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## SYNTHESIS, CHARACTERIZATION OF SOME 2-AZETIDINONE DERIVATIVES FROM 4-NITRO ETHYL BENZOATE BY MICROWAVE METHOD AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY

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### Keywords:

Schiff base, Azetidinones, 4-nitro ethyl benzoate, Hydrazine hydrate, Microwave, Methodology, Antimicrobial- screening

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**ABSTRACT:** Non classical, High-speed, environmentally benign synthesis with microwaves has attracted researchers for organic synthesis a considerable amount of attention in recent years. An expeditious one pot microwave irradiation method for preparation of 2-azetidinones is developed. This method has been assessed as greener methodology. In our present study, series of five novel azetidinones are synthesised which involves the hydrazinolysis of 4- nitro ethyl benzoate with 99% hydrazine hydrate in ethanol in microwave oven to yield the hydrazides. Then hydrazides are condensed with different substituted aromatic aldehydes in DMSO in microwave to form respective Schiff base. Then formation of Schiff bases is followed by cyclisation with chloro acetyl chloride and triethyl amine in DMF to yield corresponding azetidinones. Structures of synthesised compounds were confirmed by <sup>1</sup>H NMR, Mass spectral analysis. The compounds are evaluated for their antimicrobial activities. The activities are due to cyclic carbonyl group in azetidinones. Some of the compounds have shown comparable antimicrobial activities against all the microbial strains.

**INTRODUCTION:** Azetidin-2-one, a four-membered cyclic lactam ( $\beta$ -lactam) skeleton has been recognized a useful building block for the synthesis of a large number of organic molecules by exploiting the strain energy associated with it.

Efforts have been made in exploring such new aspects of  $\beta$ -lactam chemistry versatile intermediates for their synthesis of aromatic  $\beta$ -amino acid and their derivatives, peptides, polyamines, polyamino alcohols, amino sugars and polyamino ethers.

The cyclic 2-azetidinone skeleton has been extensively used as a template to build the heterocyclic structure fused to the four membered rings. The  $\beta$ -lactam heterocycles are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity<sup>1</sup>.

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The biological activity of  $\beta$  lactam antibiotics such as penicillins and cephalosporins are attributed to the presence of 2-azetidinone ring in them<sup>2</sup>. Compounds carrying azetidin-2- one ring are reported to exhibit certain biological activities like antagonists<sup>3</sup>, hypoglycemic<sup>4</sup>, anti-inflammatory<sup>5</sup>, Antitubercular<sup>6</sup>, anaesthetic<sup>7</sup>, analgesic<sup>8</sup>, antimalarial<sup>9</sup>, antidepressant<sup>10</sup> and enzyme inhibition activity<sup>11</sup>.

Cycloaddition of monochloroacetylchloride with imine (schiff base) result in formation of 2-azetidinone ( $\beta$ -lactam).The reaction involves direct acylation of imine with monochloroacetylchloride. The reaction is carried out with base as triethylamine gives  $\beta$ - lactam<sup>12</sup>.

## MATERIALS AND METHODS:

**Equipments:** Melting points were taken in an open capillary tube. The microwave assisted synthesis of 2-azetidinone derivatives were carried out in Godrej SLGX -20 E Microwave oven at 80% power 1H NMR spectra of the synthesized compounds were recorded on a Bruker- Avance (300 MHz) spectrophotometer using DMSO solvent and TMS as a internal standard. All the synthesized compounds are purified by recrystallization. The reactions were followed up and purity of compounds was monitored on pre-coated TLC plates using different solvent system and visualizing the spots in iodine chamber.

**Materials:** All the chemicals and solvents were obtained from E-Merck and S.D. Fine India (AR grade) and were used without further purification.

**Methodology:** Microwave-enhanced chemistry is based on the efficient heating of materials by

“microwave dielectric heating” effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat<sup>13</sup>. Microwave irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules. The application of Microwave irradiation to provide enhanced reaction rate and improved product field in chemical synthesis and it is providing quite successful in the formation of a variety of carbon-heteroatom bonds<sup>14</sup>.

Many researchers have described accelerated reaction rates, with a large number of papers that have appeared proving the synthetic utility of MORE chemistry in day to day organic synthesis. It can be termed as ‘e- chemistry’ because it is easy, effective, economical, and eco-friendly, and is believed to be a step toward achieving green chemistry objectives<sup>15</sup>. Within the framework of ‘Green Chemistry’ we have now developed an environmentally benign and novel approach for the synthesis of azetidine-2-ones.

## General Procedure:

### STEP 1: Synthesis of 4-nitro benzohydrazide:

To a solution of 4-nitro ethyl benzoate (0.01mole) in ethanol (25 ml), hydrazine hydrate (99% 0.012 mole) was added dropwise. The resultant mixture was kept at room temperature for 10 min then yellow color precipitated obtained and poured on ice cold water. The yellow precipitated was filtered off and washed thoroughly with water and crystallized from ethanol to give product as shown in Fig. 1.

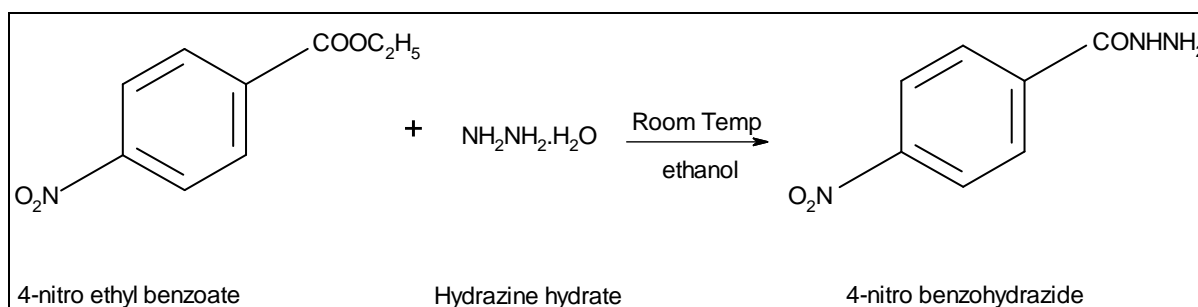
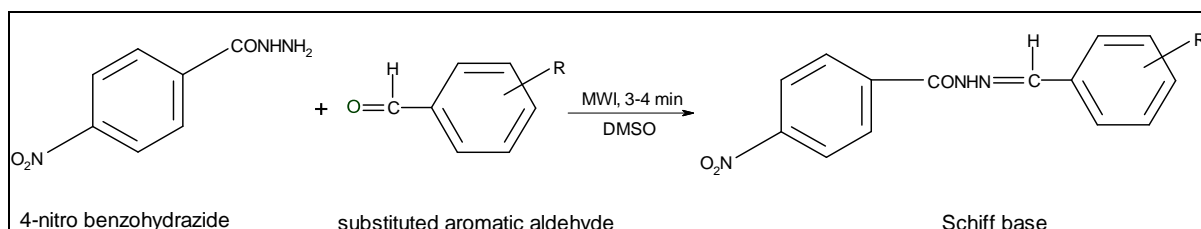


FIG. 1: SYNTHESIS OF 4-NITRO BENZOHYDRAZIDE

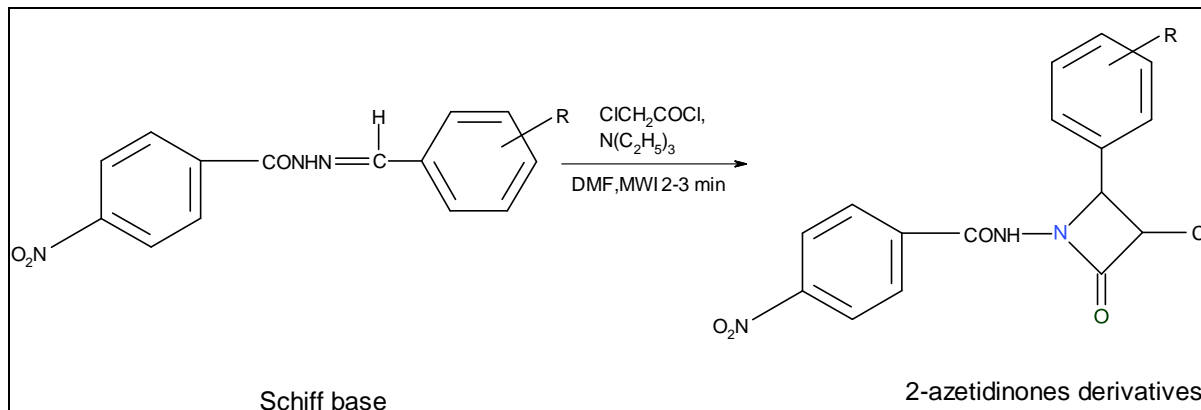
**STEP 2:**

**Synthesis of Schiff base:** 4-nitro benzohydrazide (0.01mol) is treated with substituted aromatic aldehydes (0.01mol) in

DMSO in microwave oven for 2-3 min and then mixture is cooled and poured in ice cold water to obtain Schiff bases as shown in **Fig. 2**.

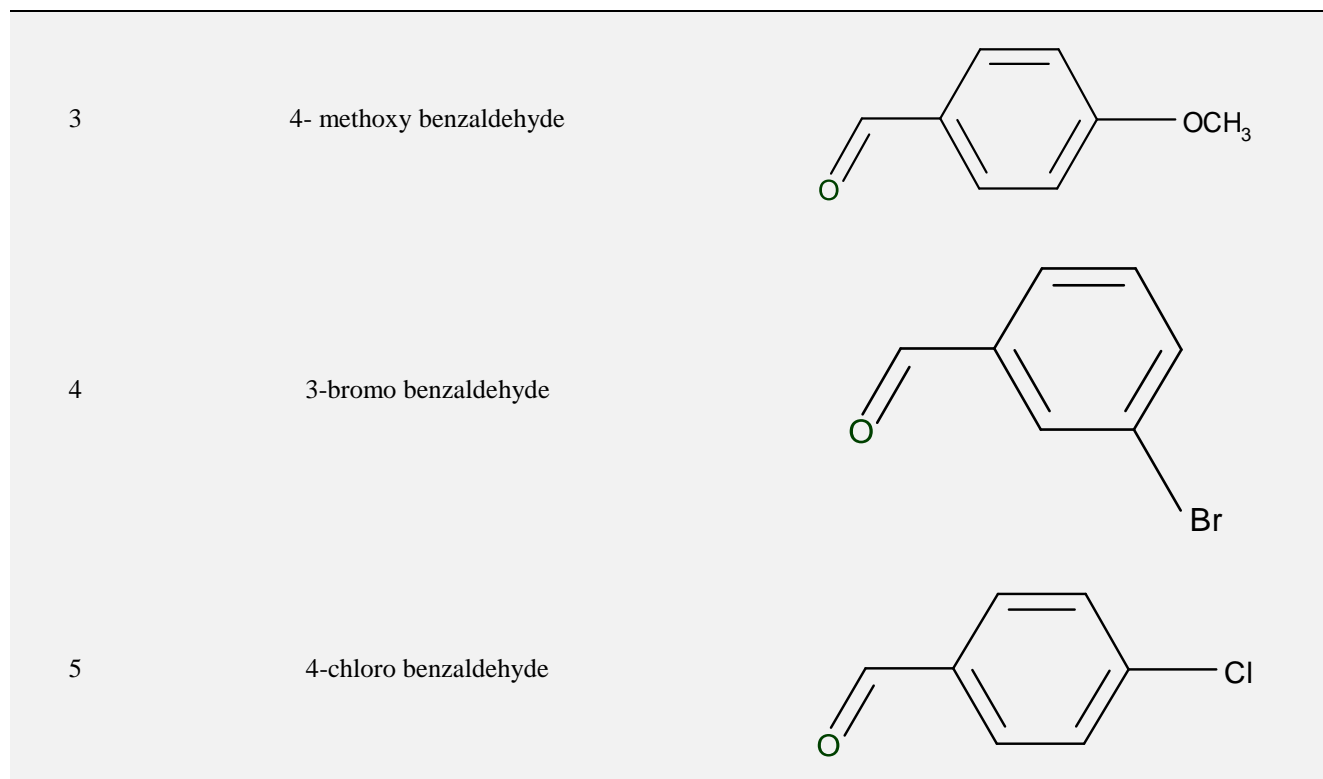
**FIG. 2: SYNTHESIS OF SCHIFF BASE****STEP 3:**

**Synthesis of 2-azetidinone derivatives:** Schiff bases obtained in step 2 (0.01mol) in DMF on further treatment with base triethyl amine  $\text{N}(\text{C}_2\text{H}_5)_3$  (0.01mol) and acylated with monochloroacetyl chloride (0.01 mol) as cyclising agent in microwave oven for 3 – 4 mins to form 2-azetidinone as shown in **Fig 3**.

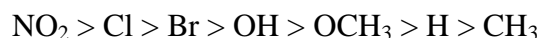
**FIG. 3: SYNTHESIS OF 2-AZETIDINONE DERIVATIVES**

Where R is

Sr. No.	Compound	Structure
1	3,4,5- trimethoxy benzaldehyde	
2	4- hydroxy benzaldehyde	



**Antimicrobial Activity:** All the prepared compounds are screened for antimicrobial activity. From the microbial study it can be concluded that compounds bearing chloro, methoxy groups are more potent than remaining substituted compounds against Gram (+) and Gram (-) bacteria. All the synthesized compounds have structure activity relationship (SAR) because activity of compounds varies with substitution. On the basis of SAR it can be concluded that activity of compounds depends on electron withdrawing nature of substituted group. The sequence of the activity is as follow;



**RESULT AND DISCUSSION:** A new method for the synthesis of various above azetidin-2-one derivatives using microwave irradiation offers significant improvements over existing procedures and thus helps facile entry into a synthesis of variety of azetidin-2-one derivatives. Also, this simple and reproducible technique affords various azetidin-2-one derivatives with short reaction times, excellent yields, and without formation of undesirable side products. The yields of different synthesized compounds were found to be in the range of 70-80% and the characterization was done by melting point, thin layer which confirm the completion of reaction. All the tested compounds showed good, moderate and poor biological activity.

**TABLE -1: PHYSICAL DATA OF THE SYNTHESIZED AZETIDINONE COMPOUNDS**

Compound	M.P	Yield	Molecular formula	Molecular weight
SDT15	160 <sup>o</sup> C	82 %	C <sub>19</sub> H <sub>18</sub> O <sub>7</sub> N <sub>2</sub> Cl	435
SDT16	210 <sup>o</sup> C	71 %	C <sub>17</sub> H <sub>14</sub> O <sub>5</sub> N <sub>3</sub> Cl	375
SDT17	190 <sup>o</sup> C	72 %	C <sub>16</sub> H <sub>11</sub> O <sub>4</sub> N <sub>3</sub> Cl <sub>2</sub>	379
SDT18	100 <sup>o</sup> C	78 %	C <sub>16</sub> H <sub>11</sub> O <sub>4</sub> N <sub>3</sub> ClBr	423
SDT19	240 <sup>o</sup> C	72 %	C <sub>16</sub> H <sub>12</sub> O <sub>5</sub> N <sub>3</sub> Cl	361

**TABLE 2: SPECTRAL ANALYSIS**

CODE	COMPOUND	<sup>1</sup> H NMR (DMSO, δ ppm)	MASS (m/z)
<b>SDT15</b>	3-chloro-4(3,4,5- trimethoxy phenyl)-N(4-nitro benzamido)-2azetidinone	8.0-8.4(6 H, Ar-H),12.06(1H,CONH),3.3-3.8(9H, OCH3),6.0(1H, CH-Cl)	435(M+), 400, 354, 278
<b>SDT16</b>	3-chloro-4(4-methoxy phenyl)-N(4-nitrobenzamido)-2azetidinone	8.0-8.4(8 H, Ar-H), 11.94 (1H,CONH),3.3-3.8(3H, OCH3),6.9(1H, CH-Cl)	375(M+), 344, 269, 223
<b>SDT17</b>	3-chloro-4(4-methyl phenyl)-N(4-nitrobenzamido)-2azetidinone	8.0-8.4(8 H, Ar-H), 12.18 (1H,CONH),4.6(1H, CH-N),7.2(1H, CH-Cl)	379(M+), 381(M+2), 344, 309, 233
<b>SDT18</b>	3-chloro-4(3-bromo phenyl)-N(4-nitro benzamido)-2azetidinone	8.0-8.4(8 H, Ar-H), 12.21 (1H,CONH),4.6(1H, CH-N),7.2(1H, CH-Cl)	423(M+), 377, 342, 263
<b>SDT19</b>	3-chloro-4(4-hydroxy phenyl)-N(4-nitro benzamido)-2azetidinone	8.0-8.4(8 H, Ar-H), 12.21 (1H,CONH),4.61(1H, CH-N),6.7(1H, CH-Cl),9.7(1H,OH)	361(M+), 360(M-1), 344, 298

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