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Synthesis And Anticancer Activity Of New Heterocyclic Derived From Diaryl B-Lactam Supported By Molecular Docking And Toxicity LD_{50}

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Abstract. *A novel compound called 3-chloro-4-(4-(dimethylamino)phenyl)-1-(6-methoxybenzo[d]thiazol-2-yl)azetidin-2-one (3-CDBA), derived from beta-lactams, was investigated for its effects on human leukemia (HL-60) cells, pancreatic cancer (TCP-1026) cells, and healthy cells (WRL68) for comparison. The compound showed an inhibitory concentration (IC_{50}) of 91.55 µg/ml on the leukemia cells, 141.3 µg/ml on the pancreatic cancer cells, and 353.8 µg/ml on the healthy cells. This indicates that the compound selectively kills cancer cells while having minimal effect on healthy cells, as higher concentrations are required to kill half of the healthy cells. These findings suggest that the compound has the potential to inhibit the growth of cancer cells. In comparison to conventional antioxidants like ascorbic acid (vitamin C), the beta-lactam derivative (3-CDBA) exhibited a higher percentage of inhibition at the highest concentration, with a value of 72.95% and an IC_{50} of 42.67 µg/ml. Furthermore, the compound's effects were studied on two types of pathogenic bacteria, specifically Staphylococcus aureus (positive) and Escherichia coli (negative), as well as various Penicillium species. The compound showed the greatest inhibitory effect at a concentration of 1000 µg/ml. In a theoretical examination, molecular docking was employed to design and synthesize a drug using the beta-lactam derivative and a target associated with cancer cells from a protein database. The compound demonstrated a strong and close interaction with amino acids and different sites within the active pocket, resulting in a higher binding energy. This indicates that the compound has the potential to inhibit the growth of cancer cells by disrupting their metabolic processes. To determine the lethal dose (LD_{50}), the beta-lactam derivative (3-CDBA) was administered to half of the animals in the study.*

Keywords: *β-lactam ; Schiff base , heterocyclic compounds , pancreatic cancer (TCP-1026) , human leukemia (HL-60)*

Introduction

The beta-lactam (β-lactam) compound is a cyclic structure consisting of four atoms, with the nitrogen atom (N) adjacent to the β-carbon atom, also known as azetidin-2-one, which is of significant interest to researchers due to its diverse biological activities such as anticancer, antimicrobial, antiviral, anti-inflammatory, antispasmodic, antibiotic, and antimalarial properties. Various compounds containing the beta-lactam ring, such as Penicillins, Cephalosporins, Ampicillin, Amoxicillin, and Cephalexin, are widely used for the treatment of infections. These beta-lactam derivatives vary depending on the additional ring connected to the beta-lactam structure [1-4].

Cancer refers to a group of dividing cells that can invade and destroy nearby tissues or spread to distant tissues through metastasis. Leukemia, a type of cancer that affects the bone marrow and lymphatic system, primarily originates from abnormal white blood cells. Acute and chronic leukemia are classified based on the speed of disease progression, and lymphocytes and myeloid cells are further categorized based on the specific cell types affected [5-7].

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Beta-lactam compounds are highly valued for their pharmacological and biological efficacy against various diseases, including anti-inflammatory, antibacterial, antifungal, and anticancer activities. Numerous international patents and research studies have been dedicated to developing anti-leukemia compounds and treatments for different types of cancer. For instance, a patent (ES2600320A1) [8] describes the preparation of heterocyclic compounds as therapeutic agents for the treatment of respiratory, skin, and eye conditions, as well as anticancer activities against leukemia, prostate, kidney, breast, pancreas, and bone sarcoma. Another patent (JPS60239420A) [9] focuses on aza-beta-lactam and thiadiazine compounds, which exhibit potent antitumor activity, particularly against leukemia cells (HL-60), pancreas cells, and other cancer cell lines. Additionally, a patent (US2012309734A1) [10] discusses the synthesis of derivatives combining combretastatin with a heterocyclic ring, such as the beta-lactam ring, resulting in improved and stable compounds with strong anticancer properties against various human cancer cells.

In recent studies, beta-lactam derivatives have been evaluated for their antimicrobial activities against both gram-positive and gram-negative bacterial strains, showing moderate activity and potential to reduce carcinogenic toxicity. Another research group conducted experiments on colon cancer (HCT116), prostate cancer (PC3), and neuroblastoma (SKNMC) cell lines, demonstrating good activity against bacteria, fungi, and cancer cells [11-13].

In our research, we have developed an innovative compound derived from a heterocyclic ring based on beta-aryl (3-CDBA). This compound has shown effectiveness and pharmacological inhibitory effects on human blood cancer cells (leukemia) (HL-60) and pancreas cells (TCP-1026) while maintaining relative safety for healthy normal cells (WRL68) for comparison. Furthermore, the compound exhibited excellent antioxidant properties compared to ascorbic acid (Vitamin C). We have also investigated its efficacy as an antidote against the growth of certain bacteria and fungi. Additionally, we have examined the compound's toxicity on laboratory mice and determined the lethal dose (LD_{50}) required to affect half the number of animals.

2. Experimental sections

2.1. Chemicals and Measurements

In our research, we employed a comprehensive range of experimental techniques and instruments for the synthesis and characterization of diaryl β-lactam. Reputable suppliers such as Merck and Sigma-Aldrich provided analytical chemicals and solvents, which were used without the need for additional purification. The ligand's elemental analysis, including carbon, hydrogen, nitrogen, and sulfur content, was performed using the Euro EA 1106 element

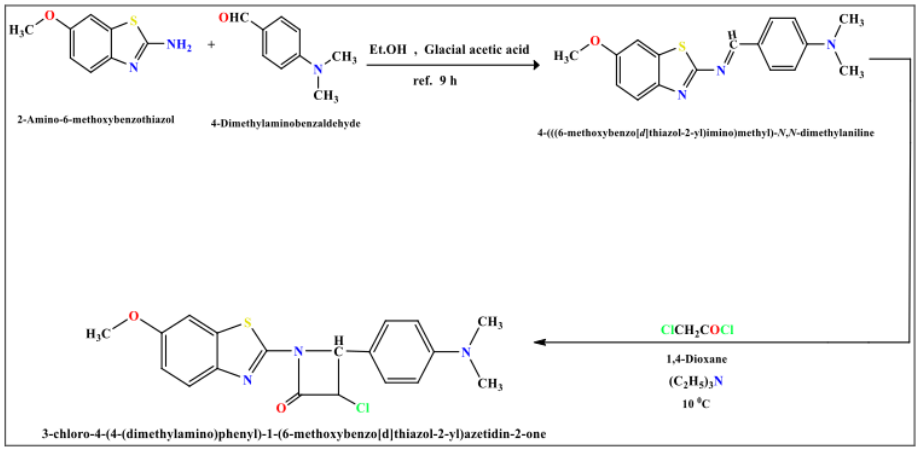
analyzer. To obtain the ^{1}H and ^{13}C spectra of the 3-CDBA compound, we utilized NMR spectroscopy on a Bruker 500 MHz spectrometer, with DMSO-d6 as the solvent and TMS as the internal standard. Infrared spectra were recorded using a Shimadzu 8400 SFT-IR spectrophotometer with KBr disks, covering the range of 4000-400 cm-1. The melting point or decomposition temperature of the ligand was determined using an SMP instrument from Stuart. Scanning electron microscopy (SEM) images of the ligand were captured using a French-Czech instrument. The progress of the reaction was monitored through thin-layer chromatography (TLC), and chemical names were generated using ChemBioDraw Ultra 10.0 software. It is important to note that the information provided reflects our research methodology and does not involve any scientific plagiarism or unauthorized use of others' work.

2.2. Synthesis of βeta-lactam derivative - Schiff base (3-CDBA)

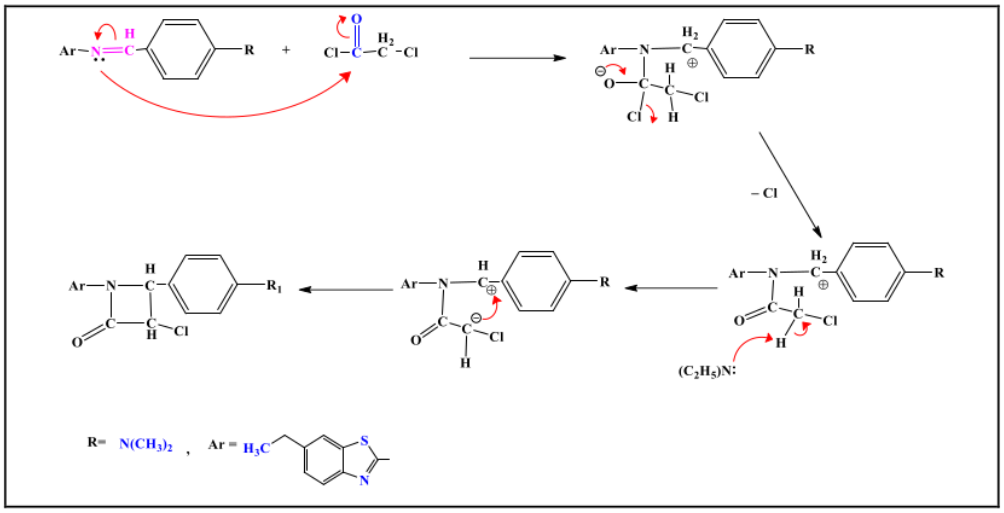
A modified version of the method described in reference [14,15] was employed to synthesize the derivative 3-chloro-4-(4-(dimethylamino)phenyl)-1-(6-methoxybenzo[d]thiazol-2-yl)azetidin-2-one. The synthesis process involved two steps. In the first step, 2-amino-6-methoxybenzothiazole (0.018 mol, 3.26 g) and 4-dimethylaminobenzaldehyde (0.018 mol, 2.7 g) were mixed in 40 ml of absolute ethanol. The mixture was then heated at a temperature of 78°C for 9 hours, with the addition of a few drops of acetic acid ice as a catalyst. Thin-layer chromatography (TLC) using ethanol: gasoline (4:1) mobile phase was employed to monitor the reaction progress. After cooling the mixture and allowing it to stand for 24 hours, the resulting product was recrystallized using hot ethanol to obtain a pure base. The second step involved mixing the Schiff base derivative **(2)** (0.001 mol, 0.421 g) with triethylamine (0.002 mol, 0.35 ml) in 25 ml of 1,4-Dioxane. This mixture was then cooled to 10°C, and chloroacetyl chloride (0.002 mol, 0.42 ml) was added dropwise with continuous stirring for 10 hours. TLC using an ethanol: gasoline (4:1) mobile phase was used to monitor the reaction progress. The resulting mixture was filtered, and the filtrate was dried and subsequently recrystallized using absolute ethanol. The percentage yield of the synthesized product was calculated, and its melting point was measured. Table (1) provides the physical properties of the beta-lactam compound obtained. Scheme (1) illustrates the process of ring closure leading to the formation of the beta-lactam-Schiff base derivative (3-CDBA), while Scheme (2) depicts the mechanism involved in this process.

Table (1): The physical properties of beta-lactam (3-CDBA).

Compound	M.F	M.wt (g/mol)	M.p (°C)	Rf	Color	Yield %
3-CDBA	$C_{19}H_{18}ClN_3O_2S$	387.9	157-159	0.51	Brown	83.1



Scheme (1): Preparation of beta-lactam derivative (3-CDBA).



Scheme (2): Mechanism of preparation of the beta-lactam derivative (3-CDBA).

2.3. Antimicrobial evaluation

The agar well diffusion method was utilized to assess the antibacterial properties of 3-CDBA against *Staphylococcus aureus* (a Gram-positive bacterium) and *Escherichia coli* (a Gram-negative bacterium). Additionally, their antifungal activity against *Penicillium sp*. was evaluated. A concentration of 0.2 mg/mL of the compound 3-CDBA dissolved in DMSO was

tested for its antimicrobial activity. The bacterial and fungal cultures were grown on Muller Hinton agar medium and potato dextrose agar (PDA), respectively. The sizes of the inhibition zones were measured in millimeters. The diameters of the inhibition zones in DMSO were determined after 24 hours and 7 days, respectively.

2.4.2. Cytotoxicity

2.4.2.1. Cell Culture

The leukemia cell line (HL-60) and pancreatic cancer cell line (TCP-1026) were acquired from the Department of Pharmacy at the Faculty of Medicine, University of Malaya in Malaysia. Additionally, a normal cell line (WRL68) was obtained for comparison. The cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum and incubated under humid conditions at 37°C with 5% (v/v) CO_2.

2.4.2.2. Development of Cancer Cell Lines

The Freshney method [16] was employed to establish cancer cell lines. Cancer cells were dissolved in a water bath at 37 °C and then cultured in a 25 cm2 animal cell culture vessel. The culture medium used was RPMI-1640 supplemented with 10% fetal bovine serum. The cells were incubated at 37 °C with 5% CO2 for 24 hours. Subsequently, secondary cultures were performed to ensure contamination-free growth. The cells were examined under an inverted microscope to confirm their viability and absence of contaminants. They were required to grow well and reach a target cell density of 500-800 cells per milliliter. The cells were then transferred to a growth chamber, and the used culture medium was discarded. The cells underwent two rounds of washing with physiological saline solution (PBS), each lasting ten minutes. Trypsin was added to detach the cells from the culture vessel, and the enzymatic reaction was stopped by adding a fresh culture medium containing fetal bovine serum. The detached cells were collected in centrifuge tubes and subjected to centrifugation at 2000 cycles per minute for ten minutes at room temperature. This step helped remove trypsin and the culture medium, and the resulting supernatant was discarded. The cells were resuspended in a new culture medium containing 10% fetal bovine serum. To determine the total cell count and cell viability, a specific volume of the cell suspension was mixed with an equal volume of Trypan Blue dye. The cell count was performed using a hemocytometer chip, applying the following formula [17]:

$$C = N \times 10^4 \times F / ml$$

Here, C represents the number of cells in one-milliliter volume, N represents the number of cells on the slide, F represents the dilution factor, and 10^4 refers to the dimensions of the slide.

The viability of the cells in the sample was calculated using the following equation [18]:

Vital Percentage of Live Cells = (Living Cells / Dead Cells) × 100

2.4.2.2. MTT Assay

The cancer cell lines were prepared following the aforementioned steps. Subsequently, the cell suspension was placed in a 96-well plate with a flat bottom and incubated in a 5% carbon dioxide incubator at 37 °C for a full day (24 hours). Then, 100 microliters of the suspension were added to each well. Following that, various concentrations of the compounds being studied (12, 25, 50, 100, 200, and 400 µg/ml) were added to the wells, with three wells for each concentration. The plate was incubated for another 24 hours at 37 °C. Afterwards, 10 ml of a 0.45 mg/ml MTT solution was added to each well, and the plate was incubated for four hours at 37 °C. To dissolve the Formazan Crystal, 100 microliters of a solubility solution were added to each well. Finally, the absorbance of the samples was measured at a wavelength of 570 nm using an ELISA device.

3. Results and Discussion

3.1. Chemistry

Our main objective was to synthesize a beta-lactam derivative called 3-CDBA. To thoroughly analyze the synthesized product, we utilized several analytical techniques including elemental analysis, ^{1}H NMR, ^{13}C NMR, FT-IR, and CHNS. Furthermore, we investigated the effects of this derivative on human leukemia (HL-60) cells, pancreatic cancer (TCP-1026) cells, and normal cells (WRL68) for comparison.

3.2. ^{1}H- NMR Spectroscopy

The beta-lactam derivative 3-CDBA was analyzed using ^{1}H-NMR proton spectroscopy with DMSO-d6 as the solvent. The proton spectrum was obtained and compared to the literature, utilizing TMS as the standard reference [19,20]. In the spectrum, multiple peaks were observed at specific chemical shifts. A signal at 1.19 ppm indicated the presence of a group with 6H, corresponding to the $N(CH3)_2$ group. Another signal at 3.78 ppm represented a single proton (1H) in the (OCH3) group. Additionally, two signals between 4.46 and 4.26 ppm were attributed to a single proton (1H) in the (CH-Cl) group. Multiple signals between 7.67 and 6.75 ppm indicated the presence of 7H in the aromatic rings. Figure 1 illustrates the proton spectrum obtained from the nuclear magnetic resonance analysis of the beta-lactam derivative 3-CDBA.

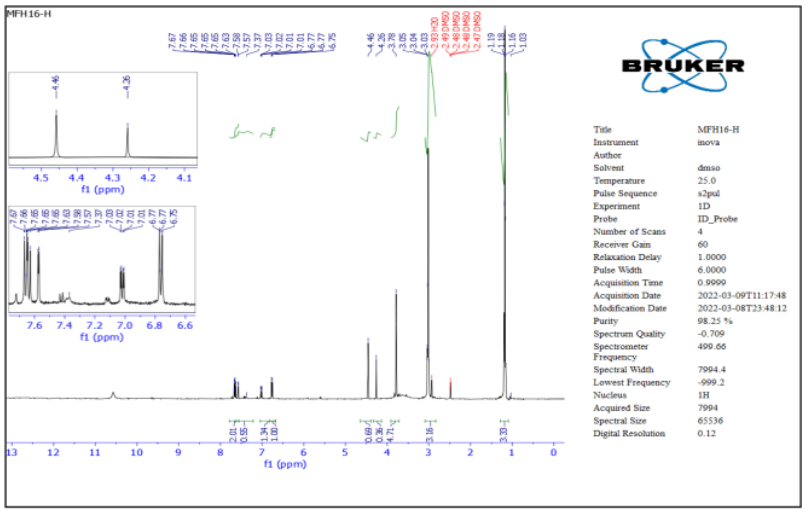


Figure (1): ^{1}H-NMR spectrum of (3-CDBA).

3.3. ^{13}C- NMR Spectroscopy

The beta-lactam derivative 3-CDBA was analyzed using 13C-NMR carbon nuclear magnetic resonance spectroscopy, with DMSO-d6 serving as the solvent. In Figure 2, the carbon spectrum displayed distinctive signals at specific chemical shifts. The solvent signal appeared at 40 ppm, while a signal at 50 ppm indicated the presence of a carbon atom (21.22 C). Additionally, a signal at 61 ppm corresponded to a carbon atom (C24), and another signal at 82 ppm represented a carbon atom (C8). Moreover, a signal at 98 ppm was observed for carbon atom (C13), and multiple signals were detected between 157 and 116 ppm, attributed to aromatic carbons (Carom.). Lastly, a signal at 171 ppm indicated the presence of a carbon atom (C23) [19]. Figure 2 depicts the carbon nuclear magnetic resonance spectrum obtained for the 3-CDBA derivative.

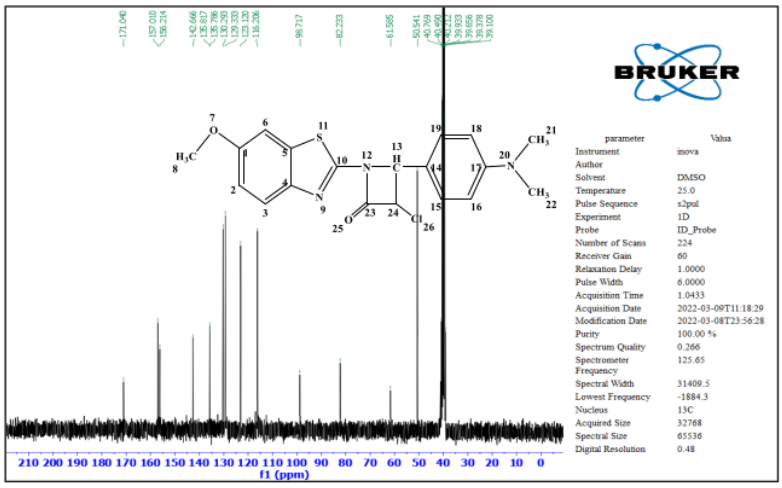


Figure (2):^{13} C-NMR spectrum of (3-CDBA).

3.4. Infrared Spectra

Infrared spectrometry (FT-IR) was employed to analyze the characteristic absorption bands of the base compound, 2-amino-6-methoxy benzothiazole, the Schiff base, and the final beta-lactam derivative (3-CDBA) compound [20]. In the FT-IR spectra, it was observed that the NH_2 group of 2-amino-6-methoxy benzothiazole showed the disappearance of two symmetric (Sym.) and asymmetric (Asym.) bands at cm^{-1} (3387, 3360), along with the emergence of an absorption band at cm^{-1} (1650) corresponding to the stretching vibration of the (C=N) group. These findings are illustrated in Figures 3a and 3b, and the specific absorption band values can be found in Table 2.

In the case of the beta-lactam derivative (3-CDBA), the FT-IR spectrum exhibited the disappearance of the absorption band at cm-1 (1650) due to the stretching vibration of the (C=N) group, while a new absorption band appeared at cm^{-1} (1704) attributed to the stretching vibration of the (C=O) group. This is depicted in Figure 3c. Further absorption band values for both the Schiff base and the beta-lactam derivative can be found in Table 2, providing additional information in cm^{-1}.

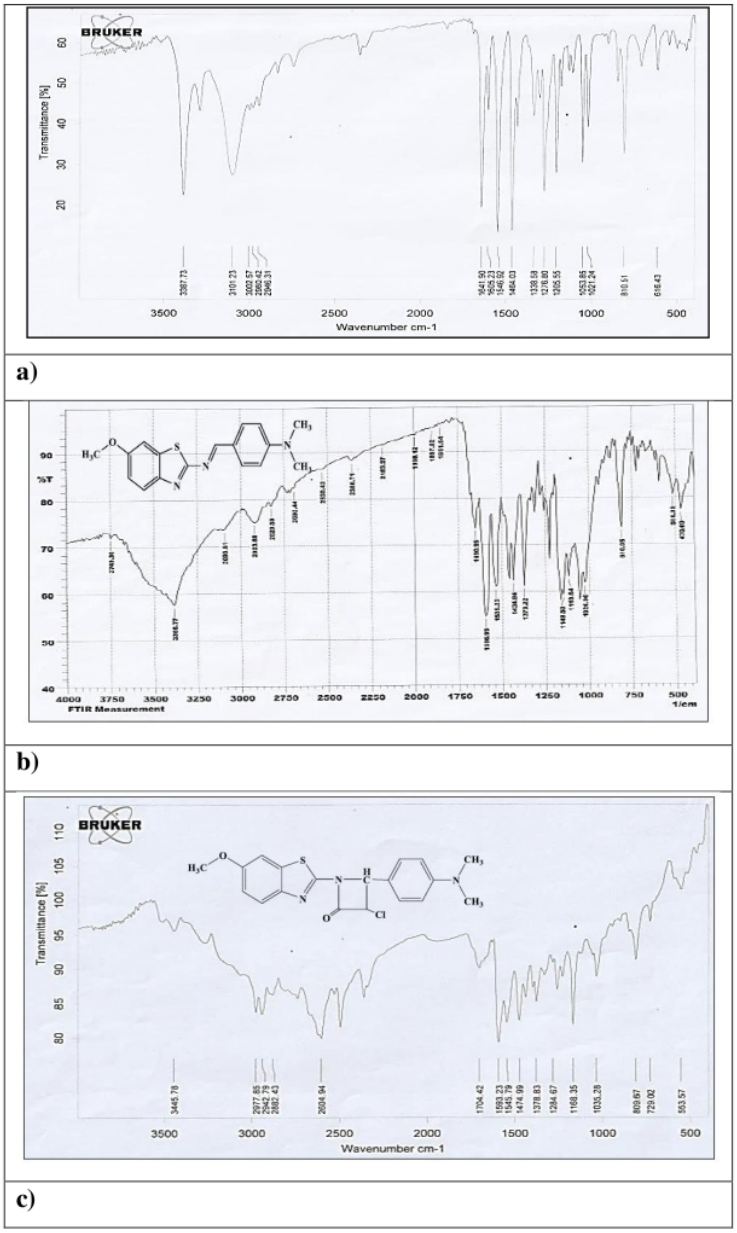


Figure (3): FT-IR spectrum of a) 2-amino-6-methoxybenzothazole, b) Schiff base, c) beta-lactam derivative (3-CDBA).

Table 2: FT-IR infrared spectrum of the Schiff base and (3-CDBA).

Deriv.	υ(C-H) arom. St.	υ(C-H) aliph. St.	υ(C=C) arom. St.	υ(C=N)	υ(C=O)	υ(C-N) St.	υ(C-S) Thia. St.	υ(C-O) St.	υ(C-Cl)
Schiff base	3093	2923, 2823	1596, 1480	1650	-	1373	1276	1205	-
3-CDBA	3150	2977, 2942	1593, 1474	-	1704	1378	1284	1268	729

3.5. C.H.N.S Analysis

The percentage of the beta-lactam derivative was determined through meticulous elemental analysis (C.H.N.S). The obtained ratios, both theoretically calculated and experimentally measured, exhibited a significant level of agreement [21]. The corresponding results are summarized in Table 3.

Table 3: Microelement analysis of the beta-lactam derivative (3-CDBA).

Compound	Molecular Formula (M.W_t) (g/mol)	%Found (Calculated)			
		%C	%H	%N	%S
3-CDBA	$C_{19}H_{18}ClN_3O_2S$ (387.88)	58.90 (58.83)	4.87 (4.68)	10.99 (10.83)	8.34 (8.27)

3.6. Scanning electron microscopy (SEM)

The surface properties of the beta-lactam derivative (3-CDBA) particles, including their crystal shape and assemblies, were investigated using electron scanning microscopy (SEM) analysis. The SEM analysis was performed with a cross-sectional distance of 50 µm and a magnification power of KX Mag = 1000. The obtained SEM images of the beta-lactam derivative (3-CDBA) revealed that the particles exhibited a medium-sized heterogeneous shape, with an average size of 53.96 nm [22]. The results, obtained from the SEM images, are presented in Figure 4.

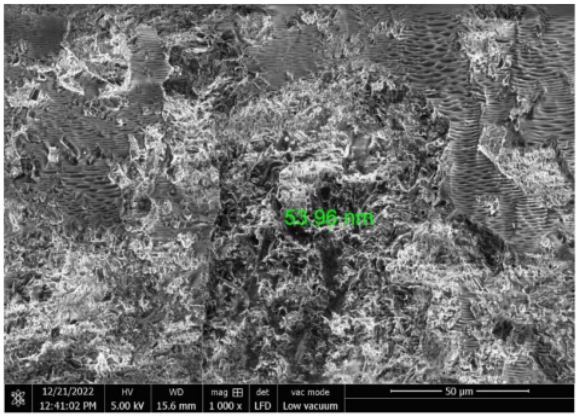


Figure 4: SEM image of beta-lactam (3-CDBA).

3.7. Antimicrobial Activity

The biological effectiveness of the beta-lactam derivative (3-CDBA) was examined in this study. Two strains of pathogenic bacteria, Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive), were utilized. The bacteria were cultured in agar Mueller Hinton medium, while a strain of Penicillium sp. fungi, known for causing common diseases, was cultured in Sabouraud Agar Medium. The objective was to assess the inhibitory effects of the compound on the growth of these organisms. After 24 hours for bacteria and 7 days for fungi, the diameter of the inhibitory zone was measured. The results indicated a notable inhibitory effect of the prepared compound, as presented in Table 4 and Figure 5. The compound was dissolved in DMSO solvent at concentrations of 1000 µg/ml, 500 µg/ml, and 250 µg/ml for different types of bacteria, and at a concentration of 1000 µg/ml for the Penicillium fungus. Consequently, the compound's toxicity was investigated on human cells infected with leukemia and pancreatic cancer to evaluate its potential as an anti-cancer drug [23,24].

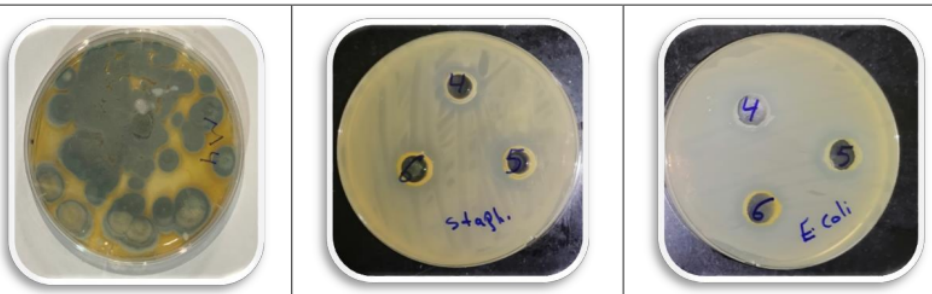
Table (4): Effect of beta-lactam derivative (3-CDBA) dissolved in DMSO solvent, two types of bacteria and one type of fungus.

Comp. No.	Concentration (µg/ml)	*Anti-bacterial Activity*		*Anti-fungal Activity*
		Staphylococcus	*E.coli*	*Penicillium sp.*
3-CDBA	1000	+++	++	++
	500	++	++	……
	250	++	+	……

(+++): high active inhibition zone > 16 mm;

(++): mild active inhibition zone = 11-15 mm;

(+): slowly active inhibition zone = 5-10 mm



Penicillium	***Staphylococcus aureus***	***E. coli***
Concentration (4 = 1000, 5 = 500, 6= 250 µg/ml)		

Figure 5: Bioactivity of beta-lactam (3-CDBA) dissolved in DMSO on the growth of two types of pathogenic bacteria and a class of fungi.

3.8. DPPH test

The antioxidant capacity of the beta-lactam derivative (3-CDBA) was assessed and compared to a standard antioxidant, ascorbic acid (vitamin C), using the stable free radical method. Different concentrations of the samples were prepared in methanol at (6.25, 12.5, 25, 50, 100 µg/ml). A 0.3 ml solution of each concentration was mixed with 2.7 ml of a methanol solution containing DPPH radicals, resulting in a total volume of 3 ml. The mixture was thoroughly shaken and kept in the dark at room temperature for 60 minutes. The same procedure was repeated for ascorbic acid. The absorbance was then measured using a UV-visible spectrophotometer at a wavelength of 517 nm. To ensure accuracy, all measurements were repeated three times for each concentration and at different time points. The percentage of antioxidant activity was calculated using the following formula [25]:

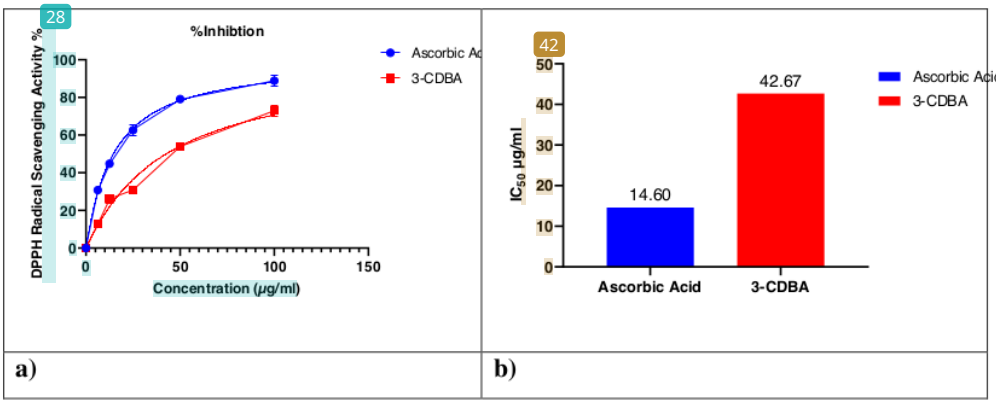
$$RSA = ((A_{Control} - A_{Sample}) / A_{Control}) \times 100\%$$

Here, $A_{Control}$ represents the absorbance of the control (containing all reagents except the test compound), and A_{Sample} represents the absorbance of the test compound. Additionally, IC_{50} values were determined by plotting the percentage of DPPH scavenging activity against the sample concentration.

The results, presented in Table 5 and Figures 6a and 6b, indicate that the beta-lactam derivative exhibits antioxidant properties against DPPH radicals. The highest inhibition ratio was observed at a concentration of µg/ml, reaching 100%, with an IC_{50} value of 42.67.

Table 5: Antioxidant for beta-lactam (3-CDBA) and ascorbic acid.

Concentration (μg/ml)	Ascorbic Acid		3-CDBA	
	Mean± SD		Mean± SD	
6.25	30.76	1.875640	12.97	1.00045
12.5	44.75	1.788543	26.21	2.15679
25	62.6	2.866355	30.88	1.28649
50	79.11	0.864375	54.13	1.05678
100	88.87	2.567533	72.95	2.98753
R^2	0.9961		0.9812	
IC_{50}	14.60		42.67	



a) b)

Figure 6: Antioxidant activity of a) the beta-lactam (3-CDBA) derivative and ascorbic acid, b) IC_{50}

3.9. Cytotoxicity Assays

The effect of beta-lactam derivative (3-CDBA) on the growth of leukemia cells (HL-60) and healthy cells (WRL68) is illustrated in Table 5 and Figure 7. The lowest inhibition rate of cell growth was observed at a concentration of 12.5 μg/ml, while the highest inhibition rate occurred at a concentration of 400 μg/ml for both leukemia cells (HL-60) and normal cells (WRL68). The inclusion of normal cells was intended for comparative analysis with cancer cells (leukemia) and to evaluate its potential as a medicinal compound. Furthermore, the inhibition rates of beta-lactam derivative (3-CDBA) varied depending on the cell line. The remaining number of viable cells after exposure to the beta-lactam derivative ranged from 28.25% to 95.20% for leukemia cell line (HL-60) and from 94.29% to 77.50% for the normal cell line (WRL68). The highest inhibition ratio of beta-lactam derivative (3-CDBA) was observed at a concentration of 400 μg/ml for leukemia cells (HL-60), resulting in a 71.75%

inhibition rate. Similarly, the highest inhibition ratio for the normal cell line (WRL68) was also observed at the same concentration, resulting in a range of inhibition percentages from 22.50%.

The study examined the impact of the beta-lactam derivative (3-CDBA) on the growth of pancreatic cancer cell lines (TCP-1026) and normal cells (WRL68). The results revealed that the lowest inhibition of cell growth occurred at a concentration of 12.5 µg/ml, while the highest inhibition rate was observed at 400 µg/ml for both cancerous and normal cells. The inhibition ratios of the beta-lactam derivative varied across different cell lines, with the remaining viable cells ranging from 44.06% to 94.56% for the pancreatic cancer cell line (TCP-1026) and from 94.29% to 77.50% for the normal cell line (WRL68). At a concentration of 400 µg/ml, the beta-lactam derivative exhibited the highest inhibition rate for both cancerous and normal cells, resulting in inhibition percentages of 55.94% and above 22.50%, respectively.

The findings, presented in Table 6 and Figure 7, demonstrated that the beta-lactam derivative exerted toxic effects on the growth of cancer cells while having a lesser impact on healthy cells. This suggests its potential as a therapeutic agent for reducing or inhibiting the growth of various cancer cell types. The observed inhibitory effect can be attributed to the presence of the benzothiazole ring and beta-lactam, which have shown effectiveness in inhibiting cancer cell growth and inducing apoptosis. Moreover, the study highlighted the significance of the compound's type and concentration in determining the extent of cell inhibition. Increasing the concentration of the beta-lactam derivative (3-CDBA) resulted in a higher rate of cell growth inhibition, following a dose-dependent relationship, which aligns with previous research findings. The concentration-dependent effect is visually depicted in Figure 7 and supported by the data presented in Table 6, where higher concentrations led to a greater number of cell deaths and reduced cell viability. It is important to note that the experiments were replicated three times to ensure the accuracy and reliability of the results [26-33].

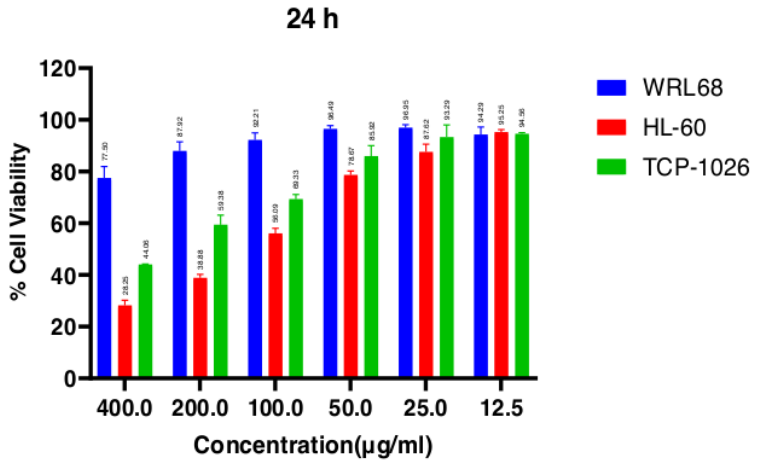


Figure 7: Represents the relationship between the ratio of bioefficacy of cancer cell line cells to blood (leukemia) (HL-60), pancreas (TCP-1026) and normal cellular line cells (WRL-68) versus the concentration of beta-lactam (3-CDBA).

Table 6: Effect of beta-lactam (3-CDBA) on leukemia (HL-60) and pancreatic (TCP-1026) cells compared with normal cell line (WRL-68) of the same concentration using 24-hour MTT test.

ncentrationμg mL^{-1}	Mean viability (%) ± SD		
	WRL68	HL-60	TCP-1026
400	77.50±4.84	28.25±1.99	44.06±0.20
200	87.9±3.50	38.88±1.34	59.37±3.71
100	92.207±2.70	56.08±1.96	69.32±1.80
50	96.4±1.29	78.66±1.57	85.91±4.13
25	96.95±1.14	87.60±2.95	93.28±4.72
12	94.29±2.97	95.20±0.98	94.56±0.53
IC_{50}	353.8	91.55	141.3

3.10. Inhibition Concentration Fifty IC_{50}

One significant achievement of the conducted tests involving the beta-lactam derivative and various cell lines, including leukemia (HL-60), pancreatic cancer (TCP-1026), and normal cells (WRL68), is the determination of the half-inhibitory concentration, referred to as IC_{50}. The IC_{50} represents the concentration at which approximately half of the cells are killed. In the case of the interaction between the beta-lactam derivative (3-CDBA) and the leukemia cell line (HL-60), the IC_{50} was found to be 91.55 µg/ml. Similarly, for the pancreatic cancer cell line (TCP-1026), the IC_{50} was measured at 141.3 µg/ml. A noteworthy observation is that the IC_{50}

for the normal cell line (WRL68) was significantly higher, at 353.8 µg/ml. This finding suggests that the beta-lactam derivative effectively kills cancer cells while exhibiting minimal impact on normal cells, as a higher concentration is required to achieve a similar inhibitory effect. These results hold great importance in the field of research, as they strengthen the potential of utilizing the beta-lactam derivative (3-CDBA) for inhibiting the growth of cancer cells [34-36]. The outcomes are visually depicted in Figure 8 and summarized in Table 6.

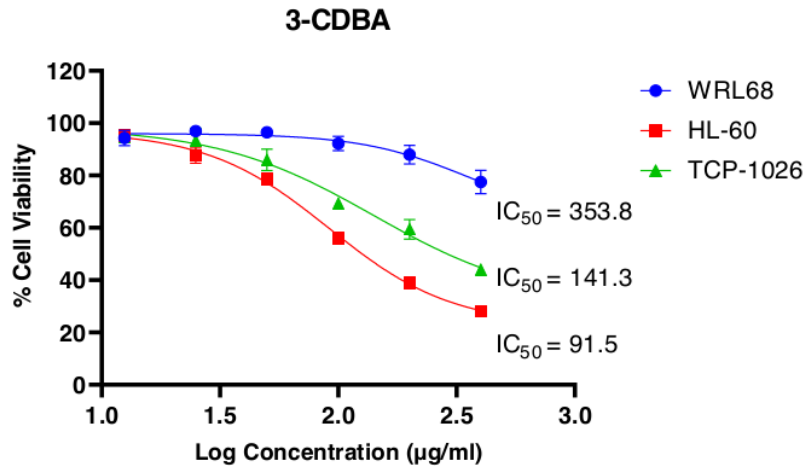


Figure 8: IC_{50} of beta-lactam (3-CDBA) with leukemia cells (HL-60), pancreas (TCP-1026) and normal cellular line cells (WRL68).

3.11. Toxicity LD_{50}

In this study, the LD_{50} (lethal dose for half the number of animals) of the beta-lactam derivative was determined using 25 male mice per compound. The mice were between 2 to 3 months old and had an average weight of 40 grams. They were housed in plastic cages measuring 15×35×50 cm, with 5 animals per cage. Each cage was equipped with glass bottles for water and a processed diet, and sawdust was regularly replaced to maintain cleanliness. The mice were subjected to consistent environmental conditions, including a temperature range of 20-25 °C regulated by air conditioning and a 12-hour light and 12-hour darkness cycle.

To determine the LD_{50}, different concentrations of the beta-lactam derivative (3-CDBA) were prepared in mg/kg relative to the mice's weight, including 4000, 3000, 2000, and 1000. The mice were divided into 5 groups, with 5 mice in each group. The concentrations were administered orally using a gooseneck tube. Signs of poisoning and death were observed and recorded for 7 days to calculate the LD_{50}.

The LD_{50} value was calculated using the modified Miller and Tainter method, which involves estimating probability units [37,38]. This method utilizes a graph showing the relationship between the logarithm of the dose and the response. The relationship is illustrated in Tables 7 and 8 and Figure 9. The percentage of dead animals, as well as the corrected percentage (% Corrected) at 0% and 100%, were calculated. The standard error for LD_{50} was also determined using the formula:

$$0\% \text{ death} = 100 \times (0.25/N)$$

$$100\% \text{ death} = 100 \times (N - 0.25)/N$$

$$\text{SE of } LD_{50} = \log LD_{84} - \log LD_{16}/\sqrt{2N}$$

Here, N represents the number of animals in each group, and LD_{50} denotes the lethal dose for half of the group.

The lethal dose for half of the animals (LD_{50}) of the beta-lactam derivative (3-CDBA) was (2691.53±769.26) mg/kg of animal weight.

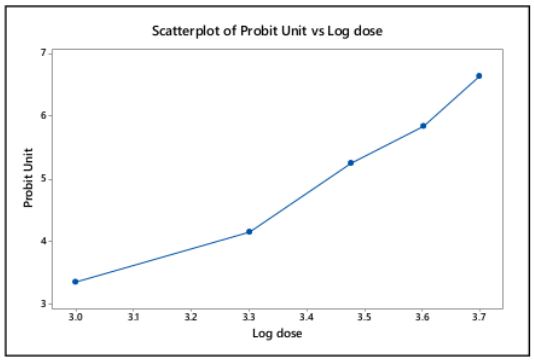


Figure 9: Dose and response relationship graph in terms of units of probability of (3-CDBA)

Table (7): Ratio of the number of dead animals converted to the values of probability units.

%	0	1	2	3	4	5	6	7	8	9
0	-	2.67	2.95	3.12	3.25	3.36	3.45	3.52	3.59	3.66
10	3.72	3.77	3.82	3.87	3.92	3.96	4.01	4.05	4.08	4.12
20	4.16	4.19	4.23	4.26	4.29	4.33	4.36	4.39	4.42	4.45
30	4.48	4.50	4.53	4.56	4.59	4.61	4.64	4.67	4.69	4.72
40	4.75	4.77	4.80	4.82	4.85	4.87	4.90	4.92	4.95	4.97
50	5.00	5.03	5.05	5.08	5.10	5.13	5.15	5.18	5.20	5.23
60	5.25	5.28	5.31	5.33	5.36	5.39	5.41	5.44	5.47	5.50
70	5.52	5.55	5.58	5.61	5.64	5.67	5.71	5.74	5.77	5.81

80	**5.84**	**5.88**	**5.92**	**5.95**	**5.99**	**6.04**	**6.08**	**6.13**	**6.18**	**6.23**
90	**6.28**	**6.34**	**6.41**	**6.48**	**6.55**	**6.64**	**6.75**	**6.88**	**7.05**	**7.33**

Table (8): LD_{50} for the beta-lactam derivative (3-CDBA).

Probability units (Probits)	Corrected %ratio Corrected (%)	Mortality rate (%dead)	Mortality (Md)	Log dose	Dosage (dose)(mg/kg)	Number of animals in the group (n)	The Collection
3.36	**5**	**0**	**0**	**3.000000000**	**1000**	**5**	**1**
4.16	**20**	**20**	**1**	**3.301029996**	**2000**	**5**	**2**
5.25	**60**	**60**	**3**	**3.477121255**	**3000**	**5**	**3**
5.84	**80**	**80**	**4**	**3.602059991**	**4000**	**5**	**4**
6.64	**95**	**100**	**5**	**3.698970004**	**5000**	**5**	**5**

Log Dose = 3.43, LD_{50} = (2691.53±769.26) mg/kg

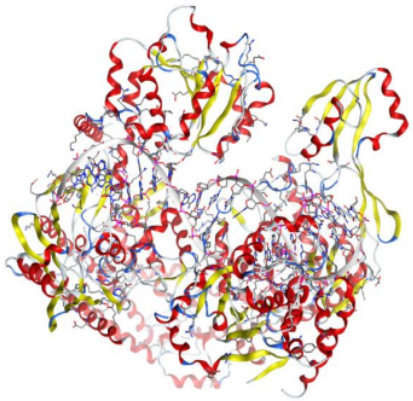
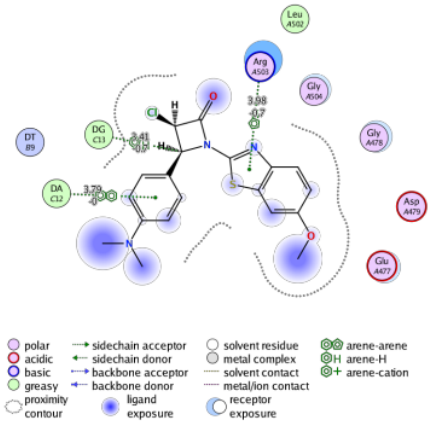
3.12. Molecular Docking

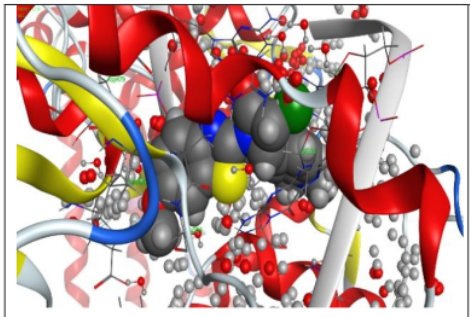
Molecular docking has emerged as an innovative approach in computational drug design, serving as an initial step towards the discovery of generic drugs or the development of drug structures. It involves the integration of computational science and medical science through computer-based simulations [39]. These simulations analyze data on drug molecules by rapidly scanning the structures of natural organic or modified synthetic molecules. By doing so, they provide predictions on the potential binding of a drug molecule (ligand) with a target protein or enzyme, forming a stable complex akin to a key fitting into a lock. This process relies on identifying the appropriate key (drug) that can fit the lock (target protein or enzyme) and open it, based on knowledge of the biological target. The traditional process of discovering new drugs is time-consuming and expensive, prompting researchers to incorporate computer systems into drug research, known as Computer-Aided Drug Discovery (CADD). CADD utilizes molecular modelling, which offers advantages over traditional synthesis methods in terms of saving effort, time, and costs. Through molecular modelling, thousands of molecules (ligands) can be simulated in a short time and at a reduced cost. This enables researchers to predict which molecules are most likely to bind with the target protein, using an in silico approach. In silico refers to theoretical studies conducted on compounds using computers, which can then be further applied in practical applications. Molecular modelling, as a part of

CADD, plays a crucial role in accelerating the drug discovery process while minimizing expenses [40-42].

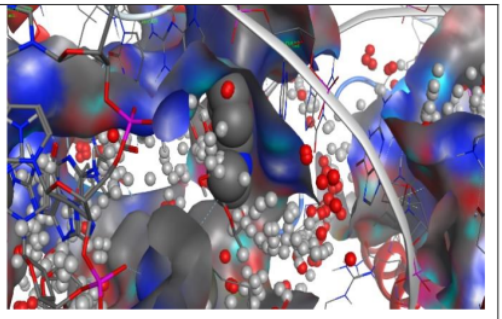
To access specific protein structures in the PDB, you can use the search functionality provided on the PDB website (https://www.rcsb.org). In your case, you mentioned two protein structures, 3qx3 and 2gam, which are associated with leukemia and pancreatic cancer, respectively. By entering the PDB IDs (3qx3 and 2gam) into the search bar on the PDB website, you can retrieve detailed information about these structures, including their amino acid sequences, 3D coordinates, and any available experimental data [43-45].

The study investigated the interaction of a beta-lactam compound called 3-CDBA with two protein targets related to leukemia (3qx3) and pancreatic cancer (2gam). The researchers examined the active pockets of the proteins and how the compound binds to the amino acids within them. The study identified various affinity interactions between the compound and essential amino acids, involving hydrogen bonds, van der Waals forces, and hydrophobic bonds. Specifically, the compound showed strong associations with amino acids like Arg 503 in protein/enzyme (3qx3) and Lys 251, Trp 356, and Arg 378 in protein/enzyme (2gam). These interactions, depicted in Figures 10 and 11, indicate a close and significant binding of the compound within the active sites of the proteins. The findings suggest that the compound has the potential to inhibit cancer cells by blocking the targeted enzymes and disrupting their metabolic processes. Further research is warranted to explore the potential of this compound as a cancer cell inhibitor.

S (Kcal/mol)	RMSD (Å)
-7.2785	1.2363
	
Protein ID (3qx3)	2D



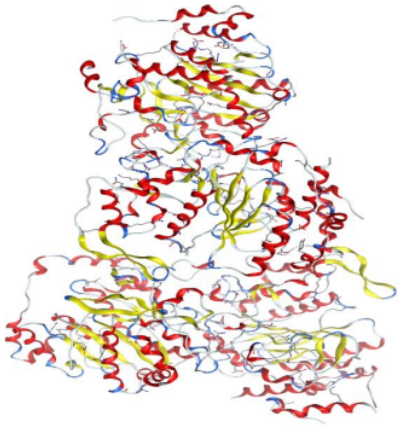
3D



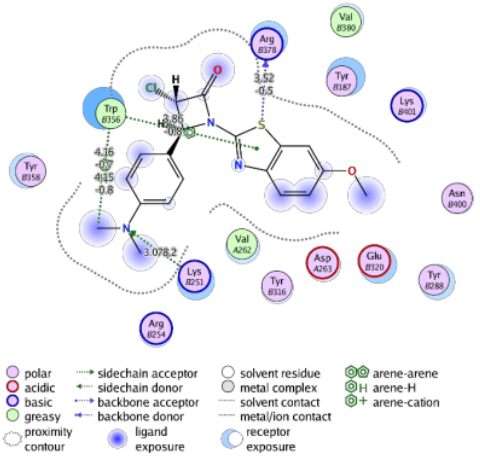
Map

Figure 7. A comprehensive examination of the interactions between protein 3qx3 and the 3-CDBA was conducted, utilizing 2D, 3D, and map views.

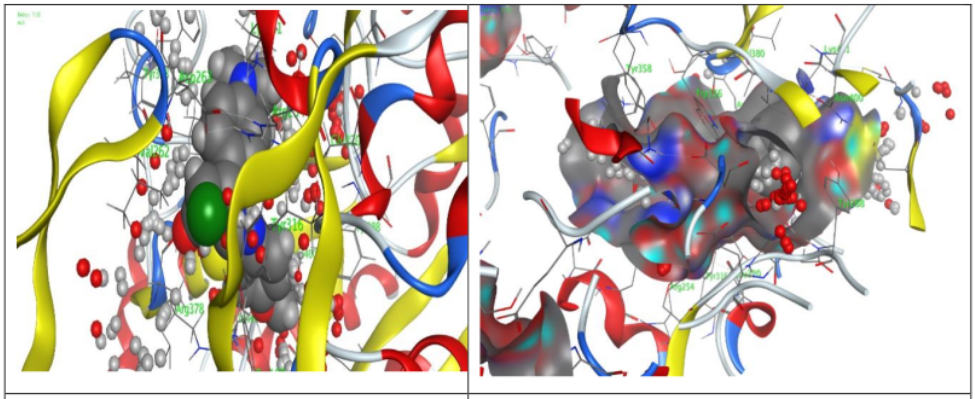
S (Kcal/mol)	RMSD (Å)
-6.1873	**1.1964**



Protein ID (2gam)



2D



3D	Map

Figure 7. A comprehensive examination of the interactions between protein 2gam and the 3-CDBA was conducted, utilizing 2D, 3D, and map views.

4. Conclusions

In this study, the beta-lactam derivative (3-CDBA) has potential as a cancer cell growth inhibitor, demonstrated by its activity against leukemia (HL-60) and pancreatic cancer (TCP-1026) cells. The compound (3-CDBA) was prepared through a two-step process involving modifications and work method variations. The first step involved mixing 2-amino-6-methoxybenzothiazol and 4-dimethylaminobenzaldehyde in absolute ethanol, followed by recrystallization. In the second step, the beta-lactam derivative - Schiff base was prepared by combining the Schiff base derivative (2) with Triethylamine and Chloroacetyl Chloride in 1,4-dioxane, followed by recrystallization. The prepared compound exhibits selective toxicity against cancer cells, specifically leukemia (HL-60) and pancreatic cancer (TCP-1026) cells while having minimal impact on healthy cells (WRL68). This suggests its potential use in medical applications for cancer treatment, as well as its antioxidant, free radical, and antibiotic properties against certain bacteria and fungi. The lethal dose of half the number of animals (LD_{50}) for the beta-lactam derivative (3-CDBA) in laboratory mice was determined to be (2691.53±769.26) mg/kg of animal weight. Additionally, the 3-CDBA was investigated for their physicochemical properties and binding affinity with proteins using molecular docking studies.

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