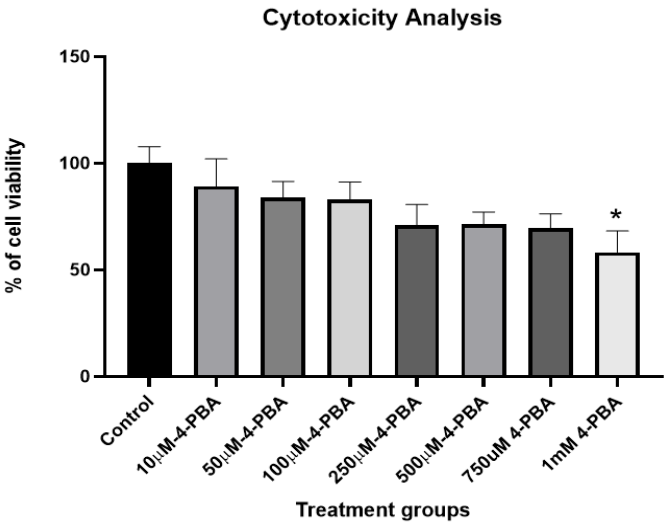

Figure 3. Cytotoxicity analysis of 4-PBA on normal lung epithelial cell line (L132) using the CCK8 assay. The statistical significance is denoted by *$p < 0.05$

Assessment of anti-bacterial activity of 4-PBA

Among the various selected concentrations of 4-PBA (10 µM, 15 µM, 20 µM, 25 µM), a minimal zone of inhibition after treatment with 25 µM of 4-PBA, was observed in *Escherichia coli* (MTCC 739) and *Staphylococcus aureus* (MTCC 737), when compared to gentamicin (C). The zone of inhibition observed was 8 mm for both strains, as shown in Figures 4a (iv) and 4b (iv).

Discussion

This study is important in understanding 4-PBA as a therapeutic agent due to its wide range of biological interactions and potential clinical applications. Investigating the binding affinity of 4-PBA to DNA sheds

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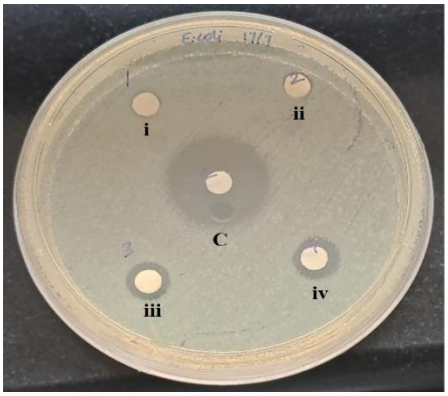

FIG: 4(a) *Escherichia coli* treated with various doses of (4-PBA)

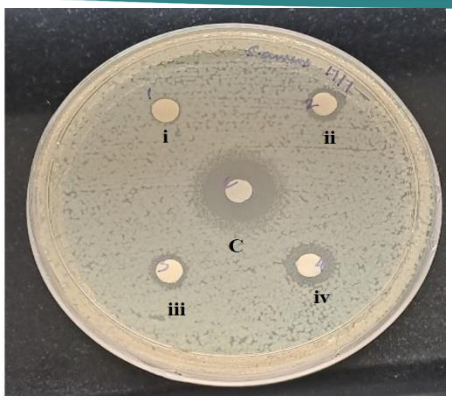

FIG: 4(b) *Staphylococcus aureus* treated with various doses of (4-PBA)

Figure 4(a-b). Antibacterial activity of 4-PBA in *Escherichia coli* (FIG: 4(a)) and *Staphylococcus aureus* (FIG: 4(b)). The zones of inhibition are depicted for varying concentrations of 4-PBA ((i) denotes 10 µM; (ii) denotes 15 µM; (iii) denotes 20 µM; (iv) denotes 25 µM; (C) denotes gentamicin), with the minimal inhibitory activity

Table 1. Table representing the zone of inhibition of 4-PBA against bacterial strains (*Escherichia coli*, and *Staphylococcus aureus*) at various concentrations (10 µM, 15 µM, 20 µM, 25 µM).

Bacterial strains	Concentrations of 4-PBA (µM)	Zone of inhibition (mm)
Escherichia coli	10 µM	0
	15 µM	0
	20 µM	4 mm
	25 µM	8 mm
Staphylococcus aureus	10 µM	0
	15 µM	4 mm
	20 µM	2 mm
	25 µM	8 mm

light on how the compound might influence gene expression and contribute to its therapeutic properties, which are essential for developing targeted therapies. The DNA binding studies revealed that 4-PBA exhibits a significant affinity towards CT-DNA, as observed by the evident hyperchromic effect observed in the UV-VIS absorption spectra. This interaction suggests that 4-PBA might stabilize DNA by intercalating between base pairs, which could affect its role in gene expression and potential therapeutic properties like anticancer and anti-inflammatory. However, the absence of a substantial shift in wavelength indicates that while 4-PBA binds effectively, it does not induce major conformational changes in DNA, which might reduce the risk of genotoxic effects. In DNA binding analysis, hyperchromic and hypochromic shifts indicate changes in absorbance due to drug interaction. A hyperchromic shift, marked by increased absorbance, suggests DNA helix unwinding or intercalation of the drug between DNA bases. In contrast, a hypochromic shift, seen as decreased absorbance, implies tighter DNA structure due to groove binding or compact stacking of strands. These shifts provide insights into the mode of drug-DNA binding and structural changes (Cox et al., 2009; Adhikari et al., 2023; Bhattacharjee et al.,2024). Subsequently, exploring 4-PBA's interactions with proteins like BSA further emphasizes its role in modulating protein function without compromising structural integrity (Balakrishnan et al., 2019), a key factor in therapeutic design. The protein binding analysis, particularly with BSA, further clarifies the molecular behavior of 4-PBA. In protein binding analysis, red shift and blue shift indicate changes in the absorption or emission wavelengths of a drug-protein complex, reflecting drug-protein interactions. A red shift suggests the drug is in a less polar environment, often due to binding in hydrophobic protein pockets, while a blue shift implies a more polar environment or a constrained molecular structure. These shifts provide

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insights into the nature of the drug's interaction with the protein and alterations in its electronic environment (Janjua et al., 2009; Lu et al., 2022). The fluorescence quenching observed with increasing concentrations of 4-PBA suggests a direct interaction where 4-PBA occupies binding sites on BSA, reducing fluorescence intensity. The lack of significant shifts in emission peaks implies that 4-PBA does not induce drastic conformational changes in BSA, which is crucial for maintaining protein function. This characteristic is important for therapeutic applications where preserving protein integrity while modulating its activity is desired (Luo et al., 2022; Sheng et al., 2013; Adhikari et al., 2024). Further, the cytotoxicity analysis demonstrated that 4-PBA does not significantly compromise the viability of normal human lung epithelial cell line (L132), even at concentrations effective in binding to DNA and proteins. This finding highlights the therapeutic potential of 4-PBA, suggesting that it can modulate biological processes without exerting harmful effects on normal cells. Moreover, the antibacterial activity of 4-PBA was evaluated against bacterial strains, revealing a minimal concentration-dependent inhibitory effect. The differential activity observed across bacterial species suggests that 4-PBA's mechanism of action may involve specific interactions with bacterial biomolecules, possibly through its binding to DNA or proteins.

Conclusion

In conclusion, the study provides comprehensive insights into the therapeutic potential of 4-PBA. The ability of 4-PBA to interact with DNA (CT-DNA) and protein (BSA) without causing significant cytotoxicity positions it as a promising candidate for further development in treating various diseases, including those involving protein misfolding. Future *in vitro* and *in vivo* studies should focus on elucidating the precise molecular mechanisms underlying these interactions and exploring the clinical applicability of 4-PBA in a broader spectrum of therapeutic contexts.

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Conflict of interest

The authors declare that there is no conflict of interest.

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