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Synthesis of some azetidinone derivatives using microwave irradiation

Md Taufique Ahmad*, Narottam Singh, Munesh Singh Bhadauria

Sun Institute of Pharmaceutical Education and Research, Lahar, Madhya Pradesh, India

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ABSTRACT

In the effort to develop new potential molecule for the betterment of the health condition, a few of novel substituted azetidinones were synthesized using microwave assisted method and characterized for antibacterial action. The IR spectra of all the compounds exhibited the stretching vibration peaks due to C-N, C=O, C=N at 1400-1000 cm^{-1}, 1765-1645 cm^{-1} and 1690-1520 cm^{-1} (medium) respectively. The other vibrations that appeared in the spectra included those from aromatic C=C and C-H, C-H alkane, C-Cl **(4e),** C-O **(4d),** C-H (methoxy), C-C (cycobutyl) and C=O (cycobutyl). The ^{1}HNMR spectra obtained displayed the peaks of aliphatic CH and aromatic CH at 2-3.3, and 6.7-7.2 ppm respectively. The mass spectra displayed the molecular ion peak and the isotopic peaks as calculated. The MIC of compounds **4c, 4d, 4e** and **4f** was found to be 6.25 µg/mL against gram positive bacteria and 12.5 µg/mL against gram negative bacteria. Compounds **4a** and **4b** exhibited were not found to be not very significant in comparison to the reference drug.

*Corresponding Author

Md Taufique Ahmad

Email: mdtaufiqueahmad06193@gmail.com

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Introduction

Azetidin-2-one **,** a four-membered cyclic lactam (ß-lactam) skeleton has been recognized as an attractive target of contemporary organic synthesis of a large number of organic molecules by exploiting the strain energy associated with it. Azetidinone have been shown to have various important biological activities such as antimicrobial (Singh et al, 2005; Mistry et al, 2005; Gunner et al, 2000), antibacterial (Chaudhari et al, 2003), antifungal (Singh et al, 2010), anti- inflammatory (Kumar et al, 2009), antitubercular (Thakre et al, 2003), anticancer (Banik et al, 2004) and cytotoxic Maia et al, 2009). Owing to the ever increasing incidences of resistance to the existing antimicrobial drugs, several researches worldwide are directed towards the development of newer antimicrobial agents. Azetidinones have been promising moieties in several antibiotic agents. The synthesis of azetidinones have been time consuming procedure that requires several hours of reflux. Microwave assisted synthesis on the other hand as been known to reduce the reaction times required to complete a reaction and hence it was envisioned to synthesize a few azetidinone derivatives reported by Malviya et al (2021) using microwave assisted procedure and evaluating the antibacterial activity of the synthesized compounds.

Material and Methods

The scheme for synthesis of azetidinone was adapted from report by Kerzare et al (2018). The synthesis of compounds was accomplished according to the scheme depicted in Figure 1.

Synthesis of (E)-4-hydrazononaphthalen-1 (4H)-one (2)

A weighed quantity of napthoquinone (15.08 g, 0.1 mol) was added to hydrazine hydrate (99%, 5.05 g, 1.1 mol) in 100 ml of absolute methanol and the mixture was irradiated using microwave at 100 Watt power for 7 min followed by cooling to room temperature. Crystals of hydrazone that precipitated out was filtered and dried. The crude product was recrystallized using ethanol to obtain the pure hydrazone.

Synthesis of Substituted (E)-4-(2-methylenehydrazono) naphthalen-1(4H)-one (3a-f)

To a solution of compound **2** (0.01 mol) in ethanol (60 mL), substituted aromatic aldehyde (0.01 mol) and with a few drops of glacial acetic acid were added. The resulting mixture was irradiated using microwave at 420 Watt power for 5 minutes. The excess of the ethanol was distilled off and the remaining

mixture was cooled, poured onto crushed ice and filtered. The crude product obtained was recrystallized from 70% ethanol.

Synthesis of (E)-3-chloro-1-(4-oxonaphthalen-1(4H)-ylideneamino) azetidin-2-one (4a-f)

A mixture of Schiff base **(3a-f)** (0.01 mol) and triethylamine (0.02 mol) was dissolved in 1, 4-Dioxane (15 mL). To this, a solution of chloroacetyl chloride (0.02 mol) was added in portions with vigorous shaking at room temperature for 20 min. The reaction mixture was heated under microwave at 420 Watt power for 7 minutes and the content was kept at room temperature for 48 h and poured into ice-cold water. The resulting solid was filtered, washed several times with water and then recrystalised from 70% ethanol.

Chemical Characterization of the synthesized Compounds:

The azetidinone derivatives were characterized for solubility, yield, physical appearance, melting point and spectral characteristics. The melting points were determined on melting point apparatus and are uncorrected. IR spectra are recorded on Bruker spectrophotometer, mass and proton NMR spectra were recorded on Jeol system.

The solvent system used for TLC of the compound was Methanol : Ethyl Acetate in the ratio 4:6 for the desired products and 8:2 / 7:3 for determining the purity (completion of reaction) of the intermediate products.

Evaluation of antibacterial action (Mishra et al, 2013)

The antibacterial action of the synthesized compounds (obtained by microwave synthesis) was evaluated against one gram positive (*Bacillus subtilis*) and one gram negative bacteria (*Pseudomonas aeruginosa*). The minimum inhibitory concentration (MIC) value of the compounds was determined using serial dilution method employing nutrient broth.

Results and Discussion

Chemistry

(E)-3-chloro-1-(4-oxonaphthalen-1(4H)-ylideneamino)-4-phenylazetidin-2-one1H, ***4a***

^{1}H NMR Spectra (d, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene)

IR (KBr): 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

Color: Yellow; Yield: 75%; Melting Point (°C): 170-173

(E)-3-chloro-4-(4-nitrophenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one, ***4b***

^{1}H NMR Spectra (d, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene)

IR (KBr): 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

Color: Brown; Yield: 72%; Melting Point (°C): 192-194

(E)-3-chloro-4-(2-nitrophenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one, ***4c***

^{1}H NMR Spectra (d, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene)

IR (KBr): 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

Color: Brown; Yield: 69%; Melting Point (°C): 201-204

(E)-3-chloro-4-(4-methoxyphenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one, ***4d***

^{1}H NMR Spectra (d, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene)

IR (KBr): 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

Color: Yellow; Yield: 71%; Melting Point (°C): 172-175

(E)-3-chloro-4-(4-chlorophenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one, ***4e***

^{1}H NMR Spectra (d, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene)

IR (KBr): 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

Color: Yellow; Yield: 68%; Melting Point (°C): 208-211

(E)-3-chloro-4-(4-(dimethylamino)phenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino) azetidin-2-one, ***4f***

^{1}H NMR Spectra (d, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene)

IR (KBr): 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

Color: Yellow; Yield: 72%; Melting Point (°C): 197-200

The structure elucidation of the compounds was performed by IR, ^{1}HNMR and mass spectroscopy. The IR spectra of all the compounds exhibited the stretching vibration peaks due to C-N, C=O, C=N at 1400-1000 cm^{-1}, 1765-1645 cm^{-1} and 1690-1520 cm^{-1} (medium) respectively. The other vibrations that appeared in the spectra included those from aromatic C=C and C-H, C-H alkane, C-Cl **(4e),** C-O **(4d),** C-H (methoxy), C-C (cycobutyl) and C=O (cycobutyl).

The ^{1}HNMR spectra obtained displayed the peaks of aliphatic CH and aromatic CH at 2-3.3, and 6.7-7.2 ppm respectively. The mass spectra displayed the molecular ion peak and the isotopic peaks as calculated.

Antibacterial Activity

The antibacterial activity of the synthesized compounds was evaluated at various concentrations to determine the MIC of each compound.

A.) A set of tubes with only the inoculated broth was used as control to determine MIC

B.) MIC is expressed by measuring the turbidity of test and control dilution tubes. A 50% decrease in turbidity was taken as MIC.

C.)All values are expressed as mean of a set of three experiments

The MIC of the reference drug Norfloxacin was 1.25 µg/mL against both the bacterial strains used for the study. The MIC of compounds **4c, 4d, 4e** and **4f** was found to be 6.25 µg/mL against gram positive bacteria and 12.5 µg/mL against gram negative bacteria. Compounds **4a** and **4b** exhibited were not found to be not very significant in comparison to the reference drug.

Conclusion

The present work focused on microwave method to synthesize few azetidinone derivatives and evaluate their antibacterial potential. The synthesized compounds with diverse substitution pattern were able to be synthesized in short time using the microwave method and exhibited antibacterial action. Further studies on new compounds of similar structure would be carried out in order to derive a relation between the structure and activity of the nucleus.

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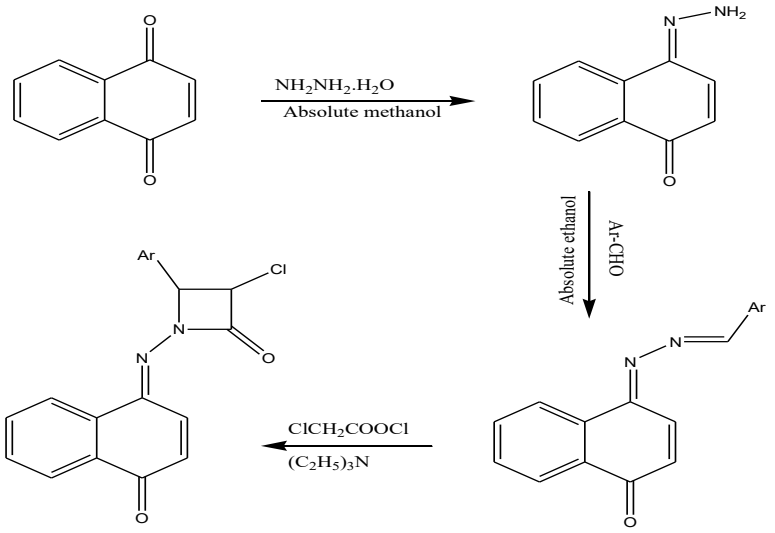

Figure 1 Scheme of the synthesis of Azetidinone Derivatives.

Table 1 MIC of the synthesized compounds against gram positive and gram negative bacteria

Code	MIC (µg/mL)[a,b,c]	MIC (µg/mL)[a,b,c]
	B. subtilis	***P. aeuroginosa***
4a	25	25
4b	12.5	25
4c	6.25	12.5
4d	6.25	12.5
4e	6.25	12.5
4f	6.25	12.5
Norfloxacin	1.25	1.25

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