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Design of some β -lactam derivatives as prospective antibacterial agents: Synthesis, characterization, computational analysis, and molecular docking studies

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ABSTRACT

A series of substituted β -lactam derivatives (3a–e) were synthesized via Schiff base intermediates using a Staudinger [2+2] cycloaddition reaction and characterized by FT-IR and ¹H NMR spectroscopy. DFT calculations (B3LYP/6-31G(d)) were performed to investigate molecular geometry, electronic properties, and reactivity descriptors. Conceptual DFT analysis revealed that compounds 3c, 3d, and 3e display high electrophilicity indices (ω = 5.84–5.99 eV), indicating strong electrophilic reactivity, while compound 3b shows the lowest electrophilicity (ω = 2.406 eV) and the largest energy gap, suggesting higher kinetic stability. Molecular electrostatic potential analysis identified key reactive sites responsible for intermolecular interactions. Molecular docking against *Escherichia coli* BepA metalloprotease (PDB: 6SAR) revealed good binding affinities (–7.2 to –8.1 kcal/mol), with compound 3d showing the strongest interaction. These results suggest that the synthesized β -lactam derivatives may serve as promising scaffolds for antibacterial drug development.

KEYWORDS

β -Lactam
Schiff bases
Escherichia coli
Molecular docking
Antibacterial activity
Density Functional Theory

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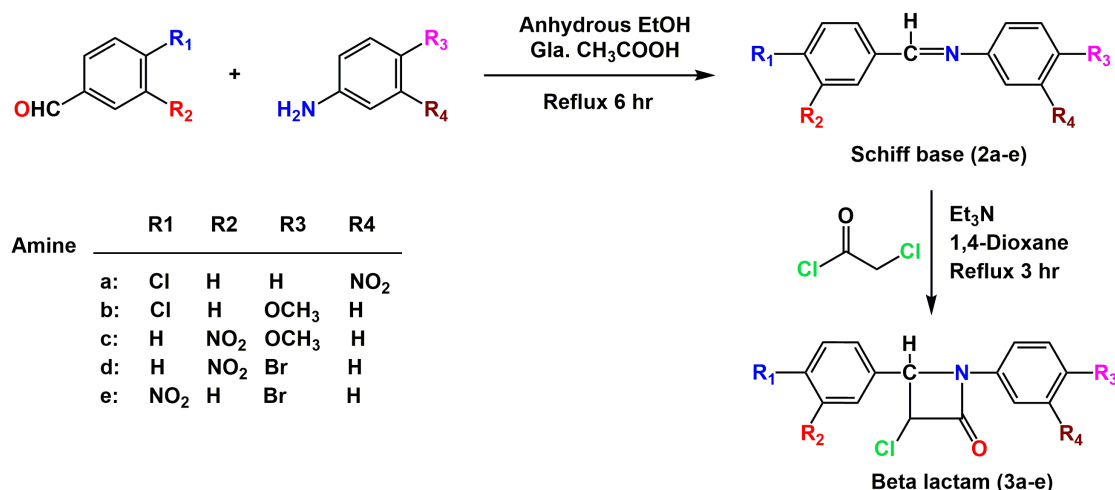
1. Introduction

β -Lactam antibiotics have been widely used since the discovery of penicillin in 1928, with the β -lactam ring serving as the key structural motif responsible for their antibacterial activity [1,2]. However, the rapid emergence of antimicrobial resistance has significantly compromised the efficacy of existing β -lactam drugs, creating an urgent need for structural modification [3]. Beyond their antibacterial activity, β -lactam scaffolds exhibit diverse biological properties, including anticancer, antiviral, enzyme-inhibitory, antitubercular, and antitumoral effects [4–8].

Although β -lactam antibiotics are active against both Gram-positive and Gram-negative bacteria [9], Gram-negative pathogens pose a significant challenge because of the limited permeability of their outer membrane. The rational design of β -lactam structures that overcome membrane impermeability and resistance mechanisms is therefore essential for the development of next-generation antibiotics [10]. Notably, the introduction of halogen substituents has been shown to enhance the stability and biological activity of the β -lactam framework [11].

From a synthetic standpoint, β -lactams are essential building blocks for numerous clinically significant antibiotics [12–17]. Among the available synthetic methodologies, the [2+2] cycloaddition of imines (Schiff bases) with ketenes remains one of the most efficient and cost-effective approaches for constructing azetidin-2-one rings [13,18,19]. Ketenes generated in situ from acid chlorides readily undergo cycloaddition with substituted imines, affording β -lactam derivatives in high yields [1,20].

In this study, we report the synthesis of a series of novel β -lactam derivatives using a cost-effective strategy designed to address the growing challenge of antimicrobial resistance (Scheme 1). The synthesized compounds were characterized by FT-IR, NMR, and UV-visible spectroscopy. Furthermore, their electronic properties and molecular reactivity were evaluated using density functional theory (DFT) calculations and molecular docking studies to identify promising candidates for future antibiotic development.

Scheme 1. Synthesis of β -lactams (3a-e) from Schiff bases (2a-e).

2. Experimental

2.1. Analytical apparatus

A Fisher-Johns electrothermal melting-point apparatus was used to record the melting temperatures of all synthesized compounds by the thin-disc method. The infrared (IR) spectra of the synthesized compounds were recorded using a NICOLET iS10 IR spectrophotometer with KBr discs. ¹H NMR spectra were obtained using a 400 MHz AVANCE Bruker NMR spectrometer with CDCl₃ as the solvent and TMS as the internal standard at the Wazed Miah Science Research Center, Jahangirnagar University, Savar, Dhaka, Bangladesh. Chemical shifts are reported in parts per million (ppm). Elemental analyses for carbon, hydrogen, and nitrogen were conducted using an Elementar Vario EL Cube instrument. The UV spectra of the synthesized compounds were recorded using a Shimadzu UV-1800 UV spectrophotometer at the Department of Chemistry, Jahangirnagar University, Savar, Dhaka. TLC was performed on Merck aluminum sheets precoated with Kieselgel 60 GF₂₅₄ to a thickness of 0.25 mm. The spots were developed in an iodine chamber and observed under an ultraviolet lamp. The synthesized compounds were purified by column chromatography using Kieselgel 100, 70–230 mesh, ASTM (Merck), as the stationary phase.

2.2. Synthesis

2.2.1. Synthesis of Schiff base derivatives (2a-e)

4-Chlorobenzaldehyde (512.00 mg, 3.64 mmol) was dissolved in anhydrous ethanol (15 mL) in a two-necked round-bottom flask. A few drops of glacial acetic acid were added to the stirred solution to control the pH (3.5–5.0). Separately, 3-nitroaniline (502.76 mg, 3.64 mmol) was dissolved in 15 mL of anhydrous ethanol, and the solution was added dropwise through a dropping funnel to the stirred 4-chlorobenzaldehyde solution. To maintain an anhydrous reaction, the mixture was flushed with nitrogen gas and refluxed for 6 h. The progress of the reaction was monitored by TLC using EtOAc:n-hexane (1:4) as the mobile phase. Upon completion of the reaction, the mixture was cooled, neutralized with 5% aqueous NaHCO₃ solution, poured onto crushed ice, and kept in a refrigerator overnight. The resulting solid was filtered, washed with water, and dried in a vacuum desiccator. The dried crude product was recrystallized from ethanol to afford the titled Schiff base 2a as

a white crystalline solid [21]. All other Schiff bases (2b–e) were synthesized following the same procedure (Scheme 1).

N-(4-Chlorobenzylidene)-3-nitrobenzenamine (2a): Color: off white. Yield: 92%. M.p.: 137–138 °C. FT-IR (KBr, ν , cm⁻¹): 3093 (C-H) (Aromatic), 2879 (C-H) (Aliphatic), 1627 (C=N), 1523 (C=C) (Aromatic), 1571 (N=O). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 8.49 (s, 1H, -CH=N), 8.12 (d, 1H, Ar-H, J_o = 7.6 Hz) 8.06 (s, 1H, Ar-H), 7.89 (d, 1H, Ar-H, J_o = 8.4 Hz), 7.56 (t, 1H, Ar-H, J_o = 8.4 Hz) 7.61 (d, 2H, Ar-H, J_o = 8.4 Hz), 7.52 (d, 2H, Ar-H, J_o = 8.4 Hz). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 276 (1.35) ($n \rightarrow \pi^*$). Anal. calcd. for C₁₃H₉Cl N₂O₂: C, 59.90; H, 3.48; N, 10.75. Found: C, 60.10; H, 3.39; N, 10.66%.

N-(4-Chlorobenzylidene)-4-methoxybenzenamine (2b): Color: off white. Yield: 87%. M.p.: 127–128 °C. FT-IR (KBr, ν , cm⁻¹): 3010 (C-H) (Aromatic), 2960 (C-H) (Aliphatic), 1620 (C=N), 1506 (C=C) (Aromatic). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 8.47 (s, 1H, -CH=N), 7.86 (d, 2H, Ar-H, J_o = 8.4 Hz), 7.46 (d, 2H, Ar-H, J_o = 8.4 Hz), 7.27 (d, 2H, Ar-H, J_o = 8.8 Hz) 6.96 (d, 2H, Ar-H, J_o = 8.8 Hz), 3.86 (s, 3H, -OCH₃). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 373 (2.6) ($n \rightarrow \pi^*$). Anal. calcd. for C₁₄H₁₂ClNO: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.34; H, 4.88; N, 5.89%.

N-(3-Nitrobenzylidene)-4-methoxybenzenamine (2c): Color: off white. Yield: 95%. M.p.: 89–90 °C. FT-IR (KBr, ν , cm⁻¹): 3097 (C-H) (Aromatic), 2964, 2835 (C-H) (Aliphatic), 1618 (C=N), 1533 (C=C) (Aromatic), 1573 (N=O). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 8.75 (s, 1H, -CH=N), 8.59 (s, 1H, Ar-H), 8.32 (dd, 1H, Ar-H, J_o = 8.0 Hz, J_m = 1.6 Hz), 8.26 (d, 1H, Ar-H, J_o = 7.6 Hz), 7.67 (t, 1H, Ar-H, J_o = 8.0 Hz) 7.32 (d, 2H, Ar-H, J_o = 8.8 Hz), 6.98 (d, 2H, Ar-H, J_o = 8.8 Hz), 3.87 (s, 3H, -OCH₃). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 275 (1.37) ($n \rightarrow \pi^*$). Anal. calcd. for C₁₄H₁₂N₂O₃: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.46; H, 4.83; N, 10.77.

N-(3-Nitrobenzylidene)-4-bromobenzenamine (2d): Color: off white. Yield: 89%. M.p.: 84–85 °C. FT-IR (KBr, ν , cm⁻¹): 3076 (C-H) (Aromatic), 2927 (C-H) (Aliphatic), 1627 (C=N), 1521 (C=C) (Aromatic), 1575 (N=O). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 8.76 (s, 1H, -CH=N), 8.54 (s, 1H, Ar-H), 8.36 (d, 1H, Ar-H, J_o = 8.0 Hz), 8.26 (d, 1H, Ar-H, J_o = 7.6 Hz), 7.71 (t, 1H, Ar-H, J_o = 8.0 Hz) 7.56 (d, 2H, Ar-H, J_o = 8.4 Hz), 7.15 (d, 2H, Ar-H, J_o = 8.4 Hz). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 362 (2.1) ($n \rightarrow \pi^*$). Anal. calcd. for C₁₃H₉BrN₂O₂: C, 51.17; H, 2.97; N, 9.18. Found: C, 50.94; H, 2.81; N, 9.32.

N-(4-Nitrobenzylidene)-4-bromobenzenamine (2e): Color: off white. Yield: 87%. M.p.: 169–170 °C. FT-IR (KBr, ν , cm⁻¹): 3099 (C-H) (Aromatic), 2846 (C-H) (Aliphatic), 1624 (C=N), 1559 (C=C) (Aromatic), 1573 (N=O). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 8.56 (s, 1H, -CH=N), 8.42 (d, 2H, Ar-H, J_o = 8.4 Hz), 8.10 (d, 2H, Ar-H, J_o = 8.0 Hz), 7.57 (d, 2H, Ar-H, J_o = 8.8 Hz) 6.96 (d,

2H, Ar-H, $J_o=8.4$ Hz). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 366 (2.1) ($n \rightarrow \pi^*$). Anal. calcd. for $C_{13}H_9BrN_2O_2$: C, 51.17; H, 2.97; N, 9.18. Found: C, 50.96; H, 2.82; N, 9.31.

2.2.2. Synthesis of β -lactam derivatives (3a-e) from Schiff bases (2a-e)

A solution of Schiff base 2a (205.00 mg, 0.78 mmol) in 1,4-dioxane (10 mL) was added to a well-stirred mixture of chloroacetyl chloride (0.124 mL, 1.56 mmol) and triethylamine (0.217 mL, 1.56 mmol) in 1,4-dioxane at 0–5 °C. The reaction mixture was stirred for 30 min, refluxed for 3 h, and subsequently kept at room temperature for 24 h. The progress of the reaction was monitored by TLC using EtOAc:n-hexane (1:3, v:v) as the mobile phase. The resulting mixture was concentrated using a rotary evaporator, and the residue was poured into ice-cold water. The resulting solid was filtered and dried overnight. The crude solid containing residual Schiff base was separated by column chromatography using EtOAc:n-hexane (1:3, v:v) as the eluent. Evaporation of the solvent afforded the desired β -lactam 3a. The remaining β -lactams (3b–e) were obtained following a similar procedure (Scheme 1).

3-Chloro-4-(4-chlorophenyl)-1-(3-nitrophenyl)azetidin-2-one (3a): Color: Brownish red. Yield: 75%. M.p.: 110–112 °C. FT-IR (KBr, ν , cm^{-1}): 3084 (C-H) (Aromatic), 2953, 2852 (C-H) (Aliphatic), 1685 (C=O), 1543 (C=C) (Aromatic), 1595 (N=O). 1H NMR (400 MHz, $CDCl_3$, δ , ppm): 8.46 (s, 1H, Ar-H), 8.07 (d, 1H, Ar-H, $J_o = 8.0$ Hz), 8.00 (d, 1H, Ar-H, $J_o = 8.0$ Hz), 7.57 (t, 1H, Ar-H, $J_o = 8.4$ Hz), 7.61 (d, 2H, Ar-H, $J_o = 8.4$ Hz), 7.52 (d, 2H, Ar-H, $J_o = 8.4$ Hz), 4.26 (s, 1H, C-H), 4.22 (s, 1H, C-H). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 331 (0.886) ($n \rightarrow \pi^*$). Anal. calcd. for $C_{15}H_{13}Cl_2N_2O_3$: C, 53.44; H, 2.99; N, 8.31. Found: C, 53.34; H, 2.80; N, 8.01%.

3-Chloro-4-(4-chlorophenyl)-1-(4-methoxyphenyl)azetidin-2-one (3b): Color: reddish-brown. Yield: 72%. M.p.: 130–131 °C. FT-IR (KBr, ν , cm^{-1}): 3074 (C-H) (Aromatic), 2956, 2852 (C-H) (Aliphatic), 1664 (C=O), 1542 (C=C) (Aromatic). 1H NMR (400 MHz, $CDCl_3$, δ , ppm): 8.42 (d, 2H, Ar-H, $J_o = 8.8$ Hz), 8.10 (d, 2H, Ar-H, $J_o = 8.8$ Hz), 7.47 (d, 2H, Ar-H, $J_o = 8.8$ Hz), 6.91 (d, 2H, Ar-H, $J_o = 8.8$ Hz), 4.21 (s, 1H, C-H), 4.14 (s, 1H, C-H), 3.82 (s, 3H, -OCH₃). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 282 (2.25) ($n \rightarrow \pi^*$). Anal. calcd. for $C_{16}H_{13}Cl_2NO_2$: C, 59.65; H, 4.07; N, 4.35. Found: C, 59.40; H, 3.92; N, 4.17%.

3-Chloro-1-(4-methoxyphenyl)-4-(3-nitrophenyl)azetidin-2-one (3c): Color: reddish-brown. Yield: 81%. M.p.: 107–108 °C. FT-IR (KBr, ν , cm^{-1}): 3076 (C-H) (Aromatic), 2850, 2835 (C-H) (Aliphatic), 1664 (C=O), 1543 (C=C) (Aromatic), 1550 (N=O). 1H NMR (400 MHz, $CDCl_3$, δ , ppm): 8.41 (d, 1H, Ar-H, $J_o = 8.4$ Hz), 8.25 (d, 1H, Ar-H, $J_o = 8.4$ Hz), 8.18 (s, 1H, Ar-H), 7.69 (t, 1H, Ar-H, $J_o = 8.0$ Hz), 7.47 (d, 2H, Ar-H, $J_o = 8.0$ Hz), 6.92 (d, 2H, Ar-H, $J_o = 8.0$ Hz), 4.21 (s, 1H, C-H), 4.12 (s, 1H, C-H), 3.82 (s, 3H, -OCH₃). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 262 (1.76) ($n \rightarrow \pi^*$). Anal. calcd. for $C_{16}H_{13}Cl_2NO_2$: C, 57.75; H, 3.94; N, 8.41. Found: C, 57.66; H, 3.74; N, 8.25%.

1-(4-Bromophenyl)-3-chloro-4-(3-nitrophenyl)azetidin-2-one (3d): Color: Reddish-brown. Yield: 60%. M.p.: 110–112 °C. FT-IR (KBr, ν , cm^{-1}): 3097 (C-H) (Aromatic), 2877 (C-H) (Aliphatic), 1672 (C=O), 1614 (C=C) (Aromatic), 1583 (N=O). 1H NMR (400 MHz, $CDCl_3$, δ , ppm): 8.74 (s, 1H, Ar-H), 8.52 (d, 1H, Ar-H, $J_o = 8.0$ Hz), 8.27 (d, 1H, Ar-H, $J_o = 8.0$ Hz), 7.79 (t, 1H, Ar-H, $J_o = 8.0$ Hz), 7.49 (d, 2H, Ar-H, $J_o = 8.8$ Hz), 7.37 (d, 2H, Ar-H, $J_o = 8.8$ Hz), 4.46 (s, 1H, C-H), 4.12 (s, 1H, C-H). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 332 (1.89) ($n \rightarrow \pi^*$). Anal. calcd. for $C_{15}H_{10}BrClN_2O_2$: C, 47.21; H, 2.64; N, 7.35. Found: C, 47.11; H, 2.48; N, 7.18%.

1-(4-Bromophenyl)-3-chloro-4-(4-nitrophenyl)azetidin-2-one (3e): Color: Off-white. Yield: 68%. M.p.: 181–182 °C. FT-IR (KBr, ν , cm^{-1}): 3078 (C-H) (Aromatic), 2922 (C-H) (Aliphatic), 1670 (C=O), 1557 (C=C) (Aromatic), 1575 (N=O). 1H NMR (400 MHz, $CDCl_3$, δ , ppm): 8.43 (d, 2H, Ar-H, $J_o = 8.4$ Hz), 8.11 (d, 2H, Ar-H, $J_o = 8.0$ Hz), 7.49 (d, 2H, Ar-H, $J_o = 8.8$ Hz), 6.92 (d, 2H, Ar-H,

$J_o = 8.8$ Hz), 4.21 (s, 1H, C-H), 4.11 (s, 1H, C-H). UV/Vis (DMSO, λ_{max} , nm, (log ϵ)): 367 (2.49) ($n \rightarrow \pi^*$).

3. Computational methods

Theoretical calculations were performed to investigate the molecular reactivity, intermolecular interaction tendencies, and potential biological activity of the synthesized molecules. Density functional theory (DFT) calculations were carried out to obtain detailed electronic and structural information.

Geometry optimizations were performed using the B3LYP functional [22]. The 6-31G(d) basis set was employed for the organic molecular frameworks [23]. The same computational level was also used to investigate the thermally prohibited [2+2] cycloaddition reaction and to evaluate global reactivity descriptors and intermolecular interaction tendencies. All optimized structures were confirmed to be true minima on the potential energy surface (PES) by the absence of imaginary vibrational frequencies.

The electronic structures and global reactivity descriptors of the studied systems were evaluated using conceptual density functional theory (CDFT) based on the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). All quantum chemical descriptors were derived from the fully optimized molecular geometries [24]. The chemical hardness (η) was calculated using Equation 1, while the chemical potential (μ) was obtained from Equation 2:

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \quad (1)$$

$$\mu = \frac{E_{HOMO} + E_{LUMO}}{2} \quad (2)$$

The global electrophilicity index (ω) was determined using Equation 3:

$$\omega = \frac{\chi^2}{2\eta} \quad (3)$$

The number of electrons transferred (N) from nucleophile to the reference compound (TCE) was calculated using Equation 4:

$$N = E_{HOMO(Nu)} - E_{HOMO(TCE)} \quad (4)$$

The global softness (S) was determined from Equation 5:

$$S = \frac{1}{2\eta} \quad (5)$$

Finally, electronegativity (χ) was calculated using Equation 6:

$$\chi = \frac{-(E_{LUMO} + E_{HOMO})}{2} \quad (6)$$

All calculated quantum chemical descriptors were used to evaluate the chemical reactivity, stability, and charge-transfer characteristics of the investigated systems. Initial molecular geometries were constructed using GaussView 6 [25] and fully optimized using Gaussian 09 software [26]. Molecular docking studies were performed using AutoDock Vina 1.2.0 to evaluate protein–ligand binding interactions. The resulting complexes were analyzed and visualized using Discovery Studio 2025 to investigate interaction patterns and binding modes [27,28].

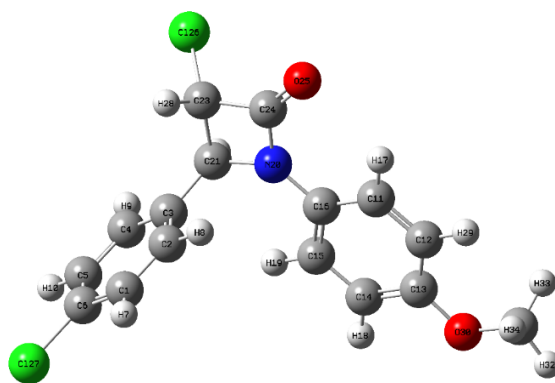


Figure 1. Optimized geometry of compound 3b.

4. Results and discussion

4.1. Synthesis and characterization

The structures of all compounds were confirmed using modern spectroscopic methods such as ^1H NMR, FT-IR, and UV analysis. A characteristic singlet at approximately δ 8.49 ppm for the downfield $\text{CH}=\text{N}$ proton in the ^1H NMR spectrum confirmed the synthesis of Schiff base 2a. Two doublets at δ 7.61 and 7.57 ppm with an *ortho* coupling constant ($J_o = 8.4$ Hz), along with a singlet at δ 8.06 ppm, confirmed the presence of substituted aromatic protons in compound 2a. In the ^1H NMR spectra, all other Schiff bases (2b–e) exhibited a strong singlet in the δ 8.47–8.76 ppm range, indicating the formation of the imine $\text{CH}=\text{N}$ group. Compound 3a showed two characteristic singlets at δ 4.26 and 4.22 ppm for the β -lactam ring protons, confirming the formation of the azetidinone ring. Two doublets were observed at δ 7.61 and 7.52 ppm with a coupling constant of $J_o = 8.4$ Hz for the substituted aromatic ring. Two doublets were also observed at δ 8.07 and 8.00 ppm with coupling constants of $J_o = 8.0$ and 8.4 Hz, respectively. A triplet at δ 7.57 ppm with a coupling constant of $J_o = 8.4$ Hz confirmed the aromatic ring proton. The IR spectrum of compound 3a showed characteristic bands at 3084 cm^{-1} for aromatic C–H stretching, 2953 and 2852 cm^{-1} for aliphatic C–H stretching, 1685 cm^{-1} for the lactam C=O group, 1595 cm^{-1} for aromatic C=C stretching, and 1533 cm^{-1} for the nitro group.

The ^1H NMR spectrum of compound 3b exhibited a singlet at δ 3.82 ppm corresponding to the $-\text{OCH}_3$ protons. Two characteristic singlets at δ 4.21 and 4.14 ppm were assigned to the lactam ring hydrogens, confirming the formation of the azetidinone moiety. Two doublets observed at δ 8.42 and 8.10 ppm with a coupling constant of $J_o = 8.8$ Hz indicated a substituted aromatic system. Additionally, two doublets at δ 7.47 and 6.91 ppm ($J_o = 8.8$ Hz) were attributed to aromatic ring protons. The IR spectrum of compound 3b showed absorption bands at 3074 cm^{-1} for aromatic C–H stretching, 2956 and 2852 cm^{-1} for aliphatic C–H stretching, 1664 cm^{-1} for the lactam C=O group, and 1512 cm^{-1} for aromatic C=C stretching.

The ^1H NMR spectrum of compound 3c displayed two characteristic singlets at δ 4.21 and 4.12 ppm corresponding to the lactam ring hydrogens, along with a singlet at δ 3.82 ppm attributed to the methoxy ($-\text{OCH}_3$) protons on the aromatic ring. Two aromatic protons appeared as doublets at δ 7.47 and 6.92 ppm with a coupling constant of $J = 8.0$ Hz, indicating substituted aromatic ring protons. Signals corresponding to a meta-substituted aromatic ring were observed as a singlet at δ 8.18 ppm, two doublets at δ 8.42 and 8.25 ppm ($J = 8.4$ Hz), and a triplet at δ 7.69 ppm ($J = 8.0$ Hz). The FT-IR spectrum showed bands at 3076 , 2850 , 1664 , 1550 , and 1512 cm^{-1} , confirming the

presence of aromatic C–H, aliphatic C–H, lactam C=O, N=O, and aromatic C=C groups.

β -Lactam 3d showed singlets at δ 4.12 and 4.46 ppm corresponding to the lactam protons. A singlet at δ 8.74 ppm, a triplet at δ 7.79 ppm with a coupling constant of $J_o = 8.0$ Hz, and two doublets at δ 8.52 and 8.27 ppm with a coupling constant of $J_o = 8.0$ Hz were assigned to substituted aromatic ring protons. Two additional doublets at δ 7.49 and 7.37 ppm with a coupling constant of $J_o = 8.8$ Hz were assigned to other substituted aromatic ring protons. The IR absorption bands at 3097 , 2877 , 1672 , 1614 , and 1583 cm^{-1} represented aromatic C–H, aliphatic C–H, lactam carbonyl, aromatic C=C, and nitro functional groups, respectively.

β -Lactam 3e showed singlets at δ 4.11 and 4.21 ppm corresponding to the lactam protons. Two doublets at δ 8.43 and 8.11 ppm with coupling constants of $J_o = 8.4$ and 8.0 Hz, respectively, were assigned to substituted aromatic protons. Two additional doublets at δ 7.49 and 6.92 ppm with a coupling constant of $J_o = 8.8$ Hz were assigned to another substituted aromatic ring. The IR absorption bands at 3078 , 2922 , 1670 , 1557 , and 1575 cm^{-1} represented aromatic C–H, aliphatic C–H, lactam carbonyl, aromatic C=C, and nitro functional groups, respectively.

4.2. Theoretical calculations

Theoretical calculations were performed to evaluate the molecular reactivity, structural stability, and potential biological relevance of the synthesized compounds. Density functional theory (DFT) calculations were carried out at the B3LYP level to obtain reliable electronic and structural parameters within Koopmans' conceptual DFT framework. Geometry optimizations were performed using the B3LYP/6-31G(d) basis set for organic frameworks. In addition, this computational protocol was applied to examine the thermally prohibited [2+2] cycloaddition reaction pathway and to analyze global reactivity descriptors and intermolecular interaction tendencies. All optimized structures were confirmed to correspond to true minima on the potential energy surface (PES), as evidenced by the absence of imaginary vibrational frequencies.

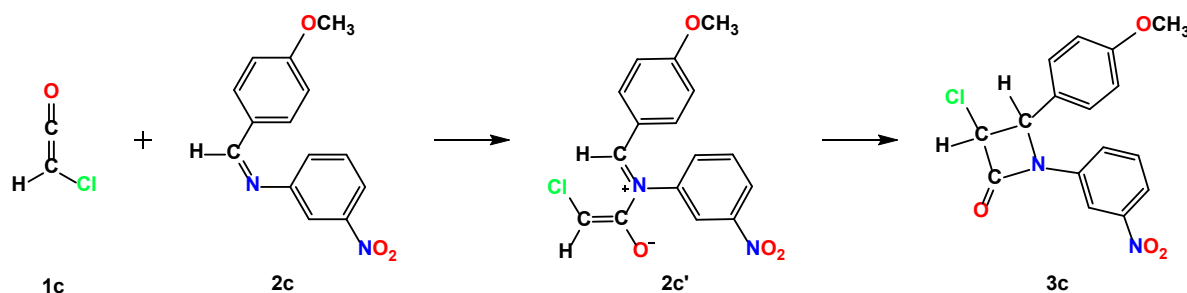
Initial molecular geometries were constructed using GaussView 6 and fully optimized using Gaussian 09 software. The representative optimized geometry of analogue 3b is shown in Figure 1. To complement the quantum chemical results, molecular docking studies were performed using AutoDock Vina 1.2.0 [28] to investigate protein–ligand binding affinities. The resulting complexes were further analyzed and visualized using Discovery Studio 2025 to elucidate interaction patterns and binding modes.

Table 1. The reactivity indices at B3LYP/6-31G(d) for the intermediate of compound 3c.

Molecular property	η (eV)	μ (eV)	ω (eV)	N (eV)
Ketene	2.19	-4.38	4.38	2.67
Imine	1.89	-4.16	4.58	3.20

Table 2. Frontier molecular orbital energies of compounds 3a-3e calculated by DFT.

Compound	ΔE (eV)	η (eV)	χ (eV)	μ (eV)	ω (eV)	N (eV)	S (eV ⁻¹)
3a	4.343	2.172	4.704	-4.704	5.094	2.354	0.460
3b	4.698	2.349	3.362	-3.362	2.406	3.519	0.426
3c	3.139	1.570	4.282	-4.282	5.843	3.378	0.637
3d	3.590	1.795	4.637	-4.637	5.989	2.798	0.557
3e	3.615	1.808	4.645	-4.645	5.968	2.777	0.553

**Scheme 2.** Mechanism of the ketene-imine Staudinger reaction.

4.2.1. Investigating the feasibility of the Staudinger reaction

The synthesis of β -lactam derivatives proceeds through a ketene-imine Staudinger reaction via a stepwise mechanism involving the formation of a zwitterionic intermediate (compound 2c) (Scheme 2). This polar cycloaddition proceeds through the nucleophilic attack of the imine nitrogen on the carbonyl carbon of the ketene [18,19]. This mechanism can be investigated using conceptual DFT for the ketene and imine. We selected one β -lactam reaction (3c) to investigate the mechanism (Scheme 2).

According to the calculated global reactivity indices, the imine behaves as the nucleophile owing to its higher nucleophilicity index ($N = 3.20$ eV), whereas the ketene acts as the electrophile with an electrophilicity index of 4.38 eV (Table 1). The electronic chemical potentials of the two reactants ($\mu_{\text{imine}} = -4.16$ eV and $\mu_{\text{ketene}} = -4.38$ eV) indicate that electron density transfer is expected to occur from the imine toward the ketene. This combination of nucleophilic and electrophilic character supports the polar nature of the first step of the ketene-imine Staudinger reaction and is consistent with the formation of a zwitterionic intermediate through nucleophilic attack of the imine nitrogen on the electrophilic carbonyl carbon of the ketene.

4.2.2. Calculation of global physicochemical descriptors

Quantum chemical descriptors such as electronegativity (χ), electrophilicity index (ω), softness (S), hardness (η), chemical potential (μ), and nucleophilicity index (N) are global indicators of molecular chemical behavior [24]. These parameters were calculated to evaluate molecular stability, chemical reactivity, and nucleophilic or electrophilic affinity. The calculated quantum chemical parameters for the synthesized β -lactams are summarized in Table 2 [29-32].

4.2.3. Hardness

Hardness (η), a measure of resistance to electron-cloud deformation, is inversely related to chemical reactivity [33]. The hardness and softness of all compounds (3a-e) were determined using Equations 1 and 5, respectively. A lower

hardness value (a softer molecule) indicates greater reactivity, and vice versa. Since compound 3b has the highest hardness value (2.349 eV) among the compounds studied, it should be less reactive. In contrast, with a hardness value of 1.57 eV, 3c is the softest molecule, suggesting greater charge-transfer capacity and reactivity.

4.2.4. Electrophilicity

A molecule's ability to act as an electrophile can be predicted using the electrophilicity index (ω) [34], which combines η and χ . Equation 3 is used to calculate the electrophilicity index (ω), a conceptual DFT descriptor that measures a molecule's capacity to accept electrons. Compounds 3a-3e have computed ω values ranging from 2.406 to 5.989 eV (Table 2). Compounds 3c-3e are more electrophilic than compounds 3a and 3b within the studied series. This pattern is consistent with the presence of electron-withdrawing substituents, especially the nitro group, which increases the relative electrophilic character of the molecules by lowering the electronic chemical potential through its strong inductive ($-I$) and resonance ($-M$) effects.

The computed ω values are employed here mainly as comparative descriptors to rank the electrophilic character of the synthesized compounds within the current series, despite the fact that they are relatively high when compared to those commonly reported for neutral organic molecules. Accordingly, compounds 3c-3e are interpreted as relatively more electrophilic than compounds 3a and 3b, rather than being classified as exceptionally strong electrophiles.

4.2.5. Chemical potential

Molecules with negative chemical potential values are considered electronically stable. Compared with the other compounds, compound 3b has the least negative chemical potential (-3.362 eV), indicating a greater electron-donating tendency. Compound 3a, on the other hand, has a more negative chemical potential (-4.704 eV), indicating a relatively lower electron-donating ability and a greater tendency to accept electronic charge.

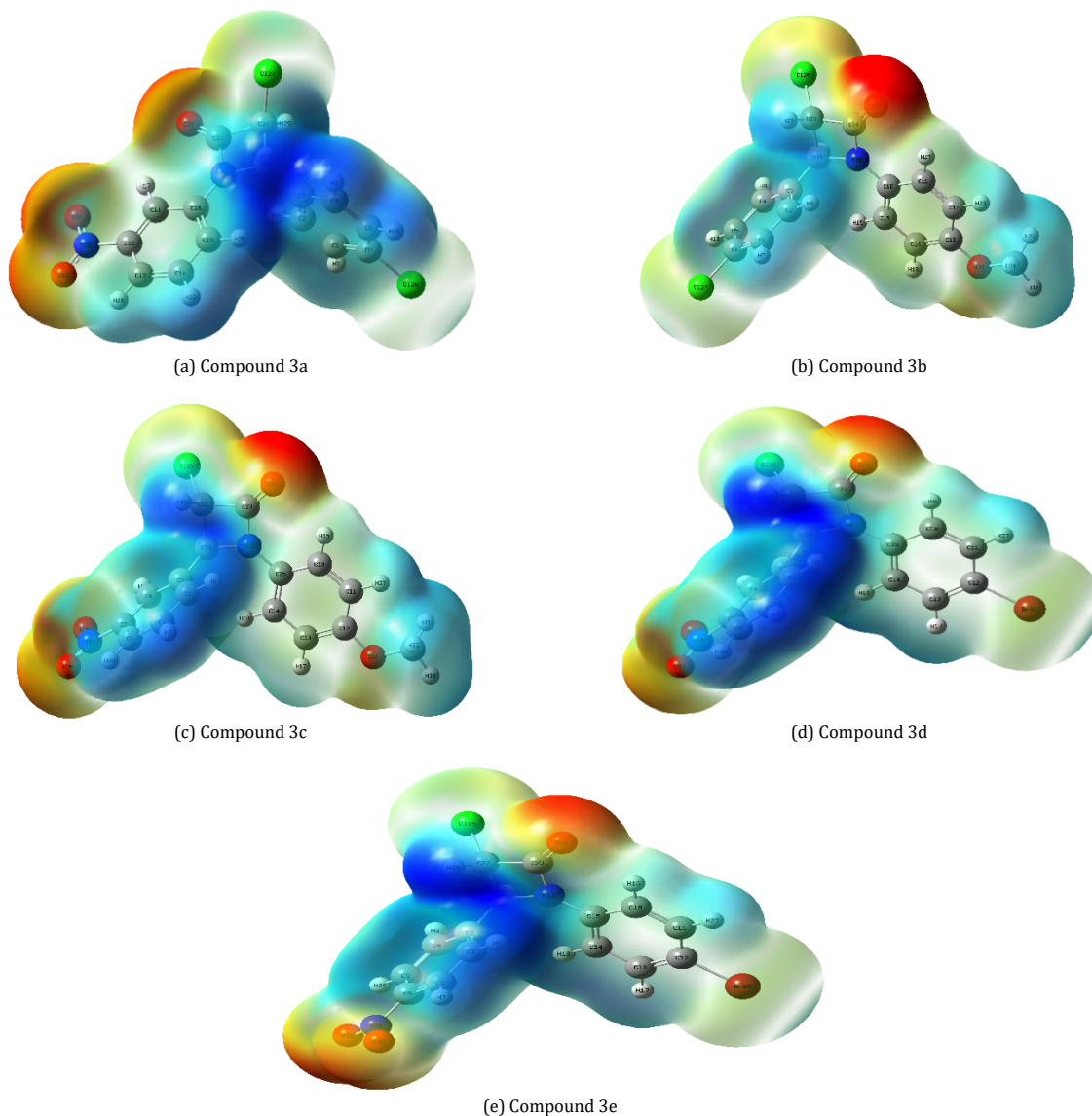


Figure 2. Molecular electrostatic potential (MEP) maps of compounds 3a–e calculated at the B3LYP/6-31G(d) level and mapped onto the 0.001 a.u. electron density isosurface. The color scale ranges from -0.05 a.u. (red, electron-rich regions) to $+0.05$ a.u. (blue, electron-deficient regions).

4.2.6. Molecular electrostatic potential

Molecular electrostatic potential (MEP) is a useful method for predicting relationships between the physicochemical properties of proposed drugs [35]. Additionally, MEP is useful for determining whether drug molecules are susceptible to nucleophilic or electrophilic attack [36]. Thus, MEP has primarily been used to describe the chemical reactivity of various biological systems involved in electrophilic and hydrogen-bonding interactions [37,38]. The MEP diagram is useful for studying the physicochemical properties of molecules because it displays their size, shape, and negative, positive, and neutral electrostatic potentials [39]. In the MEP maps, neutral regions are represented in green, while electron-rich and electron-poor regions are shown in red and blue, respectively. Variations in color correspond to different electrostatic potential values on the surface [40].

Figure 2a–e shows the clearly visualized isodensity surfaces of the synthesized molecules. In all molecules, the electronegative atoms are chlorine, bromine, oxygen, and nitrogen. However, not all of these atoms act as nucleophiles because of a lack of available electrons, as clearly shown by the

molecular electrostatic potential calculations. The MEP was calculated—on the 0.001 a.u. isodensity surface of the synthesized molecules using a color range from -0.05 a.u. (red) to $+0.05$ a.u. (blue). Red indicates electron-rich regions, while blue indicates electron-poor regions. In molecules 3a, 3b, and 3c, the deep-red regions localized on the oxygen atoms indicate electron-rich sites, suggesting their susceptibility to electrophilic attack. Bromine and chlorine show neither color. In molecules 3d and 3e, the oxygen atoms are moderately red.

Molecular docking studies were conducted to identify the most favorable binding conformations of the synthesized compounds with *Escherichia coli* BepA metalloprotease (PDB ID: 6SAR). Because BepA is a conserved periplasmic metalloprotease involved in outer-membrane protein assembly and quality control, *Escherichia coli* BepA metalloprotease (PDB ID: 6SAR) was selected [41]. The bacterial outer membrane is a barrier to antibiotics [42]. It has been demonstrated that disruption of BepA function compromises outer-membrane integrity, making cells more susceptible to antibiotics. Therefore, inhibition of BepA may disrupt membrane assembly and enhance antibacterial susceptibility in Gram-negative bacteria.

Table 3. Protein–ligand binding affinity scores, interaction types, and distances for compounds 3a–e.

Compound	Interaction types	Distance (Å)	Binding affinity (kcal/mol)
3a	Carbon-hydrogen bond	3.1979	-7.7
	Pi-sigma	3.58897	
	Pi-sigma	3.46222	
	Alkyl	4.17546	
	Pi-alkyl	4.97035	
3b	Pi-pi T-shaped	5.28873	-7.2
	Alkyl	4.42154	
	Alkyl	4.17116	
	Pi-alkyl	4.25957	
	Pi-alkyl	4.82342	
	Pi-alkyl	5.2847	
3c	Conventional hydrogen bond	2.94235	-7.9
	Pi-pi T-shaped	4.85451	
	Alkyl	5.02735	
	Pi-alkyl	5.12121	
	Pi-alkyl	4.94491	
	Pi-alkyl	5.20704	
3d	Conventional hydrogen bond	2.99599	-8.1
	Pi-pi T-shaped	4.85255	
	Pi-alkyl	5.07775	
	Pi-alkyl	5.20072	
3e	Alkyl	4.17097	-7.5
	Alkyl	4.85083	
	Alkyl	5.11395	
	Conventional hydrogen bond	2.23876	
	Conventional hydrogen bond	2.89618	
	Conventional hydrogen bond	2.66664	
	Pi-sigma	3.84718	
	Pi-sigma	3.55144	

**Figure 3.** *Escherichia coli* BepA metalloprotease (PDB ID: 6SAR).

AutoDock Vina 1.2.0 was used to prepare the optimized PDB structures of the ligands for docking. SPDB software was used to optimize the structure of *Escherichia coli* BepA metalloprotease (PDB ID: 6SAR) (Figure 3) [43]. AutoDock Vina 1.2.0 was used to perform the docking calculations, and Discovery Studio was used to display the results [27,28].

To identify potential interactions, the docking grid was centered at $x = 35.545$, $y = 52.265$, and $z = 47.355$ Å, with a box size of $60 \times 60 \times 60$ Å. After all data were processed in Discovery Studio Visualizer (DSV), the interactions were displayed as both 2D and 3D structures. The molecules contain various substituents that provide different electronic environments, resulting in diverse binding modes and activities against *Escherichia coli* BepA metalloprotease. Table 3 provides an overview of their best binding affinities, interaction types, and interaction distances.

As shown in Table 3, the calculated binding affinities ranged from -7.2 to -8.1 kcal/mol. The highest (least favorable) score, -7.2 kcal/mol, was observed for 3b, whereas the lowest (most favorable) score, -8.1 kcal/mol, was observed for 3d. Table 3 shows that molecule 3b and *Escherichia coli* BepA metalloprotease exhibit three major types of interactions (Pi–Pi T-shaped, alkyl, and Pi–alkyl). The interactions between

compound 3b and *Escherichia coli* BepA metalloprotease are visualized as 2D and 3D structures in Figure 4a and 4b, respectively. Molecule 3d and *Escherichia coli* BepA metalloprotease also exhibit three major types of interactions (Pi–Pi T-shaped, conventional hydrogen bond, and Pi–alkyl). The conventional hydrogen bond may play a crucial role in the interaction between molecule 3d and *Escherichia coli* BepA metalloprotease, which is visualized as 2D and 3D structures in Figure 5a and 5b, respectively.

Table 3 also shows that 3c has a binding score close to the most favorable score and exhibits four types of interactions (Pi–Pi T-shaped, alkyl, conventional hydrogen bond, and Pi–alkyl). These molecules have several substituents attached to their structures. Compound 3d has nitro and bromine substituents and both substituents were shown to interact. In compound 3c, the methoxy and nitro groups were shown to interact. In both molecules, the nitro group formed a conventional hydrogen bond. Therefore, nitro groups may play a crucial role in biological activity. The 2D and 3D structures of the interaction between compound 3c and *Escherichia coli* BepA metalloprotease are shown in Figure 6a and 6b, respectively.

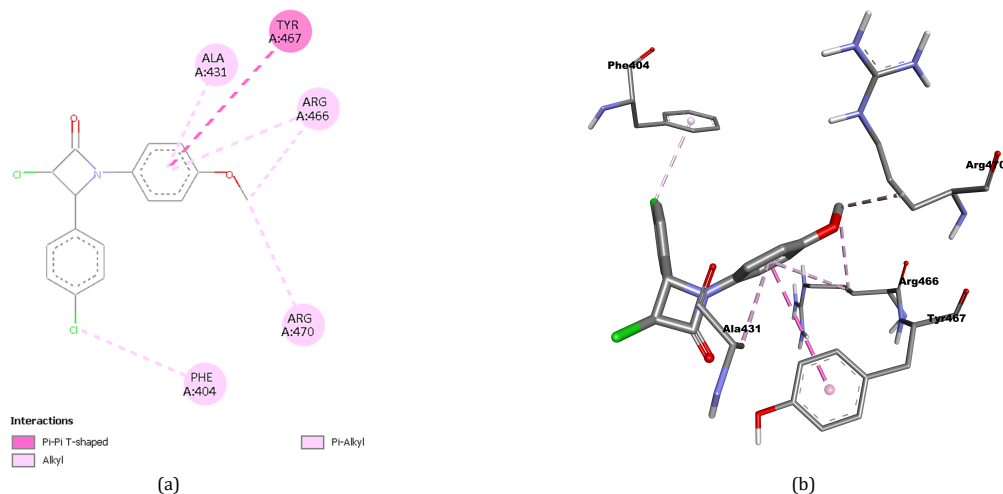


Figure 4. (a) 2D and (b) 3D interaction diagrams showing the binding mode of compound 3b with *Escherichia coli* BepA metalloprotease.

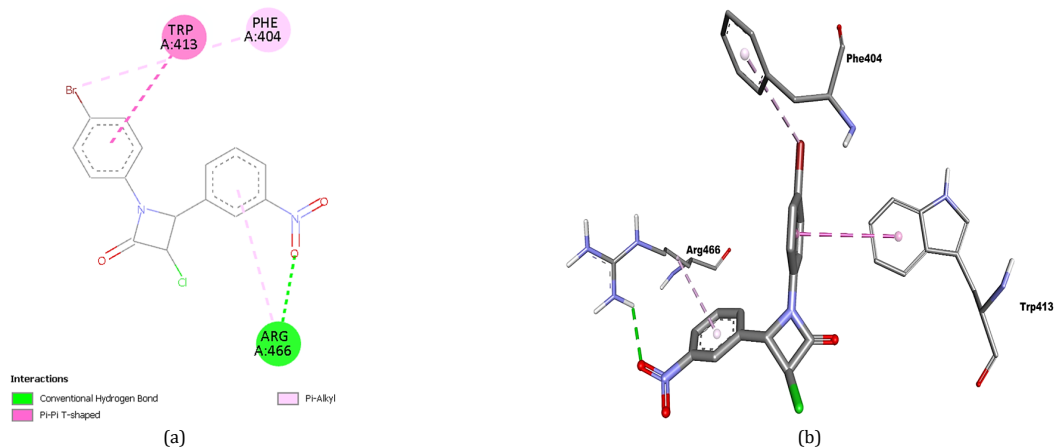


Figure 5. (a) 2D and (b) 3D interaction diagrams showing the binding mode of compound 3d with *Escherichia coli* BepA metalloprotease.

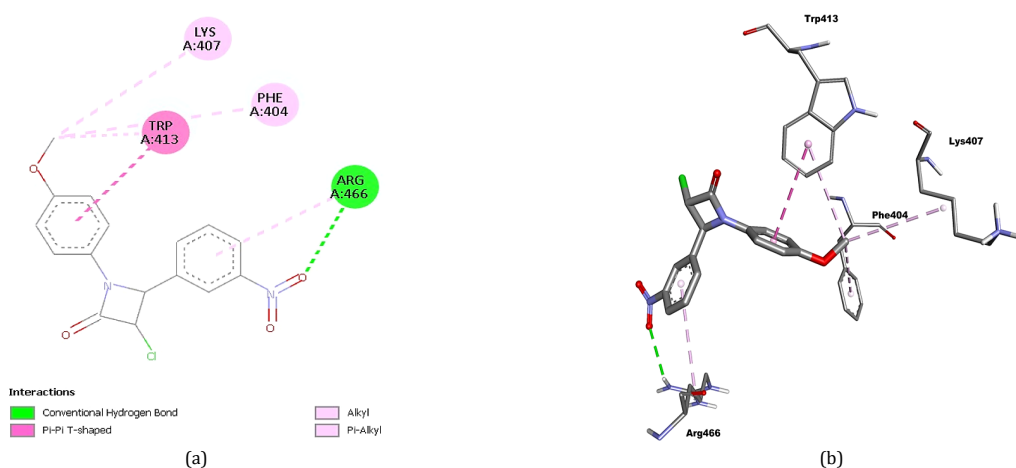


Figure 6. (a) 2D and (b) 3D interaction diagrams showing the binding mode of compound 3c with *Escherichia coli* BepA metalloprotease.

5. Conclusions

A series of novel β -lactam derivatives were successfully synthesized via Schiff base intermediates and confirmed by FT-IR and ^1H NMR analysis. The calculated CDFD descriptors (μ , η , ω , and N) characterize the relative ability of the synthesized β -lactam derivatives to participate in electron density exchange during polar processes. The combined analysis of these

descriptors provides a consistent interpretation of the polar nature of the studied reactions and the relative reactivity of the investigated compounds. Molecular electrostatic potential analysis identified oxygen-containing functional groups as the most favorable sites for intermolecular interactions. Molecular docking studies demonstrated favorable binding affinities toward *Escherichia coli* BepA metalloprotease, particularly for compound 3d, which showed the best binding score. The

presence of nitro and halogen substituents appears to enhance binding interactions. Overall, these findings suggest that the synthesized β -lactam derivatives may serve as promising candidates for antibacterial drug development and merit further biological evaluation.

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Disclosure statement

Conflict of interest: Umme Aiman Liza, Sumaiya Khan, Md Aman Ullah Aman, Md Sarwar Hossen Sogib, Md Alamgir Hossain, Anamika Sultana, and Mohammad Mamun Hossain declare that they have no conflicts of interest. Ethical approval: All ethical guidelines were followed. Sample availability: Samples of the compounds are available from Umme Aiman Liza, Sumaiya Khan, and Mohammad Mamun Hossain.

CRedit authorship contribution statement

Conceptualization: Mohammad Mamun Hossain, Sumaiya Khan; Methodology: Sumaiya Khan, Mohammad Mamun Hossain; Validation: Sumaiya Khan, Umme Aiman Liza, Mohammad Mamun Hossain; Synthesis: Md. Alamgir Hossain; Formal Analysis: Umme Aiman Liza, Sumaiya Khan, Md Aman Ullah Aman, Md Sarwar Hossen Sogib, Md. Alamgir Hossain, Anamika Sultana, Mohammad Mamun Hossain; Investigation: Sumaiya Khan, Umme Aiman Liza, Mohammad Mamun Hossain; Resources: Mohammad Mamun Hossain, Umme Aiman Liza, Sumaiya Khan; Data Correction: Umme Aiman Liza, Sumaiya Khan, Md Aman Ullah Aman, Md Sarwar Hossen Sogib, Md Alamgir Hossain, Anamika Sultana, Mohammad Mamun Hossain; Writing - Original Draft: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza, Md Aman Ullah Aman, Md Sarwar Hossen Sogib; Writing - Review and Editing: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza, Md Aman Ullah Aman, Md Sarwar Hossen Sogib; Anamika Sultana; Visualization: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Funding acquisition: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Supervision: Mohammad Mamun Hossain, Sumaiya Khan; Project Administration: Mohammad Mamun Hossain, Sumaiya Khan.

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