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Synthesis and molecular docking studies of 3-methyl-1,4-diarylazetidin-2-ones

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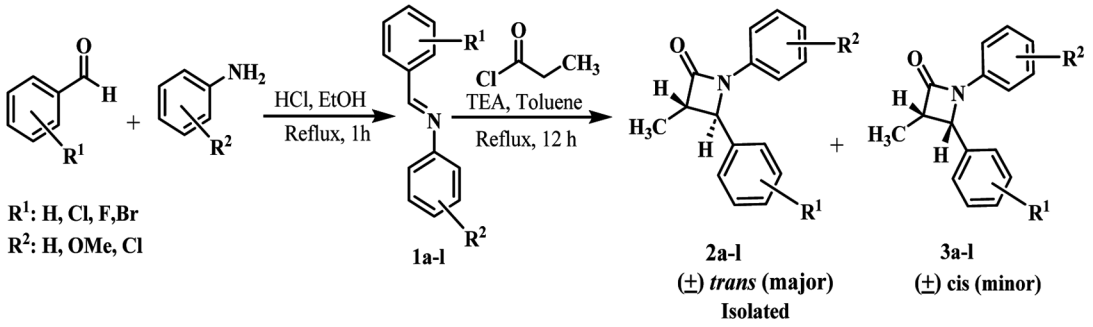
The *trans* isomers of 3-methyl-1,4-diarylazetidin-2-ones have been isolated from the reactions of *N*-1-diarylmethanimine with the ketene generated from propionyl chloride *via* [2+2] cycloaddition protocol. The reaction has been optimised by varying different parameters such as temperature, solvent and bases. The *trans* β-lactams are obtained as the major diastereomers and the structure has been confirmed from the coupling constants of the respective hydrogens from the ^{1}H NMR spectra. The structures of the β-lactams have been elucidated by ^{1}H and ^{13}C NMR spectral techniques and ESI-MS spectroscopy. The synthesized compounds have been evaluated for their binding affinities. To gain insights into the mechanism of action, the interactions between the synthesized compounds and the selected microbial target *S. aureus* DNA Gyrase B protein have been examined. These investigations have shed light on the potential binding modes of (±) *trans* 3-methyl-1,4-diarylazetidin-2-ones, enhancing our understanding of the mechanism of action.

Keywords: 1,4-Diarylazetidin-2-ones, Molecular docking, β-Lactams, Antibacterial agents

The β-lactams, commonly referred to as 2-azetidinones, constitute a class of 4-membered heterocyclic compounds with significant applications in the realm of biology. These compounds have garnered substantial interest due to their pivotal role in the synthesis of novel antibiotics[1,2]. The β-lactam core structure confers remarkable bioactivity of these molecules[3]. Notable members within this group encompass penicillin, carbapenems, cephalosporins, and monobactams[4-7]. Emanating from either natural sources or synthetic routes, these compounds have established their importance as useful intermediates[8]. Their versatility finds expression in diverse domains of biology and medicine[9], ranging from antibacterial and antifungal activities[10,11] to antioxidant, antimalarial, and antitumor properties[12-14]. Furthermore, they exhibit the ability to hinder cholesterol absorption[15].

The synthesis of β-lactams entails a [2+2] cycloaddition reaction that involves imine and ketene components[16]. Generally, the Staudinger cycloaddition leads to diastereoselective products, although attaining stereoselectivity is a challenge[17]. In the presence of a weak nucleophilic base, 2-chloropyridine, ethyl malonyl chloride reacts with imines by a [2+2] cycloaddition mechanism to form ethyl *trans* β-lactam-3-carboxylates. But in the presence of the strong nucleophilic base *N*-methylimidazole, a [2+2+2] cycloaddition involving one molecule of the imine and two molecules of the ketene was observed[18]. Approaches for generating ketenes have also been documented[19]. Employing acid chlorides and TEA stands as a conventional method for ketene generation[20,21]. Certain compounds, such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), propyl phosphonic anhydride (T3P), Mukaiyama's salt, Vilsmeier reagent and phosphonitrilic chloride have been identified as activators for carboxylic acids and ketene generators[22-26]. These activators suffer drawbacks in terms of cost and toxicity.

Addressing these gaps, the exploration of propiolactams emerged, as they have received comparatively less attention but exhibit potent antibacterial activity[27]. Functioning as intermediates in antibiotic synthesis, these β-lactams are generated through the cycloaddition of propionyl chloride, wherein *in situ* generated ketenes are reacted with imines. This avenue not only expands the scope of β-lactam research but also offers a promising alternative with the potential to overcome the limitations of existing antibacterial agents.



Scheme 1 — Synthesis of 3-methyl-1,4-diarylazetidin-2-ones

Results and Discussion

The aromatic amines were reacted with aldehydes to facilitate a nucleophilic addition followed by dehydration to yield imines. The Schiff bases **1** were synthesized from substituted aromatic aldehydes and aromatic amines, using hydrochloric acid in ethanol medium. These intermediates were then subjected to reaction with propionyl chloride in the presence of triethyl amine (TEA) base. The reaction was refluxed for 12 hours in toluene, leading to the formation of (±) *trans*-3-methyl-1,4-diarylazetidin-2-ones as the major product and *cis*-3-methyl-1,4-diarylazetidin-2-ones as the minor product (Scheme 1).

We herein report a series of twelve *trans* β-lactams (**2a-l**) synthesized by a stereoselective [2+2] ketene and imine cycloaddition. Yields were modest and the stereochemistry of the β-lactams was determined from the coupling constant of the hydrogens H-3 and H-4 [$J_{3,4}$>4.0Hz] for the cis stereoisomer and [$J_{3,4}$<3.0Hz] for the *trans* isomer, corroborating with the literature report[28].The stereochemistry of the compounds was deduced from the coupling constant values.

The optimization process for compounds **2a-l** involved adjustments of the reaction conditions, focusing on solvent selection, temperature control, and the choice of the base. An evaluation of various bases, from potassium carbonate to sodium hydride, yielded unsatisfactory results in terms of reaction time and product yield. Triethylamine emerged as the most effective base, enabling the completion of the reaction within 12 hours and resulting in good yield of the desired β-lactams. Different solvents, including dimethylformamide, 1,4-dioxane, dichloromethane, tetrahydrofuran, acetonitrile, and toluene were scrutinized. Among these, toluene demonstrated superior efficacy. Operating at 100°C, reactions carried out in toluene achieved completion in 12 hours, yielding a substantial product yield. Toluene's remarkable compatibility with reactants fostered an environment conducive to efficient interactions, translating to a higher yield compared to other solvents. With toluene established as the optimal solvent, systematic variation of reaction temperatures from 0°C to 100°C unveiled a direct relationship between temperature elevation and acceleration of the reaction rate. Additionally, changing the concentration of triethylamine, ranging from 0.5 to 3.0 equivalents, yielded intriguing insights. A concentration of 0.5 equivalent led to a 4 hours reaction with a poor yield. Conversely, increasing the concentration to 3.0 equivalents with a reaction time of 12 hours yielded an optimal 60% of **2a**.With these fine-tuned conditions, a diverse range of substituted 2-azetidinone derivatives, bearing both electron-donating and electron-withdrawing groups on the aromatic ring, were successfully synthesized and the respective yields are provided in Table 1. These results enhance the understanding of the reaction kinetics and had set the stage for the formation of several derivatives with tailored substituents.

Table 1 — Optimization of the reaction conditions for the synthesis of (±) *trans*-3-methyl-1,4-diphenylazetidin-2-one

Entry	Solvent	Base	Time (h)	Temp (°C)	Yield (%)
1	DMF	TEA	24	100	10
2	DCM	TEA	24	0	20
3	EtOH	TEA	24	80	25
4	THF	TEA	24	r.t.	20
5	ACN	TEA	24	80	30
6	1,4-dioxane	TEA	24	70	20
7	Toluene	TEA	12	100	60
8	Toluene	*t*-BuOK	24	100	10
9	Toluene	DIPEA	24	100	15
10	Toluene	Pyridine	24	100	20
11	Toluene	NaOH	24	100	30
12	Toluene	Cs_2CO_3	24	100	20
13	Toluene	NaH	24	100	15

N,1-Diphenylmethanimine (1.0 mmol), Propionyl chloride (1.2 mmol), Base (3.0 mmol), Solvent (10 mL)

The Staudinger reaction follows a clearly defined mechanistic pathway wherein the Schiff bases engage with ketenes. This process is initiated by the utilization of a base to generate ketenes *in situ* within the reaction environment. The sequence commences with the imine reacting with the ketene and leading to the formation of a zwitterionic intermediate. This intermediate then undergoes subsequent isomerization steps. Ultimately, through a concerted mechanism, the ketene and imine cooperatively facilitate the direct closure of the ring, yielding β-lactams (Fig. 1). This sequence of events displays the intricate mechanistic details between the reactants in the Staudinger reaction, culminating in the synthesis of these heterocyclic compounds. Consequently, by employing the optimized reaction conditions, several 2-azetidinone derivatives were synthesized as outlined in Fig. 2. It is noteworthy that *N*-aryl imines with electron-donating groups demonstrated better yields compared to imines containing electron-withdrawing groups.

The ligands' structure data files (SDF) as well as that of the reference drugs Ciprofloxacin and Delafloxacin were retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov)[29]. To facilitate the analysis, these compounds were converted into the .pdb chemical format using the PYMOL molecular graphics system (version 1.7.4.5). During this process, internal mobility levels and torsions were defined, polar hydrogens were introduced, and non-polar hydrogens were amalgamated with carbon atoms. Subsequently, the ligand molecules were transformed into the dockablepdbqt format using the Autodock Vina program. For investigating the interactions between the synthesized molecule and *S. aureus*, molecular docking procedures were employed on the DNA Gyrase B protein (Fig. 3) (PDB ID: 4URM), obtained from the Protein Data Bank (PDB) (https://www.rcsb.org/). These docking procedures were executed through the AutoDock tools graphical user interface. The use of AutoDock Vina 4.2 program was pivotal for understanding how antibacterial target receptor interact with the molecules. The outcomes of this study were based on

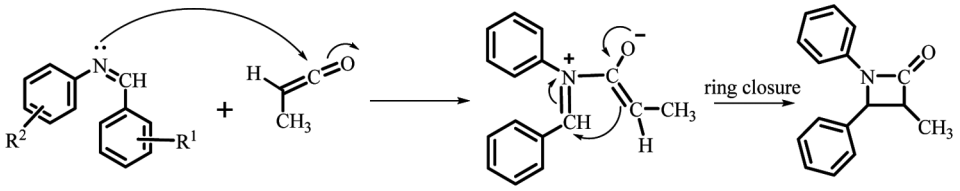


Fig. 1 — Plausible reaction mechanism for (±) *trans*-3-methyl-1,4-diphenylazetidin-2-one

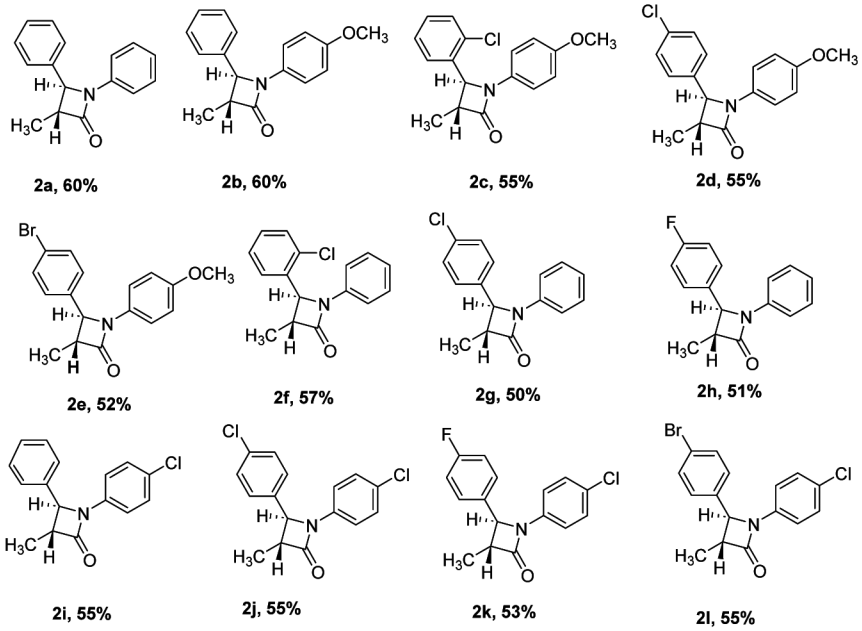


Fig. 2 — Synthesized (±) *trans*-3-methyl-1,4-diarylazetidin-2-ones

parameters such as bond lengths and binding energies, which provided insights into protein-ligand interactions. Docking scores were influenced by factors such as the number of hydrogen bonds formed, the predicted inhibitory constant kIC_{50}, and the amino acids involved in binding. Additionally, the Root Mean Square Deviation (RMSD) of the ligand and protein interaction was assessed to determine the energy associated with the interaction.

A computational study of the compounds was performed for the prediction of ADME properties. Polar surface area (TPSA), miLog P, number of rotatable bonds (n-ROTB), number of hydrogen bond donor (HBD) and acceptor (HBA) atoms, and violations of Lipinski's rule of five were calculated using Molinspiration online property calculation toolkit (Table 2)[30]. Molecular docking studies were performed in order to predict the interaction of 3-methyl-1,4-diarylazetidin-2-ones with the binding sites of DNA gyrase B[31]. AutoDock vina was used and the pdbqt files were created for both protein and ligand structures by adding torsion counts of amide bonds rotatable. Grid space was defined in the Auto grid by selecting important residues with grid box sizes of x = 40, y = 40, z = 40,and grid spacing of 0.692, which provides the search space. The grid centre was chosen with dimensions of x = 25.194, y = 16.737, z = 25.891, which was used to calculate grid parameters that aid in understanding the grid energy with equilibrated energy distribution. An exhaustiveness score of 10 was applied for enhanced precision.

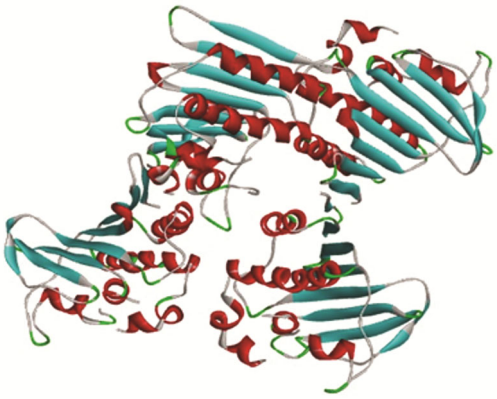


Fig. 3 — 3D Structure of DNA Gyrase B

Our findings from the docking studies revealed that 3-methyl-1,4-diarylazetidin-2-ones exhibited a higher affinity towards the DNA Gyrase B protein compared to the reference compounds. The lead compound, 3-methyl-1,4-diphenylazetidin-2-one **2a** yielded a docking score of –17.4 kcal/mol (Fig. 4). It formed hydrogen bond with Glu58 at a bond distance of 3.18 Å, and also engaged in pi-alkyl, amide-pi, and pi-sigma interactions with Ile102, Ile175, and Asn54, with bond distances of 4.65 Å, 5.15 Å, and 4.57 Å, respectively. The compound, 4-(4-fluorophenyl)-3-methyl-1-phenylazetidin-2-one **(2g)**, exhibited docking score of –16.9 kcal/mol, forming two hydrogen bonds with Glu58 and Asp81 at bond distances of 3.12 Å and 3.22 Å, along with pi-sigma and pi-alkyl interactions involving Ile86 and Ile102 at bond distances of 3.66 Å and 3.31 Å. The compound, 4-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-methylazetidin-2-one **2d**, attained a docking score of -16.4 kcal/mol, forming three hydrogen bonds with

Table 2 — Evaluation of physicochemical properties of the synthesized 3-methyl-1,4-diarylazetidin-2-ones

Compd	LogP	TPSA	natoms	MW	nON	nOHNH	Nrobt
2a	3.55	20.31	18	237.30	2	0	2
2b	3.61	29.54	20	267.33	3	0	3
2c	4.24	29.54	21	301.77	3	0	3
2d	4.29	29.54	21	301.77	3	0	3
2e	4.42	29.54	21	346.22	3	0	3
2f	4.18	20.31	19	271.75	2	0	2
2g	3.71	20.31	19	255.29	2	0	2
2h	4.23	20.31	19	271.75	2	0	2
2i	4.23	20.31	19	271.75	2	0	2
2j	4.91	20.31	20	306.19	2	0	2
2k	4.39	20.31	20	289.74	2	0	2
2l	4.94	20.31	20	350.64	2	0	2
Ciprofloxacin	–0.70	74.57	24	331.35	6	2	3
Delafloxacin	–0.70	121.69	30	440.76	8	4	3

miLogP (octanol-water dissolution) 180–500 kDa, Hydrogen bond acceptor (nON)>1–10; Hydrogen bond donor (nOHNH)>1–5, Number of rotatable bonds (Nrotb)>1–12.

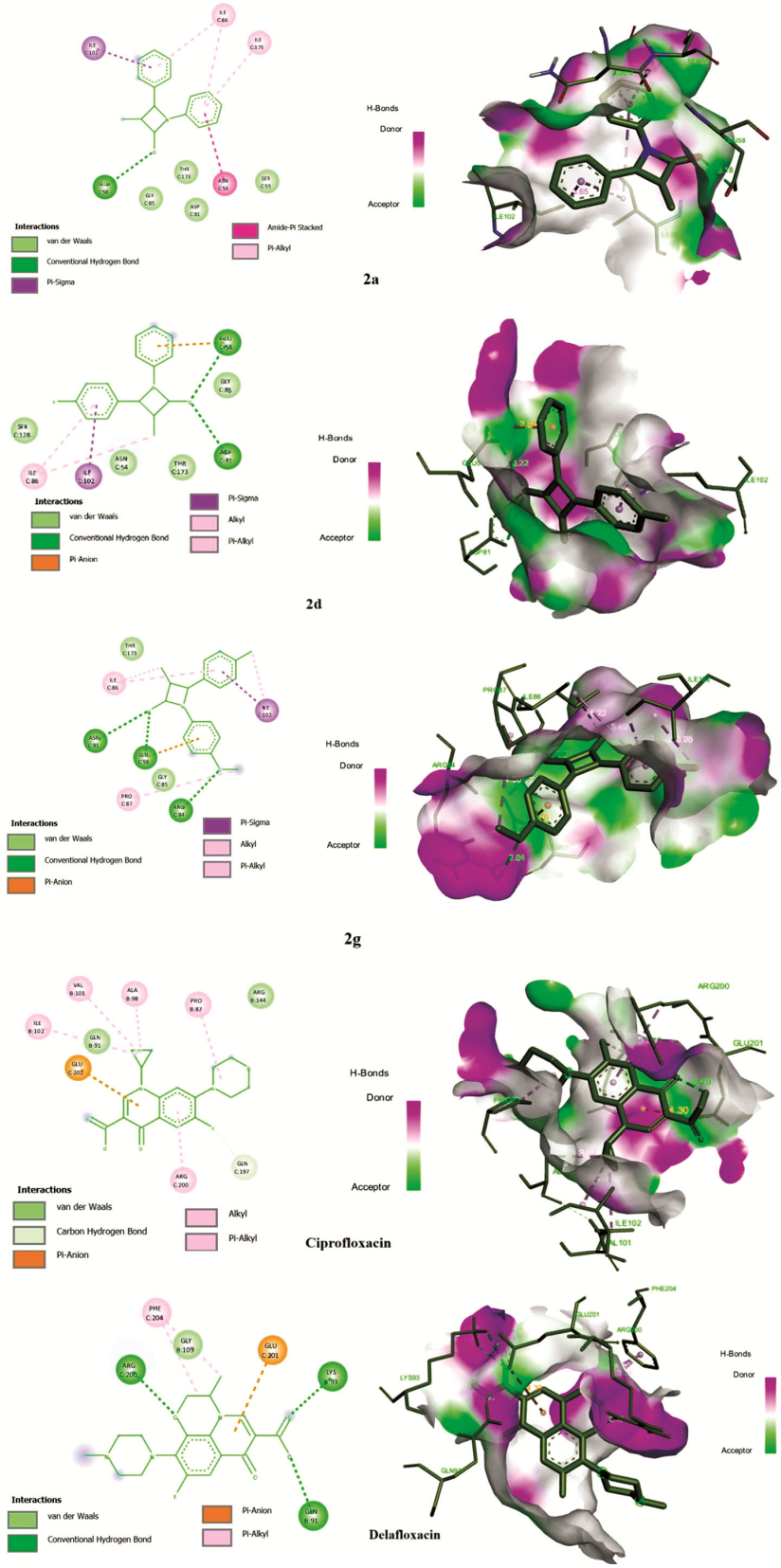


Fig. 4 — Docking studies of (±) *trans*-3-methyl-1,4-diarylazetidin-2-ones and reference compounds

Table 3 — Binding interactions of (±) *trans*-3-methyl-1,4-diarylazetidin-2-ones

Compd	Docking score (kcal/mol)	Interacting residue	Type of bond	Bond distance (Å)
2a	–17.4	Glu58, Ile102, Ile175, Asn54	H-bond, Pi-Sigma, Pi-Alkyl, Amide-Pi	3.18, 4.65, 5.15, 4.57
2b	–16.6	Asp81, Glu58, Ile102, Ile 86, Pro87	H-bond, H-bond, Pi-Sigma, Pi-Alkyl, Pi-Alkyl	3.19, 3.31, 3.70, 4.79, 3.30
2c	–18.9	Ala108, Ala98, Ile102, Val101, Pro87	Pi-Alkyl, Pi-Alkyl, Pi-Alkyl, Pi-Alkyl, Pi-Alkyl	4.2, 4.78, 4.05, 4.83, 4.98
2d	–16.4	Asp81, Glu58, Arg84, Pro87, Ile102, Ile86	H-bond, H-bond, H-bond, Pi-Alkyl, Pi-Sigma, Pi-Alkyl,	3.21, 3.30, 2.84, 3.95, 3.87, 3.83
2e	–18.9	Pro87, Ala98, Val101	Pi-Alkyl, Pi-Alkyl,Pi-Alkyl	3.83, 3.99, 4.38
2f	–17.9	Gln197, Gln91, Pro87, Ala108, Ala98, Ile102, Val101	H-bond, H-bond,Pi-Alkyl, Pi-Alkyl,Pi-Alkyl, Pi-Alkyl, Pi-Alkyl	3.25, 5.09, 5.07, 5.20, 4.74, 5.20, 4.72
2g	–16.9	Glu58, Asp81, Ile102, Ile86	H-bond, H-bond, Pi-Sigma, Pi-Alkyl	3.12, 3.22, 3.66, 3.31
2h	–16.9	Glu58, Asp81, Ile102, Ile86, Ala108	H-bond, H-bond,Pi-Sigma, Pi-Alkyl,Pi-Alkyl	3.47, 3.38, 4.17, 3.31, 4.45
2i	–16.8	Pro87, Ile102, Val101, Ala98	Pi-Alkyl, Pi-Alkyl, Pi-Alkyl, Pi-Sigma	4.16, 4.36, 3.62, 3.90
2j	–18.5	Arg84, Pro87, Ile102, Ile175, Ile86	Pi-Alkyl, Pi- Alkyl, Pi-Alkyl, Pi- Alkyl,Pi-Sigma	4.19, 3.47, 3.77, 4.73, 5.18
2k	–17.3	Glu58, Asp81, Thr173, Ile86	H-bond, H-bond, H-bond, Pi-Alkyl	3.14, 3.34, 3.20, 3.14
2l	–18.5	Ile102, Val101, Ala98, Pro87	Pi-Alkyl, Pi- Alkyl, Pi-Alkyl, Pi-Sigma	4.74, 4.17, 4.41, 4.71
Ciprofloxacin	–14.3	Ile102, Val101, Ala98, Pro87, Gln197	Pi-Alkyl, Pi-Alkyl, Pi- Alkyl, Pi-Alkyl, H-bond	5.54, 4.52, 3.64, 4.42, 3.30
Delafloxacin	–17.4	Arg200, Lys93, Gln91, Phe204	H-bond, H-bond, Pi-Alkyl, Pi-Alkyl	2.13, 2.75, 2.27, 3.94

Asp8, Glu58, and Arg84 at bond distances of 3.21 Å, 3.30 Å, and 2.84 Å, respectively. Additionally, two pi-alkyl and one pi-sigma interactions were observed with Pro87, Ile86, and Ile102 respectively, with bond distances of 3.95 Å, 3.83 Å, and 3.87 Å. Comparatively, the reference compounds delafloxacin yielded docking scores of –17.4 kcal/mol forming hydrogen bonds with Arg200 and Lys93 at bond distances of 2.13 Å, and 2.75 Å while ciprofloxacin yielded a docking score of –14.3 kcal/mol forming hydrogen bond with Gln197 at bond distances of 3.30 Å. The results underscore that 3-methyl-1,4-diarylazetidin-2-one derivatives exhibit strong binding energies, high docking scores, and close interactions with the protein in contrast to the reference drugs. These findings strongly suggest that these molecules hold promise as potential antibacterial agents (Table 3).

Conclusion

A series of 3-methyl-1,4-diarylazetidin-2-one derivatives were synthesized by the reaction of aromatic imines and ketene generated from propionyl chloride *via* Staudinger [2+2] cycloaddition reaction. The *trans* stereoisomers of these β-lactams were isolated and confirmed by spectral analysis. Molecular docking studies provided an understanding of the compounds' binding interactions with the microbial target DNA gyrase, allowing to elucidate the potential mechanism of action. Overall, the findings underscore the relevance of 2-azetidinone as versatile intermediates in pharmaceutical research and drug development.

Experimental Section

Chemicals and Instruments

Commercially available chemicals were used without purification. Reactions were conducted in oven-dried glassware under controlled atmospheric conditions. Thin-layer chromatography (TLC) with Merck Silica gel 60 F254 plates and UV light was employed for reaction monitoring. Column chromatography utilized silica gel, and elution was achieved with a hexane-ethyl acetate mixture. NMR

spectra were recorded on a Jeol ECZ 400R spectrometer, using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts were expressed in parts per million (ppm). Mass spectrometry analysis utilized an ESI quadrupole time-of-flight Agilent mass spectrometer.

General procedure for the synthesis of *N*-1-diarylmethanimine analogues

To a solution of aryl aldehyde (1.0 mmol) in EtOH (10 mL), HCl (1.0 mL) was added and stirred at room temperature for 5 minutes. To this solution aniline (1.0 mmol) was added and the reaction mixture was stirred at reflux for 1 hour. The precipitate formed was filtered, washed with ice-cold water, hexane, and dried.

General procedure for the synthesis of (±) *trans*-3-methyl-1,4-diarylazetidin-2-ones

To a mixture of substituted *N*,1-diarylmethanimine (1.0 mmol) in toluene, triethyl amine (3.0 mmol) was added and stirred for 5 minutes. Propionyl chloride (1.2 mmol) was then added slowly to this solution. After the completion of the addition, reaction mixture was heated at 100°C with constant stirring for 12 hours. The reaction mixture was cooled to room temperature, concentrated, diluted with water, and extracted into EtOAc. The combined organic extracts were concentrated under vacuum and the resultant crude was subjected to purification by column chromatography on silica gel (60-120 mesh) using hexane-ethyl acetate solvent mixture (10:1) as the mobile phase to obtain the desired product.

***trans*-3-Methyl-1,4-diphenylazetidin-2-one, 2a**: White solid, Yield: 60%, m.p: 110-112°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.40 (m, 5H), 7.29 (m, *J* = 8.6, 1.2Hz, 2H), 7.20-7.26 (m, 2H), 6.99-7.06 (m, 1H), 4.58 (d, *J* = 2.4Hz, 1H), 3.06-3.19 (m, *J* = 7.4, 2.4Hz, 1H), 1.48 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.40, 137.98, 137.87, 129.17, 129.06, 128.47, 125.85, 123.77, 116.99, 62.72, 55.36, 13.13; Mass (ESI): m/z calcd. for $C_{16}H_{15}NO$ $[M+H]^+$: 238.17; Found: 238.20.

***trans*-1-(4-Methoxyphenyl)-3-methyl-4-phenylazetidin-2-one, 2b**: White solid, Yield: 60%, m.p: 88-90°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.38 (m, 5H), 7.20-7.26 (m, 2H), 6.75-6.80 (m, 2H), 4.53-4.55 (m, *J* = 2.3Hz, 1H), 3.73 (s, 3H), 3.08-3.15 (m, *J* = 7.4, 2.3Hz, 1H), 1.47 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.79, 155.92, 138.05, 131.46, 129.13, 128.43, 125.89, 118.25, 114.30, 62.81, 55.44, 55.33, 13.13. Mass (ESI): m/z calcd. for $C_{17}H_{17}NO_2$ $[M+H]^+$: 268.13, Found: 268.00.

***trans*-4-(2-Chlorophenyl)-1-(4-methoxyphenyl)-3-methylazetidin-2-one, 2c**:White solid, Yield: 55%, m.p: 84-86°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, *J* = 9.9, 2.8Hz, 1H), 7.16-7.26 (m, 5H), 6.79-6.84 (m,2H), 5.06 (d, *J* = 2.2Hz, 1H), 3.75 (s, 3H), 3.02-3.09 (m, *J* = 7.4, 2.3Hz, 1H), 1.58 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.62, 156.06, 135.59, 132.62, 131.28, 129.87, 129.16, 127.46, 126.52, 118.22, 114.42, 59.08, 55.46, 54.67, 13.85; Mass (ESI): m/z calcd. for $C_{17}H_{16}ClNO_2$ $[M+H]^+$: 302.09, Found: 302.00.

***trans*-4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-methylazetidin-2-one, 2d**: White solid, Yield: 55%, m.p: 88-86°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40-7.46 (m, 4H), 7.13-7.18 (m, 2H), 6.84-6.91 (m, 2H), 4.85 (d, *J* = 2.3Hz, 1H), 3.68 (s, 3H), 3.05-3.14 (m, *J* = 7.3, 2.2Hz, 1H), 1.37 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.43, 156.07, 137.15, 132.30, 131.16, 127.60, 122.30, 118.22, 114.39, 62.13, 55.45, 55.36, 13.11; Mass (ESI): m/z calcd. for $C_{17}H_{16}ClNO_2$ $[M-H]^+$: 299.09, Found: 299.00.

***trans*-4-(4-Bromophenyl)-1-(4-methoxyphenyl)-3-methylazetidin-2-one, 2e**: White solid, Yield: 52%, m.p: 130-132°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4Hz, 2H), 7.21 (m, *J* = 8.6, 7.2Hz, 4H), 6.78 (d, *J* = 9.0Hz, 2H), 4.51 (d, *J* = 2.1Hz, 1H), 3.72 (s, 3H), 3.02-3.13 (m, *J* = 7.3, 2.2Hz, 1H), 1.47 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.43, 156.07, 137.15, 132.30, 131.16, 127.60, 122.30, 118.22, 114.39, 62.13, 55.45, 55.36, 13.11; Mass (ESI): m/z calcd. for $C_{17}H_{16}BrNO_2$ $[M+H]^+$: 348.09, Found: 348.00.

***trans*-4-(2-Chlorophenyl)-3-methyl-1-phenylazetidin-2-one, 2f**: White solid, Yield: 57%, m.p: 110-112°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.45 (m,1H), 7.26-7.31 (m, 4H), 7.16-7.25 (m, 3H), 7.02-7.09 (m, 1H), 5.09 (d, *J* = 2.3Hz, 1H), 3.04-3.12 (m, *J* = 7.4, 2.4Hz, 1H), 1.59 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.24, 137.70, 135.48, 132.58, 129.90, 129.19, 127.49, 126.49, 123.96, 117.06, 116.98, 59.07, 54.68, 13.86; Mass (ESI): m/z calcd. for $C_{16}H_{14}ClNO$ $[M+Na]^+$: 294.08, Found: 294.15.

***trans*-4-(4-Chlorophenyl)-3-methyl-1-phenylazetidin-2-one, 2g**: White solid,Yield:50%, m.p: 108-110°C, ^{1}H NMR (400 MHz, $CDCl_3$): 7.30-7.36 (m, 2H), 7.22-7.28 (m, 4H), 7.01-7.09 (m, 3H), 4.57 (d, *J* = 2.3Hz, 1H), 3.06-3.14 (m, *J* = 7.4, 2.4Hz, 1H), 1.48 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.24, 137.70, 129.90, 129.19, 127.49, 126.49, 123.96, 117.06, 116.98, 59.07, 54.68, 13.86; Mass (ESI): m/z calcd. for $C_{16}H_{14}FNO$ $[M+Na]^+$: 294.08, Found: 294.20.

***trans*-4-(4-Fluorophenyl)-3-methyl-1-phenylazetidin-2-one, 2h**: White solid, Yield: 51%, m.p: 110-112°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56-7.64 (m,1H), 7.45 (s, 3H), 7.29 (t, *J* = 7.9Hz, 2H),7.18-7.22 (m, 2H), 7.04 (m, *J* = 10.5, 4.2Hz, 1H), 4.90 (d, *J* = 2.4Hz, 1H), 3.08-3.19 (m, *J* = 7.3, 2.4Hz, 1H), 1.37 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.24, 137.70, 129.90, 129.19, 127.49, 126.49, 123.96, 117.06, 116.98, 59.07, 54.68, 13.86; Mass (ESI): m/z calcd. for $C_{16}H_{14}FNO$ $[M+Na]^+$: 278.11, Found: 278.15.

***trans*-1-(4-Chlorophenyl)-3-methyl-4-phenylazetidin-2-one, 2i**: Slight yellow solid, Yield: 55%, m.p: 86-88°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38-7.42 (m, 4H), 7.35 (m, *J* = 9.8, 4.6, 2.9Hz, 3H), 7.21-7.25 (m, 2H), 4.88 (d, *J* = 2.4Hz, 1H), 3.12-3.19 (m, *J* = 7.3, 2.4Hz, 1H),1.38 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.43, 138.21, 136.76, 129.56, 129.47, 128.80, 127.75, 126.61, 118.70, 61.74, 55.22, 13.10; Mass (ESI):m/z calcd. for $C_{16}H_{14}ClNO$ $[M+Na]^+$: 294.08, Found: 294.15.

***trans*-1,4-bis(4-Chlorophenyl)-3-methylazetidin-2-one, 2j**: White solid, Yield: 55%, m.p: 128-130°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.53 (m, 2H), 7.14-7.26 (m, 6H), 4.54 (d, *J* = 2.4Hz, 1H), 3.04-3.16 (m, *J* = 7.4, 2.4Hz,1H), 1.47 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.72, 136.70, 136.19, 132.43, 129.18, 128.88, 127.46, 122.55, 118.13, 62.35, 55.70, 12.93; Mass (ESI): m/z calcd. for $C_{16}H_{13}Cl_2NO$ $[M+H]^+$: 306.04, Found: 306.00.

***trans*-1-(4-Chlorophenyl)-4-(4-fluorophenyl)-3-methylazetidin-2-one, 2k**: Pale yellow solid, Yield: 53%, m.p: 86-88°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33-7.36 (m, 2H), 7.25-7.29 (m, 2H), 7.19 (s, 4H), 4.55 (d, *J* = 2.4Hz, 1H), 3.05-3.16 (m, *J* = 7.4, 2.4Hz,1H), 1.48 (d, *J* = 7.4Hz, 3H); ^{13}C NMR(100 MHz, DMSO-d_6) δ: 167.69, 136.23, 136.20, 134.55, 129.46, 129.16, 129.07, 127.13, 118.13, 62.34, 55.76, 12.89; Mass (ESI): m/z calcd. for $C_{16}H_{13}ClFNO$ $[M-H]^+$: 288.07, Found: 288.00.

***trans*-4-(4-Bromophenyl)-1-(4-chlorophenyl)-3-methylazetidin-2-one, 2l**: White solid, Yield: 55%, m.p: 136-140°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45-7.50 (m, 2H), 7.34-7.38 (m, 2H), 7.19-7.25 (m, 4H), 4.91 (d, *J* = 2.4Hz,1H), 3.13-3.20 (m, *J* = 7.3, 2.4Hz, 1H), 1.37 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.38, 136.63, 129.60, 128.91, 128.82, 127.79, 118.72, 116.42, 116.20, 60.98, 55.18, 13.04; Mass (ESI): m/z calcd for $C_{16}H_{13}BrClNO$ $[M+H]^+$: 351.99, Found: 352.00.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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