

# The 21st International Electronic Conference on Synthetic Organic Chemistry

“Ultrasound assisted synthesis of 4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide .”

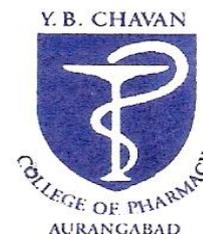
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# Graphical Abstract:



# “Ultrasound assisted synthesis of 4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)benzamide”

## Abstract:

- ▶ A series of 4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide **6a-j** were synthesized in good yield by cyclo-condensation of Schiff's bases with chloro acetyl chloride in the presence of tri ethylamine as catalyst and solvent DMF by using ultrasonication as one of the green chemistry tool.
- ▶ The use of ultrasound to promote chemical reactions is called Sono-chemistry, it is complementary technique for promoting chemical reactions by ecofriendly green synthetic protocol. Ultrasound assisted synthesis are used to reduce the amount of undesired hazardous chemicals and solvents, reduce energy consumption and increase the selectivity towards the given product.
- ▶ Schiff bases **5a-j** were obtained by condensation 4-(benzyloxy)benzo hydrazide with various aromatic aldehydes and their further cyclization lead to the final product Azetidinone **6 a-j**.
- ▶ Azetidinone with  $\beta$ -lactam ring are known to exhibit various biological activities like anti-tubercular, antibacterial and antifungal. Hence we are introducing the eco-friendly protocol for the synthesis of substituted azetidinone derivatives. All the synthesized compounds were characterized by FTIR,  $^1\text{H}$ NMR,  $^{13}\text{C}$ NMR and mass spectral analysis.

**Keywords:** Schiff bases, Azetidinone, Multistep synthesis, Green Chemistry, Ultra sonication.

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## Introduction

► Schiff bases are the compounds carrying imine or azomethine ( $-C=N-$ ) functional group reported first time by Hugo Schiff in 1964[1-2]. These are the condensation products of easy commercially available and inexpensive primary amines with carbonyl compounds. In azomethine linkage( $-C=N-$ ) the electrophilic carbon and nucleophilic nitrogen confers the Schiff bases possibility to interact with several biological targets and have gained importance in medicinal and pharmaceutical fields exhibiting broad spectrum of biological activities like anti-tubercular [3-4], antimicrobial [5], anti-inflammatory [6] analgesic [7], anticancer [8], anticonvulsant [9], antioxidant [10], anthelmintic [11], and so forth.

► The four-membered cyclic amides commonly known as 2-azetidinones or  $\beta$ -lactam occupy a eminent place in organic and medicinal chemistry since the structure of penicillin showed the presence of  $\beta$ -lactam ring in it and various potent activities of penicillin are due to the presence of  $\beta$ -lactam ring. The discovery of several  $\beta$ -lactam antibiotics such as, carbapenams, cephalosporin's, monobactams, trinemis, etc [12-14] plays very important role for the treatment of microbial infections in human kind. The research has directed towards the development of several novel methodologies for designing of drugs containing  $\beta$ -lactam ring. Azetidinone are known to exhibit various biological activities particularly anti-tubercular [15-20] antibacterial and antifungal activities [21-22].

► Sono-chemistry is the application of ultrasound technique has undergone very intensive research and development in the last 15-20 years to carry out chemical transformation. Ultrasound offers potential for cleaner reactions called green protocol keeping in mind to protect environment clean and green through improved product yields and selectivity towards desired product, reduce the time of completion of reaction [23-25] and enhanced ease of product recovery. When liquids are irradiated with ultrasound, the alternating expansive and compressive acoustic waves creates bubbles i.e., cavities. The effects of ultrasound on organic reactions are attributed to cavitation effect, a physical process that generates, increases, and collapses gaseous and vaporous cavities in an irradiated liquid [26]. The cavitation induces very high local temperatures and pressures inside the cavities, leading to a turbulent flow in the liquid and enhanced mass transfer [27]. Ultrasound-promoted synthesis has various advantages over conventional synthesis techniques such as reactions were carried at room temperature and require much less time for completion hence saves time and electricity, highly accelerated reaction rate, requires use of very less amount of solvents, shortened work-up procedure. practically good yield of product, simple instrument with control on reaction parameters, and most important is eco- friendly neat and clean synthetic protocol.

► In this research work we are reporting the synthesis of *4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide* **6a-j** derivatives in excellent yield using eco- friendly, prompt and suitable ultrasound-assisted green chemistry protocol.

## NEED OF STUDY

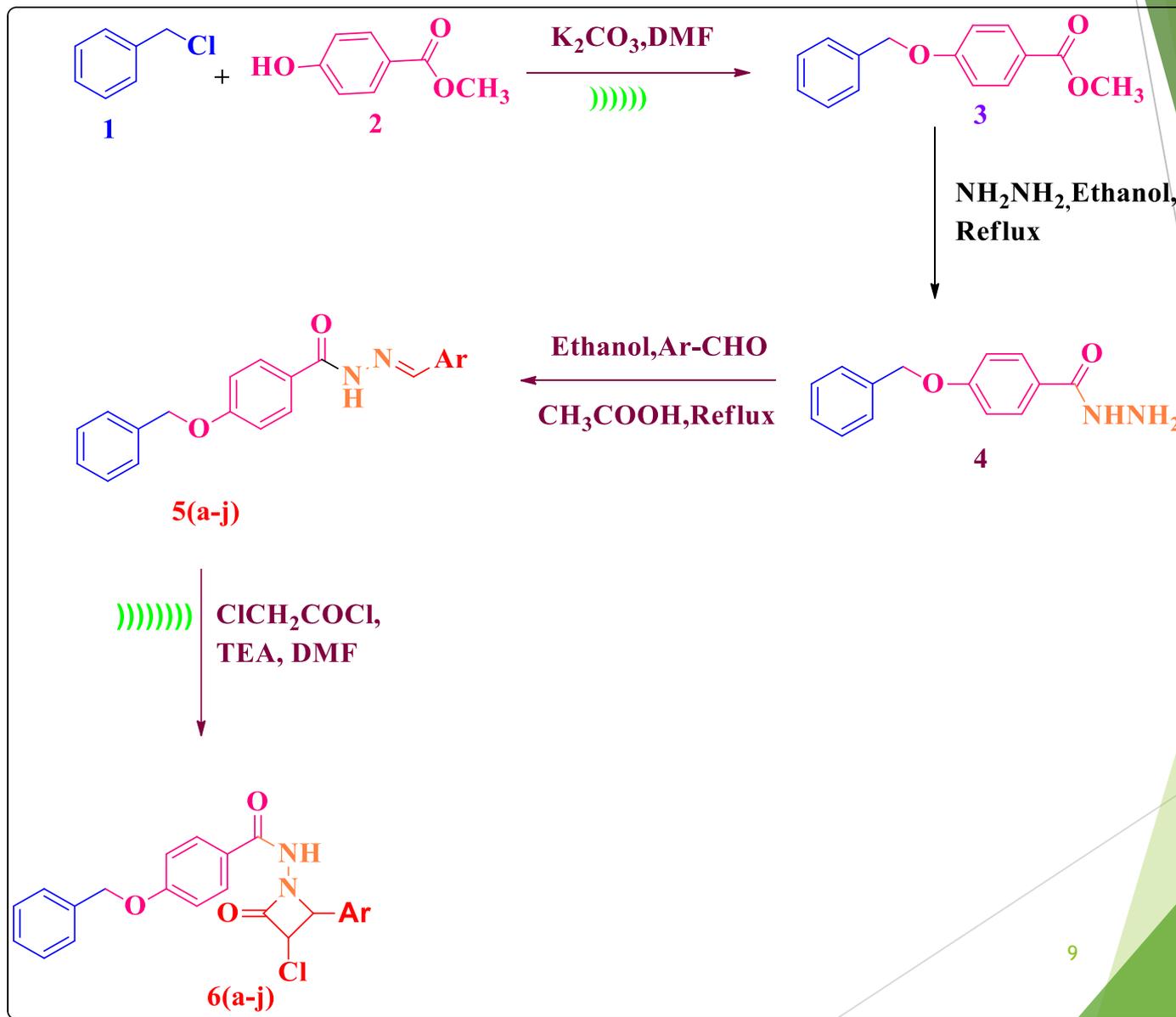
► The shortcomings associated with conventional method of synthesis of 4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide **6a-j**. like stirring at room temperature required 20–28 hr and by refluxing nearly takes 8–10 hours for completion of reaction which consumes more time and electricity. Green chemistry is a new branch of chemistry which become a major motivation for organic chemists and druggist to develop environmentally gentle path for synthesis of organic compounds of biological importance. Ultrasound offers potential tool for cleaner reactions called green protocol keeping in mind to protect environment clean and green through improved product yields and selectivity towards desired product, reduce the time of completion of reaction [23-25] and enhanced ease of product recovery.

2-azetidinones or  $\beta$ -lactam occupy an eminent place in organic and medicinal chemistry since the structure of penicillin showed the presence of  $\beta$ -lactam ring in it and various potent activities of penicillin are due to the presence of  $\beta$ -lactam ring. Hence, there is a need to synthesised the derivatives containing 2-azetidinones scaffold.

## OBJECTIVE OF STUDY

- To design and synthesize the novel, 4-(benzyloxy)-N-(3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl) benzamide **6a-j** derivatives by using ultrasonic processor.
- To conduct physicochemical characterization of intermediates and synthesized compounds.
- To confirm the structures of synthesized compounds by analytical and spectral techniques such as TLC, FT-IR, ES-MS,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR .
- Evaluation of the synthesised series for anti-tubercular activity.

# SCHEME OF SYNTHESIS



## ► Results and discussion

### ► Chemistry

► Herein, we are reporting the synthesis 4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide **6a-j** as illustrated in Scheme 1 by four steps.

► The starting material methyl 4-(benzyloxy) benzoate **3** was synthesized by the reaction of benzyl chloride **1** and methyl 4-hydroxybenzoate **2** in potassium carbonate as a catalyst in solvent N, N dimethyl formamide in an ultra -sonicator up to 4 h. The compound **3** obtained in good yield in step I was refluxed further with hydrazine hydrate to get 4-(benzyloxy) benzohydrazide **4**. Schiff bases were obtained by condensation 4-(benzyloxy)benzohydrazide with various aromatic aldehydes to give **5a-j** which had undergone cyclo-condensation with chloro acetyl chloride in the presence of tri ethylamine as a catalyst in solvent DMF by ultra-sonication to give final product **6a-j**.

► All the synthesized compounds were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, mass spectroscopy and IR. Physical characterization data of Schiff bases **5 a-j** were shown in **Table1**.

**Table1.** Physical characterization of 4-(benzyloxy)-N'-(substituted benzylidene) benzo hydrazide i.e. Schiff bases **5a-j**

Code No. of Schiff's bases	Mol. Wt.	Yield (%)	M.P.(°C)	Analysis (%) Found and [calculated]
5a	346.38	90	215	C, 72.79; H, 5.27; N, 8.07; O, 13.84[C, 72.82; H, 5.24; N, 8.09; O, 13.86]
5b	360.41	88	155	C, 73.34; H, 5.56; N, 7.75; O, 13.35[C, 73.32; H, 5.59; N, 7.77; O, 13.32]
5c	348.37	80	207	C, 72.43; H, 4.95; F, 5.42; N, 8.03; O, 9.16[C, 72.40; H, 4.92; F, 5.45; N, 8.04; O, 9.19]
5d	364.82	82	110	C, 69.11; H, 4.73; Cl, 9.70; N, 7.66; O, 8.76[C, 69.14; H, 4.70; Cl, 9.72; N, 7.68; O, 8.77]
5e	375.38	87	222	C, 67.17; H, 4.59; N, 11.15; O, 17.02 [C, 67.19; H, 4.56; N, 11.19; O, 17.05]
5f	390.43	85	190	C, 70.73; H, 5.70; N, 7.15; O, 16.41[C, 70.75; H, 5.68; N, 7.17; O, 16.39]
5g	376.41	78	148	C, 70.18; H, 5.37; N, 7.40; O, 17.03[C, 70.20; H, 5.36; N, 7.44; O, 17.00]
5h	390.43	83	240	C, 70.73; H, 5.65; N, 7.19; O, 16.35 [C, 70.75; H, 5.68; N, 7.17; O, 16.39]
5i	436.50	75	235	C, 77.06; H, 5.51; N, 6.39; O, 11.02[C, 77.04; H, 5.54; N, 6.42; O, 11.00]
5j	336.41	86	162	C, 67.82; H, 4.76; N, 8.28; O, 9.51; S, 9.58 [C, 67.84; H, 4.79; N, 8.33; O, 9.51; S, 9.53]

► For the optimization of reaction conditions in step 4, the model reaction was carried out by cyclization of intermediate *4-(benzyloxy)-N'-(4-hydroxybenzylidene) benzohydrazide* with chloro acetyl chloride to give the derivative *4-(benzyloxy)-N-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl) benzamide 6a*, in various solvents, by using catalyst with conventional refluxing and ultrasound assisted modern green technique as shown in **Table 2**. No product was obtained without use of catalyst hence triethyl amine was selected as catalyst which gave desired product in good yield with solvent DMF.

► **Table 2.** Optimization of reaction conditions for *4-(benzyloxy)-N-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl) benzamide 6a* derivative using various solvent with and without use of catalyst.

Entry	Catalyst	Solvent	Method A Conventional Reflux		Method B Ultrasound Assisted	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	No Catalyst	Benzene	22	-	6	-
2	No Catalyst	1,4-Dioxane	15	-	6	-
3	No Catalyst	DMF	12	-	5	-
4	Triethyl amine(TEA)	Benzene	16	55	4	65
5	Triethyl amine(TEA)	1,4-Dioxane	12	60	3	75
6	<b>Triethyl amine(TEA)</b>	<b>DMF</b>	08	70	<b>2</b>	<b>88</b>

► The synthesis of all derivatives of *4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide 6a-j* was carried out by refluxing and ultrasonic irradiation methods for comparison of conventional and modern green chemistry tool using ultra-sonication. The time required for completion of reaction with yield in percent is mentioned in **Table 3**.

► **Table 3.** Comparison of reaction kinetics of conventional refluxing and ultrasonic irradiation methods for the synthesized compounds **6a–j**

Entry	Conventional Refluxing		Ultrasonic Irradiation	
	Time(hr)	Yield(%)	Time(hr)	Yield(%)
6a	8	70	2	88
6b	6	65	2	82
6c	6.5	72	2.10	80
6d	7	70	2.20	79
6e	7.5	71	2.15	80
6f	8	65	2	79
6g	7.5	67	2	86
6h	7.5	61	2.30	81
6i	8	66	2	78
6j	8	65	2	79

**Table 4.** Physical characterization of 4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide **6 a-j**

Code No.	Mol. Wt.	Yield (%)	M.P.(°C)	Analysis (%) Found and [calculated]
6a	422.86	88	175	C, 65.30;H,4.51;Cl,8.36;N,6.64;O,15.11. [C,65.33;H,4.53;Cl,8.38;N,6.62;O,15.13]
6b	436.89	82	170	C, 65.95;H,4.87;Cl,8.13;N,6.39;O,14.68. [C,65.98;H,4.84;Cl,8.11;N,6.41;O,14.65]
6c	424.85	80	144	C, 65.0;H,4.25;Cl,8.33;F,4.49;N,6.57;O,11.27. [C,65.02;H,4.27;Cl,8.34;F,4.47;N,6.59;O,11.30]
6d	441.31	79	152	C, 62.63;H,4.09;Cl,16.06;N,6.33;O,10.85. [C,62.60;H,4.11;Cl,16.07;N,6.35;O,10.88]
6e	451.86	80	198	C, 61.1;H,4.03;Cl,7.88;N,9.27;O,17.68[C,61.14;H,4.02;Cl,7.85;N,9.30;O,17.70]
6f	466.91	79	182	C, 64.32;H,4.95;Cl,7.60;N,6.03;O,17.11.[C,64.31;H,4.97;Cl,7.59;N,6.00;O,17.13]
6g	452.89	86	164	C, 63.62;H,4.65;Cl,7.80;N,6.21;O,17.67. [C,63.65;H,4.67;Cl,7.83;N,6.19;O,17.66]
6h	466.91	81	156	C, 64.36;H,4.95;Cl,7.56;N,6.02;O,17.15. [C,64.31;H,4.97;Cl,7.59;N,6.00;O,17.13]
6i	512.98	78	180	C, 70.22;H,4.89;Cl,6.93;N,5.44;O,12.47. [C,70.24;H,4.91;Cl,6.91;N,5.46;O,12.48]
6j	412.89	79	172	C, 61.07;H,4.17;Cl,8.61;N,6.75;O,11.60;S,7.74. [C,61.09;H,4.15;Cl,8.59;N,6.78;O,11.62;S,7.77]

## MATERIALS AND METHODS:

All the chemicals used for synthesis were procured from Merck (Mumbai, Maharashtra, India), Sigma (Mumbai), HiMedia (Mumbai) or Qualigens (Mumbai) and used without further purification. The progress of each reaction was monitored by ascending thin layer chromatography (TLC) using pre-coated silica gel F254 aluminum TLC sheets (Merck) and the spots were visualized by UV light and iodine vapors. Elemental analyses (C, H, and N) were done with a FLASH EA 112 Shimadzu' analyzer (Mumbai) and all analyses were consistent (within 0.4%) with theoretical values. Infrared (IR) spectra were recorded on a PS 4000 FTIR (JASCO, Tokyo, Japan) using KBr pellets.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR (200 MHz) spectra were recorded on a ACF 200 spectrometer (Bruker, Billerica, MA, USA) fitted with an Aspect 3000 computer and all the chemical shifts (ppm) were referred to internal TMS for  $^1\text{H}$  and chloroform- $d$  for  $^{13}\text{C}$ -NMR.  $^1\text{H}$ -NMR data are reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad; br s, broad singlet; m, multiplet and/or multiple resonance), number of protons. A Micro TOF-Q-II (Bruker Daltonics, Billerica, MA, USA) with electron spray ionization (ESI) was used to obtain the HRMS data. For ultrasound irradiation Vibra cell VCX-500 with solid probe was used (Sonics, Newtown, CT, USA).

# EXPERIMENTAL WORK & PHYSICAL CONSTANTS DATA

## ► Step I: General procedure for the synthesis of 4-(benzyloxy)benzoate (3):

► Synthesis of methyl-4-(benzyloxy) benzoate was carried out in ultrasonic processor by taking equivalent ratio of benzyl chloride and methyl-4-hydroxybenzoate (0.01mol) using DMF as solvent in beaker with catalytic amount of  $K_2CO_3$ . Reaction was completed in four hr. The completion of reaction was monitored by TLC. The reaction mixture was poured into ice-water. The product obtained was filtered, dried and recrystallized from ethanol. Colour: White M.P.105 $^{\circ}$ C

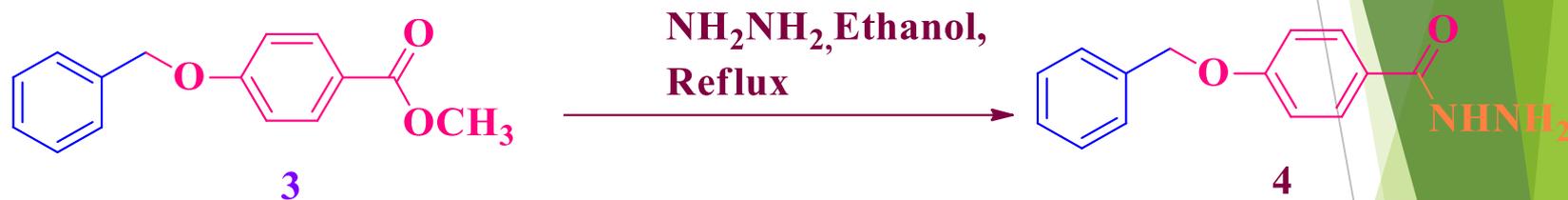


Compound Code	Molecular Formula	Molecular Weight	Percentage Yield (%)	Melting point	R <sub>f</sub> value
3	C <sub>15</sub> H <sub>14</sub> O <sub>3</sub>	242.27	90%	105 $^{\circ}$ C	0.46

Solvent system chosen for R<sub>f</sub> value determination was benzene :ethanol (8:2).

## Step II: General procedure for the synthesis of 4-(benzyloxy) benzohydrazide (4):

► Synthesis of substituted benzo hydrazines was carried out by refluxing mixture of corresponding esters (20 mmol), 85% hydrazine hydrate (20 mmol) in ethanol (35 ml) for 6 hr. The completion of reaction was monitored by TLC. The reaction mixture was poured into ice-water. The solid obtained was filtered, dried and recrystallized from ethanol. Colour: White M.P.80°C

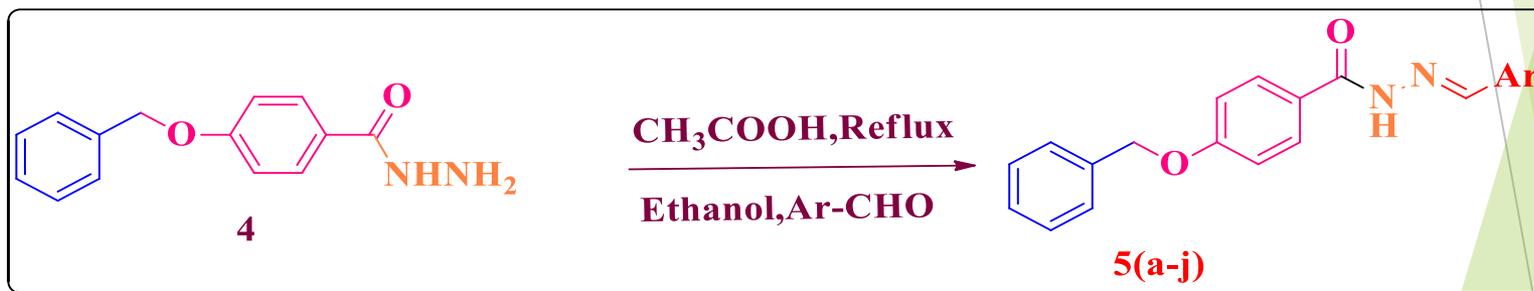


Compound Code	Molecular Formula	Molecular Weight	Percentage Yield (%)	Melting point	R <sub>f</sub> value
4	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	241	88%	80	0.24

Solvent system chosen for R<sub>f</sub> value determination was benzene : methanol (8:2).

## Step III: General procedure for the synthesis of Schiff bases 5

► Schiff's bases **5a-j** were obtained by condensation of equimolar quantities of 4-(benzyloxy)benzohydrazide (0.01 mol) and different substituted aldehydes (0.01 mol) in the presence of glacial acetic acid (0.02 mol) as a catalyst in absolute ethanol (25 ml) refluxed for for 2 to 3 hours. The completion of reaction was monitored by TLC. The reaction mixture was concentrated and cooled. The obtained solid was filtered and dried. The product was recrystallized from ethanol. The melting point and yield were recorded and are given in **Table1**.



Solvent system chosen for  $R_f$  value determination was n-hexane : ethyl acetate (8:2).

#### Step IV: General procedure for synthesis of 4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide 6a-j:

► In a borosil beaker, a mixture of Schiff's base (0.01 mol), chloroacetyl chloride (0.02 mol) and triethyl amine (0.02 mol) was dissolved in DMF (5 ml), and was subjected to ultra-sonication at room temperature for 2 to 2.30 hrs. The completion of reaction was monitored by TLC. The resulting solid was filtered, washed several times with water, dried and then recrystallized from ethanol. The melting point and yield were recorded and are given in **Table 4**.



Solvent system chosen for R<sub>f</sub> value determination was n-hexane :ethyl acetate (8:2).

## Spectral Characterization:

### ***4-(benzyloxy)-N-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl) benzamide 6a:***

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 3497.24 O-H stretching, 3430 NH stretching, 3108–3009 aromatic CH stretching, 2880–2880 aliphatic CH stretching, 1630.56 C=O stretching of amide, <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 5.10(d,1H, -CH-), 5.22(s,2H, -CH<sub>2</sub>-), 5.39(s,1H, -OH), 5.51(d,1H, -CH-), 6.70-7.88 (m,5H,4H,4H of three Ar. ring) <sup>13</sup>C-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 64.1, 67.4, 70.8, 114.4(2), 115.7(2), 124.3, 127.0(2), 127.1(2), 127.6, 128.5(2), 128.9(2), 136.1, 136.7, 156.5, 162.4, 163.5 and 163.7. MS (ESI) *m/z* 422.10 (100.0%), 424.10 (32.1%), 423.11 (25.2%) Molecular Formula: C<sub>23</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>4</sub> Elemental Analysis: Calculated (C, H, Cl, N, O) 65.33,4.53,8.38,6.62,15.13 Found:65.30,4.51,8.36,6.64,15.11.

### ***4-(benzyloxy)-N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl) benzamide 6b:***

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 3335.41 N-H stretching, 3152.77 C-H stretching of aromatics, 2876.58 C-H stretching of alkyl, 1640.56, C=O stretching of amide, 1215.22, C-O stretching of -OCH<sub>3</sub> <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 3.79(s,3H, -OH), 5.03(d,1H, -CH-), 5.10(s,2H, -CH<sub>2</sub>-), 5.49(d,1H, -CH-), 6.99-7.92(m,5H,4H,4H of three Ar. ring) <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 55.8, 64.1, 67.4, 70.8, 114.1(2), 114.4(2), 124.3, 126.6(2), 127.1(2), 127.6, 128.5(2), 128.9(2), 135.8, 136.7, 158.6, 162.4, 163.5 and 163.7. MS (ESI) *m/z* 436.12 (100.0%), 438.12 (33.0%), 437.12 (26.8%) Molecular Formula: C<sub>24</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>4</sub> Elemental Analysis: Calculated (C, H, Cl, N, O) 65.98,4.84,8.11,6.41,14.65 Found:65.95,4.87,8.13,6.39,14.68.

### ***4-(benzyloxy)-N-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl) benzamide 6c:***

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 3530 NH stretching, 3160–3080 aromatic CH stretch, 2879–2819, aliphatic CH stretch, 1670.56 C=O stretching of amide, 1260 C-F stretching, <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 5.05(d,1H, -CH-), 5.19(s,2H, -CH<sub>2</sub>-), 5.51(d,1H, -CH-), 7.02-7.97(m,5H,4H,4H of three Ar.

ring)<sup>13</sup>C-NMR (DMSO-d<sub>6</sub>), δ ppm: 64.1, 67.4, 70.8, 114.4(2), 115.3(2), 124.3, 127.1(2), 127.6, 128.5(4), 128.9(2), 136.7, 139.1, 160.9, 162.4, 163.5 and 163.7 MS (ESI) m/z: 424.10 (100.0%), 426.10 (32.8%), 425.10 (25.7%) Molecular Formula: C<sub>23</sub>H<sub>18</sub>ClFN<sub>2</sub>O<sub>3</sub> Elemental Analysis: Calculated (C, H, Cl, F, N, O) 65.02,4.27,8.34,4.47,6.59,11.30 Found:65.05,4.25,8.33,4.49,6.57,11.27.

***4-(benzyloxy)-N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl) benzamide 6d:***

IR (KBr)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3590 NH stretching, 3177–3050 aromatic CH stretch, 2880–2890, aliphatic CH stretch, 1670.56 C=O stretching of amide, 744 C-Cl stretching, <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>), δ ppm: 5.03(d,1H, -CH-), 5.12(s,2H, -CH<sub>2</sub>-), 5.49(d,1H, -CH-), 7.10-7.88(m,5H,4H,4H of three Ar. ring)<sup>13</sup>C-NMR (DMSO-d<sub>6</sub>), δ ppm: 64.1, 67.4, 70.8, 114.4(2), 124.3, 127.1(2), 127.2(2), 127.6, 128.5(2), 128.6(2), 128.9(2), 132.3, 136.7, 141.6, 162.4, 163.5 and 163.7MS (ESI) m/z 440.07 (100.0%), 442.07 (64.7%), 441.07 (25.7%) Molecular Formula: C<sub>23</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub> Elemental Analysis: Calculated (C, H, Cl, N, O) 62.60,4.11,16.07,6.35,10.88 Found:62.63,4.09,16.06,6.33,10.85.

***4-(benzyloxy)-N-(3-chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl) benzamide 6e:***

IR (KBr)  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3520 NH stretching, 3150–3040 aromatic CH stretch, 2877–2880, aliphatic CH stretch, 1680.56 C=O stretching of amide, 1345 NO<sub>2</sub> stretching, <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>), δ ppm: 5.05(d,1H, -CH-), 5.19(s,2H, -CH<sub>2</sub>-), 5.50(d,1H, -CH-), 7.12-8.20(m,5H,4H,4H of three Ar. ring)<sup>13</sup>C-NMR (DMSO-d<sub>6</sub>), δ ppm: 64.1, 66.4, 70.8, 114.4(2), 120.5, 121.9, 124.3, 127.1(2), 127.6, 128.5(2), 128.9(2), 129.4, 133.0, 136.7, 144.4, 147.7, 162.4, 163.5 and 163.7MS (ESI) m/z 451.09 (100.0%), 453.09 (32.2%), 452.10 (25.3%) Molecular Formula: C<sub>23</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>5</sub> Elemental Analysis: Calculated (C, H, Cl, N, O) 61.14, 4.02,7.85, 9.30,17.70 Found:61.16,4.03,7.88,9.27,17.68.

**4-(benzyloxy)-N-(3-chloro-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-1-yl) benzamide 6f:** IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 3590 NH stretching, 3166–3044 aromatic CH stretch, 2880–2820, aliphatic CH stretch, 1649.56 C=O stretching of amide, 1400 C-OCH<sub>3</sub>, <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 3.85(s,6H, -OCH<sub>3</sub>), 5.10(d,1H, -CH-), 5.22(s,2H, -CH<sub>2</sub>-), 5.47(d,1H, -CH-), 6.70-7.89(m,5H,4H,3H of three Ar. ring)<sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 56.1(2), 64.1, 67.7, 70.8, 109.8, 114.4(2), 118.9, 121.9, 124.3, 127.1(2), 127.6, 128.5(2), 128.9(2), 136.7, 136.8, 147.8, 149.6, 162.4, 163.5 and 163.7 MS (ESI) m/z 466.13 (100.0%), 468.13 (33.2%), 467.13 (28.0%) Molecular Formula: C<sub>25</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>5</sub> Elemental Analysis: Calculated (C, H, Cl, N, O) 64.31, 4.97, 7.59, 6.00, 17.13 Found: 64.32, 4.95, 7.60, 6.03, 17.11.

**4-(benzyloxy)-N-(3-chloro-2-(4-hydroxy-3-methoxyphenyl)-4-oxoazetidin-1-yl) benzamide 6g:** IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 3500 OH, 3480 NH stretching, 3100–3070 aromatic CH stretch, 2880–2830, aliphatic CH stretch, 1670.56 C=O stretching of amide, 1440 C-OCH<sub>3</sub>, <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 3.79(s,3H, -OCH<sub>3</sub>), 5.12(d,1H, -CH-), 5.21(s,2H, -CH<sub>2</sub>-), 5.39(s,1H, -OH), 5.48(d,1H, -CH-), 6.58-7.97(m,5H,4H,3H of three Ar. ring).<sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 56.1, 64.1, 67.7, 70.8, 110.2, 114.4(2), 115.4, 119.3, 124.3, 127.1(2), 127.6, 128.5(2), 128.9(2), 136.7, 137.1, 146.7, 147.3, 162.4, 163.5 and 163.7 MS (ESI) m/z 452.11 (100.0%), 454.11 (32.2%), 453.12 (26.4%) Molecular Formula: C<sub>24</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>5</sub> Elemental Analysis: Calculated (C, H, Cl, N, O) 63.65, 4.67, 7.83, 6.19, 17.66 Found: 63.62, 4.65, 7.80, 6.21, 17.67.

**4-(benzyloxy)-N-(3-chloro-2-(3-ethoxy-4-hydroxyphenyl)-4-oxoazetidin-1-yl) benzamide 6h:** IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 3530(OH), 3470 NH stretching, 3160–3087 aromatic CH stretch, 2890–2890, aliphatic CH stretch, 1690.56 C=O stretching of amide, 1440 stretching C-OCH<sub>3</sub>, <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 1.27(t,3H, -OCH<sub>3</sub>), 4.02(q,2H, -CH<sub>2</sub>), 5.09(d,1H, -CH-), 5.21(s,2H, -CH<sub>2</sub>-), 5.42(s,1H, -OH), 5.52(d,1H, -CH-), 6.61-7.99(m,5H,4H,3H of three Ar. ring)<sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 14.8, 64.1, 64.9, 67.7, 70.8, 110.3, 114.4(2), 115.0, 118.6, 124.3, 127.1(2), 127.6, 128.5(2), 128.9(2), 136.7(2), 146.8, 148.0, 162.5, 163.5 and 163.7 MS (ESI) *m/z* 466.13 (100.0%), 468.13 (33.2%), 467.13 (28.0%) Molecular Formula: C<sub>25</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>5</sub> Elemental Analysis: Calculated (C, H, Cl, N, O) 64.31,4.97,7.59,6.00,17.13 Found:64.36,4.95,7.56,6.02,17.15.

**4-(benzyloxy)-N-(2-(4-(benzyloxy) phenyl)-3-chloro-4-oxoazetidin-1-yl) benzamide 6i:**

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 3480 NH stretching, 3170–3080 aromatic CH stretch, 2879–2833, aliphatic CH stretch, 1648.56 C=O stretching of amide, <sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 5.05(d,1H, -CH-), 5.10(s,4H, -CH<sub>2</sub>-), 5.49(d,1H, -CH-), 6.90-7.95(m,5H,4H,4H,5H of four Ar. ring)<sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 64.1, 67.4, 70.8(2), 114.1(2), 114.4(2), 124.3, 126.6(2), 127.1(4), 127.6(2), 128.5(2), 128.9(4), 135.8, 136.7(2), 157.0, 162.4, 163.5 and 163.7 MS (ESI) *m/z* 512.15 (100.0%), 513.15 (33.3%), 514.15 (33.0%) Molecular Formula: C<sub>30</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>4</sub> Elemental Analysis: Calculated (C, H, Cl, N, O) 70.24,4.91,6.91,5.46,12.48 Found:70.22,4.89,6.93,5.44,12.47.

**4-(benzyloxy)-N-(3-chloro-2-oxo-4-(thiophen-2-yl) azetidin-1-yl) benzamide 6j:**

IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 3530 NH stretching, 3100–3010 aromatic CH stretch, 2880–2860, aliphatic CH stretch, 1660.56 C=O stretching of amide,<sup>1</sup>H-NMR(DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 5.02(d,1H, -CH-), 5.11(s,2H, -CH-), 5.51(d,1H, -CH-), 6.77(d,1H,3<sup>rd</sup> -CH- of Thiophene), 6.89(t,1H,4<sup>th</sup> -CH- of Thiophene),7.47(m,1H,5<sup>th</sup> -CH- of Thiophene), 7.11-8.0(m,5H,4H,-Ar.ring)<sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>),  $\delta$  ppm: 64.6, 64.8, 70.8, 114.4(2), 124.3, 127.0, 127.1(2), 127.6, 127.7, 128.0, 128.5(2), 128.9(2), 129.3, 136.7, 162.4, 163.5 and 163.7 MS (ESI) *m/z* 412.06 (100.0%), 414.06 (36.5%), 413.07 (23.0%) Molecular Formula: C<sub>21</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>S Elemental Analysis: Calculated (C, H, Cl, N, O, S) 61.09, 4.15,8.59, 6.78,11.62,7.77 Found:61.07,4.17,8.61,6.75,11.60,7.74.

## ► Conclusion:

In the current study, we have developed an ecofriendly and efficient ultrasound assisted synthesis of *4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide 6a-j*. The remarkable benefits of ultra-sonication as a green synthetic strategy are as follows: (1) reactions were carried at room temperature (2) required much less time for completion of reaction as compared to conventional refluxing hence the ultrasound methodology saves time and electricity, (3) highly accelerated reaction rate (4) the use of very less amount of benign solvent DMF (5) and shortened and clean work-up procedure.

The structure analogy of the reported azetidinone derivatives with  $\beta$ -lactam ring, enhance the potential of *4-(benzyloxy)-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide* to be developed as antimicrobial agents and can act as an excellent scaffold for lead optimization and drug discovery.

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# Thank You !