Zeolite-Supported One-Pot Synthesis of Bis-azetidinones under Microwave Irradiation

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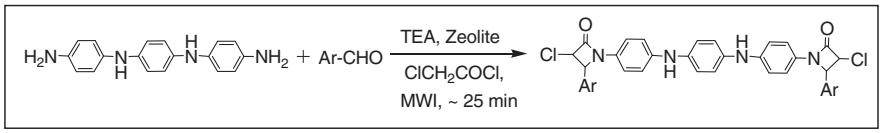

In an attempt to synthesize antibacterial agents effective against gram-positive and gram-negative bacteria, the efficient synthesis of novel bis-azetidinones (**3a–j**) has been established. Thus, cycloaddition reaction of substituted bis-imines with chloroacetylchloride under microwave irradiation in the presence of zeolite yielded bis-azetidinones (**3a–j**). Structures of the synthesized compounds have been elucidated on the basis of their elemental analysis and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra). The synthesized bis-azetidinones were screened for their antibacterial activity against five microorganisms: *Bacillus subtilis*, *Proteus vulgaris*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Escherichia coli*. They were found to exhibit good to moderate antibacterial activity.

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INTRODUCTION

High-speed synthesis using microwave (MW) heating technology has attracted a considerable amount of attention in recent years. More than 4000 articles have been published in the area of MW-assisted organic synthesis since the first reports on the use of MW heating to accelerate organic chemical transformations were published in 1986 [1–3]. Controlled MW heating under sealed vessel conditions has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared with conventional synthetic methods [4,5]. The many advantages of MW-assisted organic synthesis are reported in literature cycloaddition reactions [6], heterocyclic synthesis [7], the rapid preparation of radio labeled materials [8], transition metal catalyzed processes [9], solvent-free reactions [10] and phase-transfer catalysis [11], and medicinal chemistry/drug discovery [12]. The study has also penetrated fields such as polymer synthesis [13], material sciences [14], nanotechnology [15], and biochemical processes [16]. MW to organic synthesis has been developed with environmentally benign methods for synthesizing bis-imines (**2a–j**), and bis-azetidinones (**3a–j**) were obtained good yields as compared with the synthesis by the conventional method.

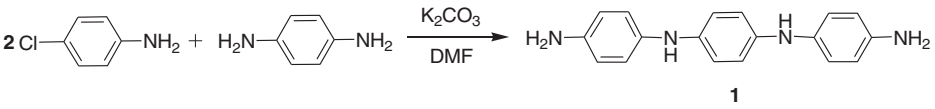
Nitrogen heterocycles occupy a premier position in both natural product chemistry and pharmaceutical science, and azetidin-2-ones (β-lactams) are the most investigated ring systems because of their well-documented impact on small-molecule drug discovery. Natural and synthetic β-lactam derivatives occupy a central place among medicinally important compounds because of their diverse and interesting antibiotic activities [17–20]. β-Lactam antibiotics, which are a large class of antibiotics characterized by the presence of a 2-azetidinone ring, proved to be therapeutic agents of unique effectiveness, conjugating a broad spectrum of activity with low toxicity [21]. 2-Azetidinone antibiotics are still the main drugs given, in the form of penicillins and cephalosporins, to treat infections caused by bacteria [22]. The utility of azetidinones as synthons for various biologically active compounds, as well as their recognition as cholesterol absorption inhibitors [23–27] and enzyme inhibitors [28,29], has given impetus to these studies [30–33].

Ojima has shown the utility of bis-β-lactams for the synthesis of peptides [34]. Various methods are available for the synthesis of β-lactams; the Staudinger cycloaddition reaction is the most widely used [35], mainly because of the simplicity in reaction procedures. Hence, herein we report the one-pot synthesis of bis-β-lactams using the Staudinger cycloaddition reaction from different substituted aromatic aldehydes and aromatic bis-amines in the presence of zeolite as a catalyst under MW irradiation (Scheme 3).

RESULTS AND DISCUSSION

We initially prepared N1-(4-(4-aminophenylamino)phenyl) benzene-1,4-diamine (**1**) from benzene-1,4-diamine on reacting with 4-chlorobenzenamine in potassium carbonate and DMF by classical method (Scheme 1). The compounds **2a–j** (N1,N4-bis(4-(substituted phenylideneamino)phenyl) benzene-1,4-diamine) were synthesized by condensation of compound **1** and different substituted aryl aldehydes under

Scheme 1. Synthesis of N1-(4-(4-aminophenylamino)phenyl)benzene-1,4-diamine (**1**).



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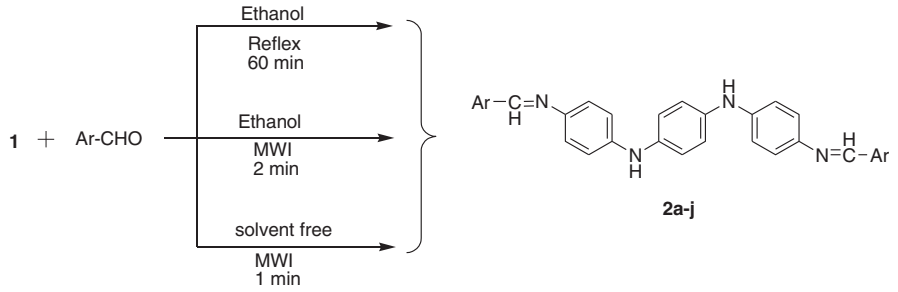
MW irradiation in the presence of solvent and solvent-free conditions as compared with that of conventional reflux reactions (Scheme 2). The comparison of isolated yields and reaction time of the three conditions employed showed MW-assisted solvent-free reactions as the most efficient synthetic method in terms of energy and time consumption. The reaction time and yield comparison between classical and MW irradiation are given in Table 1.

Microwave-assisted synthesis of substituted bis-azetidinones (**3a–j**) is represented in Scheme 3 (Table 2). Reactions were carried out by mixing amine (**1**) with different substituted aryl aldehydes by using zeolite as an acid catalyst. TEA and chloroacetyl chloride in DMF was added to the reaction mixture under MW irradiation. This support allows for easy separation of the solid catalyst and product by simple filtration, and in optimal conditions the supported catalyst can be reused multiple times. This study describes a successful approach for the synthesis of substituted bis-azetidinones using a laboratory MW reactor. MW irradiation has been found to be easier, convenient, and eco-friendly, and the reaction time has been drastically reduced as compared with that in the conventional method. The same reaction under thermal conditions (**3a–j**) is summarized in Scheme 4. All the compounds synthesized were adequately characterized by their elemental analysis and spectral IR, ^{1}H-NMR, and mass spectra.

Antibacterial studies. From Table 3, the investigation of antibacterial screening data revealed that most of the tested compounds showed moderate to good bacterial inhibition. Compounds **3c**, **3e**, and **3h** were found to be active against *Bacillus subtilis*; **3e** and **3h** against *Proteus vulgaris*; **3c**, **3d**, and **3h** against *Staphylococcus aureus*;

Scheme 2. Synthesis of Schiff bases (**2a–j**) by MW as well as classical method.



2a-j

Table 1

Time and yield comparison between classical and MW irradiation (**2a–j**).

		MW with solvent (solvent-free)		Classical method	
Compound	Ar	Reaction time (min)	Yield (%)[a]	Reaction time (min)	Yield (%)[a]
2a	C_6H_5	2 (1)	87 (95)	60	65
2b	*o*-OHC_6H_4	2 (1)	79 (94)	60	64
2c	*p*-OHC_6H_4	2 (1)	84 (90)	60	62
2d	*p*-$N(Me)_2C_6H_4$	2 (1)	78 (92)	60	65
2e	*p*-$OCH_3C_6H_4$	2 (1)	82 (94)	60	59
2f	*m*-OHC_6H_4	2 (1)	79 (95)	60	57
2g	*m*-ClC_6H_4	2 (1)	80 (91)	60	61
2h	*p*-ClC_6H_4	2 (1)	76 (92)	60	60
2i	*p*-$NO_2C_6H_4$	2 (1)	85 (90)	60	63
2j	*m*-$CH_3C_6H_4$	2 (1)	88 (95)	60	65

[a]Isolated yields.

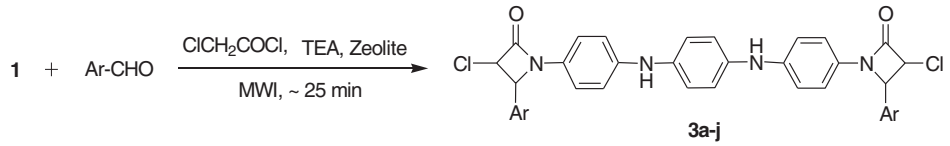
Table 2

Time and yield comparison between classical and MW irradiation (**3a–j**).

		MW method		Classical method	
Compound	Ar	Reaction time (min)	Yield (%)[a]	Reaction time (h)	Yield (%)[a]
3a	C_6H_5	25	88	15	63
3b	*o*-OHC_6H_4	21	92	17	69
3c	*p*-OHC_6H_4	23	89	14	67
3d	*p*-$N(Me)_2C_6H_4$	25	92	17	70
3e	*p*-$OCH_3C_6H_4$	25	90	18	68
3f	*m*-OHC_6H_4	24	87	14	62
3g	*m*-ClC_6H_4	23	87	15	64
3h	*p*-ClC_6H_4	24	90	15	60
3i	*p*-$NO_2C_6H_4$	26	85	16	60
3j	*m*-$CH_3C_6H_4$	26	87	15	62

[a]Isolated yields.

Scheme 3. Microwave-assisted one-pot synthesis of substituted bis-2-azetidinones (**3a–j**).



Scheme 4. Synthesis of substituted bis-2-azetidinones by classical method (**3a–j**).

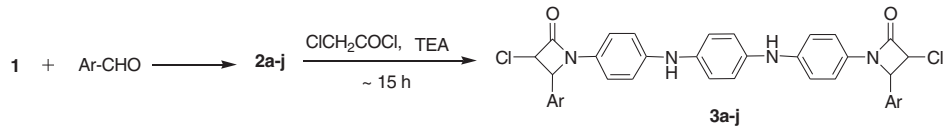


Table 3

Antibacterial activity of bis-2-azetidinone derivatives (zone of inhibition in mm).

	Bacteria (MIC at 100 μg/mL)				
	Gram positive			Gram negative	
Compound	BS	PV	SA	EC	KP
3a	+	−	+	+	+
3b	++	+	++	+++	++
3c	+++	++	+++	++	++
3d	++	++	+++	+++	+++
3e	+++	+++	++	++	++
3f	++	++	+	++	+++
3g	++	++	++	+	++
3h	+++	+++	+++	+++	+++
3i	++	−	+	++	+
3j	+	++	++	+	+
Ampicillin	+++	+++	+++	+++	+++

Key to symbols:
Gram positive bacteria: BS, *Bacillus subtilis*; PV, *Proteus vulgaris*; SA, *Staphylococcus aureus*.
Gram negative bacteria: EC, *Escherichia coli*; KP, *Klebsiella pneumoniae*.
−, inactive (inhibition zone <5 mm); +, slightly active (inhibition zone 5–10 mm); + +, moderately active (inhibition zone 11–16 mm); + + +, highly active (inhibition zone >17 mm).

3b, **3d**, and **3h** against *Escherichia coli*; and **3d**, **3f**, and **3h** against *Klebsiella pneumoniae*; these showed very good activity almost equivalent to that of the standard against all the bacterial strains. The compounds **3b**, **3d**, **3f**, **3g**, and **3i** showed moderate activity against *B. subtilis*; **3c**, **3d**, **3f**, 3**g**, and **3j** against *P. vulgaris*; **3b**, **3e**, **3g**, and **3j** against *S. aureus*; **3c**, **3e**, **3f**, and **3i** against *E. coli*; **3b**, **3c**, **3e**; and **3g** against *K. pneumoniae*.

EXPERIMENTAL

Starting materials and solvents were obtained from Merck and were used without further purification. Melting points were taken in an open capillary tube. The MW-assisted synthesis was carried out in a CEM-908010, bench mate model, 300 W laboratory MW reactor. IR spectra were recorded on a Shimadzu Dr-8031 instrument. Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400. ^{1}H-NMR spectra of the synthesized compounds were recorded on a Bruker-Avance (300 MHz) and Varian-Gemini (200 MHz) spectrophotometer using $CDCl_3$ solvent and TMS as the internal standard. EIMS spectra were determined on a LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an electron impact (EI) source.

Evaluation of antimicrobial activity (agar diffusion method). Antimicrobial activity of all synthesized compounds was determined by agar diffusion method. All human pathogenic bacteria, viz., *B. subtilis*, *K. pneumoniae*, *S. aureus*, *P. vulgaris*, and *E. coli* were obtained from the Kakatiya University, Warangal, India. Stock solutions of compounds were diluted in DMSO to give a final concentration for determining the minimum inhibitory concentration (MIC) value. MIC was defined as the lowest concentration of compound required for a complete inhibition of the bacterial growth after incubation time. For antibacterial activity, Muller Hinton agar was used. The wells of 6 mm diameter were filled with 0.1 mL of each compound diluted separately for each test of bacterial strain. The antibiotic ampicillin was used as reference antibacterial agent for comparison. Inoculated plates were then incubated at 37°C for antibacterial activity for 24 h. After incubation, the antimicrobial activity was measured in terms of the zone of inhibition in millimeters as shown in Table 3. Biological screening results were mentioned in millimeters, with diameters of inhibition zone categorized as 0–5 mm for mild, 6–12 mm for moderate, and 13–17 mm for efficacy.

Synthesis of N1-(4-(4-aminophenylamino)phenyl)benzene-1,4-diamine (1). To a solution of 4-chlorobenzenamine (0.5 mmol) and benzene-1,4-diamine (0.25 mmol), K_2CO_3 (0.75 mmol) and 20 mL of DMF were refluxed for 5 h. The completion of the reaction was monitored by TLC. The reaction mixture was poured in chilled water, and the precipitate was filtered out and dried. The crude product was recrystallized with methanol.

Synthesis of Schiff base (2a–2j).

Microwave method without solvent. Aromatic aldehyde (0.008 mol) and N1-(4-(4-aminophenylamino)phenyl)benzene-1,4-diamine (0.004 mol) were thoroughly mixed in a glass tube which was loosely closed. The reaction mixture was irradiated for 1 min with 100 W MWs at 110°C in MW oven in the temperature control mode. The completion of the reaction was monitored by TLC. The crude product was recrystallized with methanol.

Microwave method with solvent. A mixture of aromatic aldehyde (0.008 mol), N1-(4-(4-aminophenylamino)phenyl) benzene-1,4-diamine (0.004 mol), and ethanol was placed in a glass tube and was monitored by TLC. The reaction mixture was allowed to attain room temperature. The crude product was recrystallized with methanol.

Classical method. A quantity of 0.008 mol of aromatic aldehyde, 0.004 mol of N1-(4-(4-aminophenylamino)phenyl) benzene-1,4-diamine, and 20 mL of ethanol was refluxed for 60 min. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was set aside to cool. The air which separates may be induced to crystallize by rubbing with a glass rod. The solid deposit was collected by filtration, and the crude product was recrystallized with ethanol.

N1-(4-(4-(Benzylideneamino) phenylamino) phenyl)-N4-benzylidenebenzene-1,4-diamine (2a). IR (KBr, cm^{-1}): 1620.3 (–C═N–), ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.38 (s, 2H, CH═N), 10.22 (br s, 2H, NH), 6.5–7.7 (m, 22H, Ar–H); ^{13}C-NMR: δ 119.51–135.06 for aromatic carbons, 159.05 (–CH═N–); mass spectra, ($C_{32}H_{26}N_4$): *m/z* = 466. Elemental analysis: Calcd (found): C, 82.38 (82.32); H, 5.62 (5.58); N, 12.01 (11.97).

4,4′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene))bis(azan-1-yl-1-ylidene)bis(methan-1-yl-1-ylidene)diphenol (2b). IR (KBr, cm^{-1}): 1610.6 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.42 (s, 2H, CH═N), 12.55 (s, 2H, OH), 10.37 (br s, 2H, NH), 6.6–7.6 (m, 20H, Ar–H); ^{13}C-NMR: δ 115.98–157.96 for aromatic carbons, 160.89 (–CH═N–); mass spectra, ($C_{32}H_{26}N_4O_2$): *m/z* = 498. Elemental analysis: Calcd (found): C, 77.09 (77.04); H, 5.26 (5.22); N, 11.24 (11.21).

2,2′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene))bis(azan-1-yl-1-ylidene)bis(methan-1-yl-1-ylidene)diphenol (2c). IR (KBr, cm^{-1}): 1608.2 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.35 (s, 2H, CH═N), 11.42 (s, 2H, OH), 10.46 (br s, 2H, NH), 6.5–7.8 (m, 20H, Ar–H); ^{13}C-NMR: 116.06–160.15 for aromatic carbons, 162.23 (–CH═N–); mass spectra, ($C_{32}H_{26}N_4O_2$): *m/z* = 498. Elemental analysis: Calcd (found): C, 77.09 (77.06); H, 5.26 (5.20); N, 11.24 (11.25).

N1,N1′-(1,4-Phenylene)bis(N4-(4-(dimethylamino) benzylidene) benzene-1,4-diamine) (2d). IR (KBr, cm^{-1}): 1615.8 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.61 (s, 2H, CH═N), 3.05 (s, 12H, $N(CH_3)_2$), 10.32 (br s, 2H, NH), 6.6–7.9 (m, 20H, Ar–H); ^{13}C-NMR: δ 40.55 {$N(CH_3)_2$}, 115.04–151.28 for aromatic carbons, 160.53 (–CH═N–); mass spectra ($C_{36}H_{36}N_6$): *m/z* = 552. Elemental analysis: Calcd (found): C, 78.23 (78.20); H, 6.57 (6.53); N, 15.21 (15.18).

N1-(4-(4-(4-Methoxybenzylideneamino) phenylamino) phenyl)-N4-(4-methoxybenzylidene) benzene-1,4-diamine (2e). IR (KBr, cm^{-1}): 1627.5 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.45 (s, 2H, CH═N), 3.92 (s, 6H, –OCH_3), 10.28 (br s, 2H, –NH), 6.6–7.6 (m, 20H, Ar–H); ^{13}C-NMR: δ 57.42 (O–CH_3), 113.45–156.81 for aromatic carbons, 161.05 (–CH═N–); mass spectra ($C_{34}H_{30}N_4O_2$): *m/z* = 526. Elemental analysis: Calcd (found): C, 77.54 (77.51); H, 5.74 (5.69); N, 10.64 (10.61).

4,4′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene))bis(azan-1-yl-1-ylidene)bis(methan-1-yl-1-ylidene) diphenol (2f). IR (KBr, cm^{-1}): 1623.2 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.63 (s, 2H, CH═N), 10.91 (s, 2H, OH), 10.42 (br s, 2H, NH), 6.6–7.8 (m, 20H, Ar–H); ^{13}C-NMR: δ 115.22–154.69 for aromatic carbons, 158.95 (–CH═N–); mass spectra ($C_{32}H_{26}N_4O_2$): *m/z* = 498. Elemental analysis: Calcd (found): C, 77.09 (77.06); H, 5.26 (5.23); N, 11.24 (11.20).

N1-(3-Chlorobenzylidene)-N4-(4-(4-(3-chlorobenzylideneamino) phenylamino)phenyl)benzene-1,4-diamine (2g). IR (KBr, cm^{-1}): 1632.7 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.9 (s, 2H, CH═N), 10.72 (br s, 2H, NH), 6.5–7.5 (m, 20H, Ar–H); ^{13}C-NMR: δ 117.19–149.52 for aromatic carbons, 156.68 (–CH═N–); mass spectra, ($C_{32}H_{24}Cl_2N_4$): *m/z* = 535. Elemental analysis: Calcd (found): C, 71.78 (71.73); H, 4.52 (4.49); N, 10.46 (10.41).

N1-(4-(4-(4-Chlorobenzylideneamino) phenylamino) phenyl)-N4-(4-chlorobenzylidene) benzene-1,4-diamine (2h). IR (KBr, cm^{-1}): 1630.5 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.1 (s, 2H, CH═N), 10.78 (br s, 2H, NH), 6.5–7.7 (m, 20H, Ar–H); ^{13}C-NMR: δ 116.89–152.93 for aromatic carbons, 159.79 (–CH═N–); mass spectra, ($C_{32}H_{24}Cl_2N_4$): *m/z* = 534. Elemental analysis: Calcd (found): C, 71.78 (71.75); H, 4.52 (4.50); N, 10.46 (10.43).

N1-(4-(4-(4-Nitrobenzylideneamino) phenylamino) phenyl)-N4-(4-nitrobenzylidene)benzene-1,4-diamine (2i). IR (KBr, cm^{-1}): 1644.7 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.8 (s, 2H, CH═N), 10.65 (br s, 2H, NH), 6.5–7.8 (m, 20H, Ar–H); ^{13}C-NMR: δ 112.97–155.35 for aromatic carbons, 158.28 (–CH═N–); mass spectra, ($C_{32}H_{24}N_6O_4$): *m/z* = 556. Elemental analysis: Calcd (found): C, 69.06 (69.0); H, 4.35 (4.32); N, 15.10 (15.05).

N1-(3-Nitrobenzylidene)-N4-(4-(4-(3-nitrobenzylideneamino) phenylamino)phenyl)benzene-1,4-diamine (2j). IR (KBr, cm^{-1}): 1640.3 (–C═N–); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.60 (br s, 2H, NH), 9.5 (s, 2H, CH═N), 6.5–7.7 (m, 20H, Ar–H); ^{13}C-NMR: δ 111.68–153.84 for aromatic carbons, 160.09 (–CH═N–); mass spectra, ($C_{32}H_{24}N_6O_4$): *m/z* = 556. Elemental analysis: Calcd (found): C, 69.06 (69.02); H, 4.35 (4.30); N, 15.10 (15.07).

Synthesis of azetidinones (3a–3j) by microwave method. Aromatic aldehyde (0.008 mol), N1-(4-(4-aminophenylamino) phenyl)benzene-1,4-diamine (**1**) (0.004 mol), and zeolite (montmorillonite K-10) (0.2 g) were stirred with glass rod in DMF (2 mL). To this solution were added triethylamine (0.024 mol) and a solution of chloroacetylchloride (0.008 mol) in DMF (3 mL). The reaction mixture was irradiated for ~25 min with 100 W MWs at 110°C in MW oven in the temperature control mode. The completion of the reaction was monitored by TLC. After the irradiation was over, the reaction mixture was cooled and added into water. After filtering the zeolite particles, the residue was purified by column chromatography (ethyl acetate/petroleum ether, v/v = 1:8).

Synthesis of azetidinones (3a–3j) by classical method. A solution of chloroacetylchloride (0.01 mol) in dry dichloromethane was added dropwise to a well-stirred solution of appropriate Schiff base (0.01 mol) and triethylamine (0.02 mol) in anhydrous dichloromethane (50 mL). After the addition had been completed, the solution was stirred for 15 h. The completion of the reaction was monitored by TLC. The reaction mixture was washed with water and dried over sodium sulfate. The residue was purified by column chromatography (ethyl acetate/petroleum ether, v/v = 1:8).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis(3-chloro-4-phenylazetidin-2-one) (3a). IR (KBr, cm^{-1}): 1752 (C═O β-lactam): 1365 (CN); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.1 (d, 2H, –CH–C═O), 4.1 (s, 2H, –N–CH), 10.24 (br s, 2H, NH), 6.5–7.6 (m, 22H, Ar–H); ^{13}C-NMR: δ 160.2 (cyclic, >C═O), 66.5 (>CH–N<), 61.8 (>CH–Cl), 115.7–152.5 (Ar–C); mass spectra, ($C_{36}H_{28}Cl_2N_4O_2$): *m/z* = 618. Elemental analysis: Calcd (found): C, 69.79 (69.76); H, 4.56 (4.53); N, 9.04 (9.1).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis(3-chloro-4-(2-hydroxyphenyl) azetidin-2-one) (3b). IR (KBr, cm^{-1}): 1756 (C═O β-lactam), 1355 (CN); ^{1}H-NMR: δ = 12.52 (s, 2H, Ar–OH); 4.3 (s, 2H, –N–CH); 5.44 (d, 2H, CH–Cl); 10.34 (br s 2H, NH), 6.4–7.5 (m, 20H, Ar–CH); ^{13}C-NMR: δ 162.5 (cyclic, >C═O), 56.3 (>CH–N<), 62.6 (>CH–Cl), 113.9–155.1 (Ar–C); mass spectra, ($C_{36}H_{28}Cl_2N_4O_4$): *m/z* = 650. Elemental analysis: Calcd (found): C, 66.36 (66.38); H, 4.33 (4.37); N, 8.60 (8.55).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis(3-chloro-4-(4-hydroxyphenyl) azetidin-2-one) (3c). IR (KBr, cm^{-1}): 1745 (C═O β-lactam), 1335 (CN); ^{1}H-NMR: δ = 11.45 (s, 2H, Ar–OH); 4.1 (s, 2H, –N–CH), 10.43 (br s, 2H, NH); 5.44 (d, 2H, CH–Cl); 6.5–7.6 (m, 20H, Ar–CH); ^{13}C-NMR: δ 159.2 (cyclic, >C═O), 59.7 (>CH–N<), 60.2 (>CH–Cl), 111.6–159.7 (Ar–C); mass spectra, ($C_{36}H_{28}Cl_2N_4O_4$): *m/z* = 650. Elemental analysis: Calcd (found): C, 66.34 (66.37); H, 4.32 (4.37); N, 8.60 (8.62).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis (3-chloro-4-(4-(dimethylamino) phenyl)azetidin-2-one) (3d). IR (KBr, cm^{-1}): 1743 (C═O β-lactam), 1347 (CN); ^{1}H-NMR: δ = 3.10 (s, 12H), (Ar–$N(CH_3)_2$); 4.2 (s, 2H, –N–CH), 10.38 (br s, 2H, NH); 5.44 (d, 2H, CH–Cl); 6.7–7.8 (m, 20H, Ar–CH); ^{13}C-NMR: δ 41.7 {N(CH3)2}, 159.2 (cyclic, >C═O), 65.4 (>CH–N<), 55.1 (>CH–Cl), 110.8–152.4 (Ar–C); mass spectra, ($C_{40}H_{38}Cl_2N_6O_2$): *m/z* = 705. Elemental analysis: Calcd (found): C, 68.08 (68.12); H, 5.43 (5.47); N, 11.91 (11.86).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis(3-chloro-4-(4-methoxyphenyl) azetidin-2-one) (3e). IR (KBr, cm^{-1}): 1749 (C═O β-lactam), 1388 (CN); ^{1}H-NMR: δ = 3.73 (s, 6H, OCH_3); 10.26 (br s, 2H, NH–Ar); 5.44 (d, 2H, CH–Cl); 4.1 (s, 2H, –N–CH), 6.4–7.6 (m, 20H, Ar–CH); ^{13}C-NMR: δ 156.8 (cyclic, >C═O), 59.4 (>CH–N<), 62.8 (>CH–Cl), 116.8–168.3 (Ar–C); mass spectra, ($C_{38}H_{32}Cl_2N_4O_4$): *m/z* = 678. Elemental analysis: Calcd (found): C, 67.16 (67.12); H, 4.75 (4.72); N, 8.24 (8.27).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis(3-chloro-4-(3-hydroxyphenyl)azetidin-2-one) (3f). IR (KBr, cm^{-1}): 1732 (C═O β-lactam): 1362 (C–N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 4.3 (s, 2H, –N–CH), 10.40 (br s, 2H, NH), 10.92 (s, 2H, –OH), 5.35 (d, 2H, CH–Cl), 6.5–7.6 (m, 20H, Ar–H); ^{13}C-NMR: δ 161.2 (cyclic, >C═O), 56.9 (>CH–N<), 61.5 (>CH–Cl), 117.2–164.6 (Ar–C); mass spectra, ($C_{36}H_{28}Cl_2N_4O_4$): *m/z* = 650. Elemental analysis: Calcd (found): C, 66.36 (66.32); H, 4.33 (4.29); N, 8.60 (8.56).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis(3-chloro-4-(3-chlorophenyl) azetidin-2-one) (3g). IR (KBr, cm^{-1}): 1750 (C═O β-lactam), 1355 (CN); ^{1}H-NMR: δ = 10.73 (br s, 2H, NH–Ar); 4.3 (s, 2H, –N–CH), 5.30 (d, 2H, CH–Cl); 6.5–7.7 (m, 20H, Ar–CH); ^{13}C-NMR: δ 162.9 (cyclic, >C═O), 60.7 (>CH–N<), 62.8 (>CH–Cl), 119.8–154.2 (Ar–C); mass spectra, ($C_{36}H_{26}Cl_4N_4O_2$): *m/z* = 688. Elemental analysis: Calcd (found): C, 62.81 (62.76); H, 3.81 (3.74); N, 8.14 (8.09).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis (3-chloro-4-(4-chlorophenyl) azetidin-2-one) (3h). IR (KBr, cm^{-1}): 1768 (C═O β-lactam), 1375 (CN); ^{1}H-NMR: δ = 4.1 (s, 2H, –N–CH), 10.76 (br s, 2H, NH); 5.44 (d, 2H, CH–Cl); 6.4–7.3 (m, 20H, Ar–CH); ^{13}C-NMR: δ 164.2 (cyclic, >C═O), 58.9 (>CH–N<), 61.7 (>CH–Cl), 120.5–155.5 (Ar–C); mass spectra, ($C_{36}H_{26}Cl_4N_4O_2$): *m/z* = 688. Elemental analysis: Calcd (found): C, 62.81 (62.75); H, 3.81 (3.77); N, 8.14 (8.08).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis(3-chloro-4-(4-nitrophenyl)azetidin-2-one) (3i). IR (KBr, cm^{-1}): 1764 (C═O β-lactam), 1336 (CN); ^{1}H-NMR: δ = 4.3 (s, 2H, –N–CH), 10.66 (br s, 2H, NH–Ar); 5.44 (d, 2H, CH–Cl); 6.6–7.5 (m, 20H, Ar–CH); ^{13}C-NMR: δ 155.9 (cyclic, >C═O), 59.9 (>CH–N<), 60.3 (>CH–Cl), 120.1–152.8 (Ar–C); mass spectra, ($C_{36}H_{26}Cl_2N_6O_6$): *m/z* = 708. Elemental analysis: Calcd (found): C, 60.94 (60.89); H, 3.69 (3.66); N, 11.84 (11.79).

1,1′-(4,4′-(1,4-Phenylenebis(azanediyl))bis(4,1-phenylene)) bis(3-chloro-4-(3-nitrophenyl)azetidin-2-one) (3j). IR (KBr, cm^{-1}): 1759 (C═O β-lactam), 1365 (CN); ^{1}H-NMR: δ = 4.2 (s, 2H, –N–CH), 10.59 (br s, 2H, NH); 5.44 (d, 2H, CH–Cl); 6.7–7.7 (m, 20H, Ar–CH); ^{13}C-NMR: δ 158.4 (cyclic, >C═O), 61.4 (>CH–N<), 63.5 (>CH–Cl), 117.8–157.3 (Ar–C); mass spectra, ($C_{36}H_{26}Cl_2N_6O_6$): *m/z* = 708. Elemental analysis: Calcd (found): C, 60.94 (60.91); H, 3.69 (3.66); N, 11.84 (11.80).

CONCLUSION

In conclusion, we have developed a general and highly efficient method for the synthesis of a series of differently substituted bis-2-azetidinones that were prepared via Staudinger cycloaddition reaction in the presence of zeolite catalyst under MW irradiation. The controlled MW heating under sealed vessel conditions has shown several advantages including fast, highly efficient, and environmentally friendly solvent-free procedure that reduces reaction time, increases product yield, and enhances product purity compared with conventional synthetic methods. Several compounds could be identified as the most biologically active members in comparison with the ampicillin drug. By this study, the titled bis-2-azetidinones represent a class that needs further investigation with the hope of finding new antimicrobial agents.

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