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FULL PAPER

Microwave Assisted Synthesis and Antimicrobial Study of Some Novel 2-Azetidinones Derived from 2-(1-Phenylimino-ethyl)-naphthalen-1-ol

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Abstract:

Several substituted 2-azetidinone derivatives 2a-q have been synthesized from halogenohydroxy substituted imines 1a-q under microwave irradiation technique. The reactions were carried out using 2-methoxyethanol as an efficient reaction media to afford high yield of product. The structures of newly synthesized compounds have been established on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, GC-MS and elemental data. Further, all newly synthesized compounds were screened for their in vitro antimicrobial activity. The antifungal and antibacterial effects of the tested compounds are due to their molecular structure and substituent present.

Keywords: 2-azetidinones; halogenohydroxy; Schiff bases; microwave irradiation; antimicrobial activity

1. Introduction

In recent years, focusing on green chemistry by using eco-friendly benign media and reaction conditions is one of the most interesting developments in synthesis of organic compounds. Microwave irradiation as an alternative and unconventional energy source has been increasingly used in organic synthesis [1]. Microwave-assisted organic synthesis could obtain rapid, reproducible, and scalable processes to prepare new compounds in high yields compared with the traditional heating methods [2]. It is reported that the organic compound was easily polarized to generate electronic polarization, atom polarization, orientation polarization and interfacial polarization in the microwave irradiation [3]. Also, electronic and atom polarization rates are much faster than the frequency of the microwave, and the other polarization rates are close to the frequency of the microwave [4]. Thus, microwave irradiation resulting in the motion state of organic molecules was transformed from original thermal motion to alternating arrangement corresponding to the frequency of the microwave, oscillation intensifying, further generating thermal efficiency [5]. As a result, microwave irradiation as dielectric heating is a process in which the organic compounds consume electromagnetic energy, which can accelerate the reaction rate for several times, 10 times or even tens of thousands of times compared with the conventional heating [6].

2-azetidinones (β-lactam, **Figure 1)** are important classes of heterocyclic compounds and attractive targets both in medicinal chemistry and organic synthesis in recent years. Azetidinones, which are part of antibiotics structures, are known to exhibit interesting biological activities. A large number of 3-chloro monocyclic β-lactam possesses powerful antimicrobial, anticancer [7], cytotoxic [8], anticonvulsant [9] and antitubercular [10] activities. They also function as enzyme

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inhibitors and are effective on the central nervous system [11]. The classical synthesis of these compounds involves cycloaddition of monochloroacetyl chloride with imines (Schiff base) resulting in formation of 2-azetidinone [12].

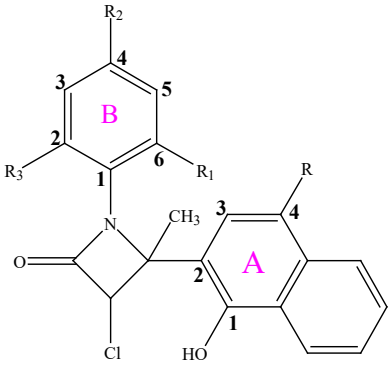


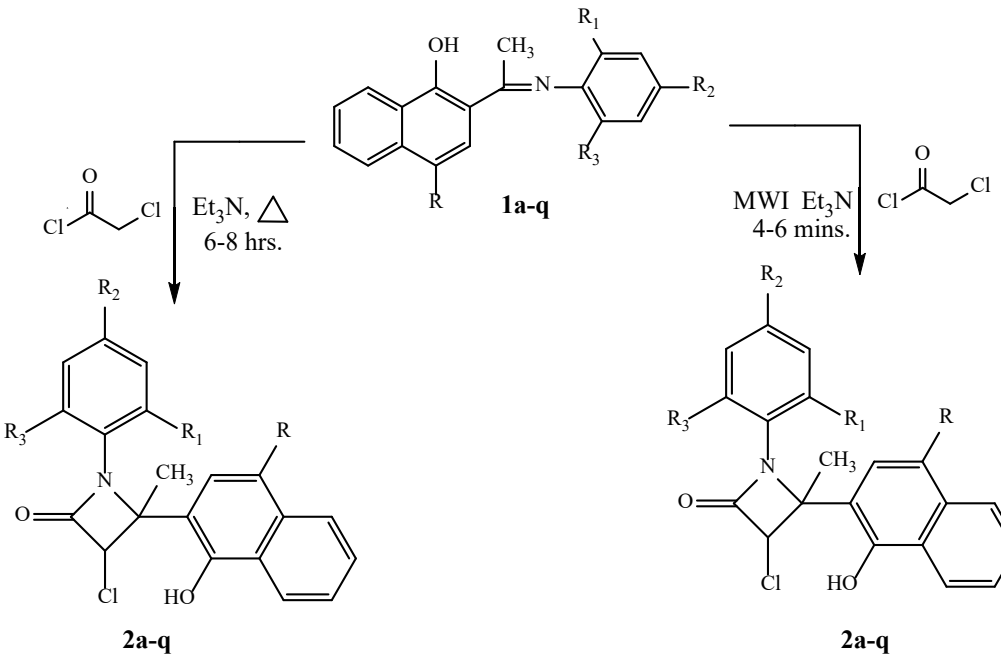
Figure 1. General structure for 2-azetidinones.

As a part of our interest towards the development of novel heterocyclic compounds such as 1, 5-benzodiazepines [13], 1,5-benzothiazepines [14], 2-*H* pyrazolines [15], *N*-formyl pyrazolines [16], and 4-thiazolidinones [17], herein we wish to report the synthesis of some novel 2-azetidinone derivatives.

2. Results and Discussion

Chemistry

In view of the importance of 2-azetidinones and in continuation of earlier research work towards synthesis of heterocyclic compounds using microwave technique [18-19], we plan to prepare the novel 2-azetidinones derived from 2-(1-Phenylimino-ethyl)-naphthalen-1-ol. The experimental procedure reported here for synthesis of 2-azetidinones **2a-q** involves the cyclocondensation reaction of imines **1a-q** with monochloroacetyl chloride in presence of Et_3N using 2-methoxyethanol as a novel and eco-friendly solvent under microwave irradiation (**Scheme 1, Table 1**).



2a: R, I; R_1, I; R_2, Cl; R_3, H
2b: R, Br; R_1, I; R_2, Cl; R_3, H
2c: R, Cl; R_1, I; R_2, Cl; R_3, H
2d: R, I; R_1, NO_2; R_2, I; R_3, H
2e: R, Br; R_1, NO_2; R_2, I; R_3, H
2f: R, Cl; R_1, NO_2; R_2, I; R_3, H
2g: R, I; R_1, Cl; R_2, I; R_3, H
2h: R, Br; R_1, Cl; R_2, I; R_3, H
2i: R, Cl; R_1, Cl; R_2, I; R_3, H

2j: R, I; R_1, I; R_2, NO_2; R_3, H
2k: R, Br; R_1, I; R_2, NO_2; R_3, H
2l: R, Cl; R_1, I; R_2, NO_2; R_3, H
2m: R, Cl; R_1, Cl; R_2, Cl; R_3, H
2n: R, Br; R_1, Cl; R_2, Br; R_3, H
2o: R, Br; R_1, I; R_2, COOH; R_3, I
2p: R, I; R_1, I; R_2, COOH; R_3, I
2q: R, Cl; R_1, I; R_2, COOH; R_3, I

Scheme 1. Microwave assisted synthesis of some novel 2-azetidinones.

Table 1. Synthesis of differently substituted 2-azetidinones 2a-q.

Product	R	R_1	R_2	R_3	m.p. (°C)	Method A		Method B	
						Time (h)[a]	Yield (%)	Time (min)	Yield (%)[b]
2a	I	I	Cl	H	135-137	6.0	68	5.2	82
2b	Br	I	Cl	H	146-148	6.5	62	6.0	80
2c	Cl	I	Cl	H	123-126	5.5	70	5.3	78
2d	I	NO_2	I	H	138-140	6.4	66	6.2	84
2e	Br	NO_2	I	H	148-150	6.2	60	6.4	80
2f	Cl	NO_2	I	H	132-134	5.3	65	5.2	85
2g	I	Cl	I	H	127-130	5.4	62	4.3	90
2h	Br	Cl	I	H	136-138	7.3	68	6.5	84
2i	Cl	Cl	I	H	152-155	6.5	60	5.4	75
2j	I	I	NO_2	H	157-159	6.5	58	5.3	78
2k	Br	I	NO_2	H	162-164	7.5	70	4.0	84
2l	Cl	I	NO_2	H	153-155	6.2	68	4.3	88
2m	Cl	Cl	Cl	H	149-151	5.4	65	4.5	85
2n	Br	Cl	Br	H	154-157	6.4	64	5.2	82
2o	Br	I	COOH	I	183-185	7.3	60	6.4	73
2p	I	I	COOH	I	172-174	7.2	55	6.0	76
2q	Cl	I	COOH	I	188-190	6.5	58	6.2	78

[a]Isolated yield of the product by conventional method.
[b]Isolated yield of the product by microwave method.

In classical methods the heating path of reaction passes from outer surface to the inner surface of the vessel which leads to improper collision of molecules. Therefore classical synthesis involves energy transfer from the source to outer wall of vessel to the mixture and then to reacting particles, maximum temperature of reaction can be achieved is limited to boiling point of the solvent, all the components of the mixture is heated equally and speed of heating is raised slowly and gradually. To overcome these disadvantages of classical method in comparison to microwave irradiation technique which involves heating directly to inside the mixture by electromagnetic waves, direct contact with the higher temperature source when the vessel is kept in the microwave cavity, heating mechanisms involve dielectric polarization and conduction and interfacial polarization, temperature of the reaction can be raised above the boiling point of the solvent and achieve superheating, reaction particles each is heated specifically, speed of heating is very much faster than the conventional way. To optimize and determine the reaction conditions for synthesis 2-azetidinones using microwave technique, we attempted the reaction between 2-[1-(2-Chloro-4-iodo-phenylimino)-ethyl]-4-iodo-naphthalen-1-ol and monochloroacetyl chloride in presence of Et_3N using 2-methoxyethanol. The reaction went to completion within 4.3 min and corresponding product **2g** was obtained in 90% yield. To compare these reaction conditions, we carried out above reaction in different reaction medium such as methanol, ethanol, acetic acid, dioxane, DMSO, acetonitrile and DMF (**Table 2**, **Figure 2**). We found that 2-methoxyethanol as an efficient reaction medium in terms of clean reaction conditions, not expensive, yields and environmentally eco-friendly. In all cases, reaction proceeded efficiently in high yields using 2-methoxyethanol.

Table 2. Optimization of reaction condition for cyclocondensation of imines to 2-azetidinone (2g).

Entry	Reaction solvent	Method A		Method B	
		Time (h)[a]	Yield (%)	Time (min)	Yield (%)[b]
1	Methanol (40 mL)	08	45	25	60
2	Ethanol (35 mL)	10	48	28	58
3	Acetic acid (35 mL)	10.45	45	28	55
4	Dioxane (30 mL)	08	50	23	58
5	Dimethyl sulphoxide (DMSO) (30 mL)	6.35	54	20	60
6	Acetonitrile (25 mL)	07	51	22	62
7	Dimethyl formamide (DMF) (30 mL)	08	52	20	64
8	**2-Methoxyethanol (20 mL)**	**03**	**58**	**4.3**	**90**

[a]Isolated yield of products without purification.
[b]Isolated yield of products with purification.

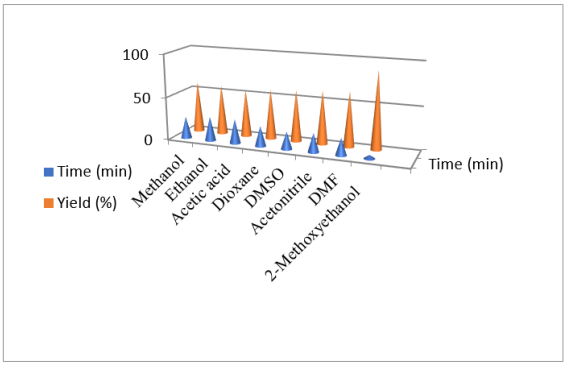


Figure 2. Graphical representation for different solvent using microwave method.

The structures of newly synthesized compounds **2a**-**q** have been confirmed by IR, ^{1}H NMR and MS spectral studies. In IR spectra of corresponding product display the absence of characteristic absorption band near 1580-1590 cm^{-1} due to C=N stretching of imines and appearances of 1670 cm^{-1} of C=O stretch indicate the formation of four membered β-lactum ring. In ^{1}H NMR spectra of 2-azetidinones obtained at δ value 1.5 ppm and 5.2 ppm is due to proton of CH_3C-N and CH-Cl, respectively. The singlet of OH proton obtained near δ value around 5.8 ppm.

Antimicrobial study

All the synthesized 2-azetidinones derivatives (**2a-q**) were screened for their *in vitro* antimicrobial activity and showed good inhibitory activity at 10.5µg/mL, 12.5µg/mL & 25µg/mL concentration. Antimicrobial activity tested against *Escherichia coli* (MTCC 2736), *Staphylococcus aureus* (MTCC 4275), *Candia crusei* (MTCC 10125) and *Candida albicans* (MTCC 28130). The results of these studies in terms of zone of inhibition (ZOI) and minimum inhibitory concentrations (MICs) are summarized in **Table 3**. The compounds **2a**, **2b**, **2c**, **2g**, **2i**, and **2m** shows good to moderate inhibitory activity against all tested microbes. The moderate antimicrobial activity is attributed due to presence of pharmacological active halo groups (**2a, 2b, 2c, 2g, 2h, 2n**). The compounds **2i** and **2m** has higher inhibitory activity in comparison with any other compounds due to presence of more activating group –Cl attached at 2nd and 4th position of aromatic ring A and B (**Figure 1**).

Table 3. Antimicrobial screening of synthesized 2-azetidinones **2a-q** (MIC µg/mL).

Entry	Zone of inhibition in mm			
	E. Coli **MTCC 2736**	***S. aureus*** **MTCC 4275**	***C. crusei*** **MTCC 10125**	***C. albicans*** **MTCC 28130**
2a	30(15.5)	28(12.5)	20(25)	30(25)
2b	26(20.5)	22(<10.5)	28(25)	26(25.5)
2c	28(15.5)	25(12.5)	22(25)	28(25)
2d	18(<150)	16(<150)	12(<200)	14(<200)
2e	10(<200)	12(<200)	10(<200)	08(<200)
2f	14(<200)	10(<200)	12(<200)	08(<200)
2g	30(15.5)	18(<10.5)	22(25)	30(25)
2h	20(<200)	28(12.5)	16(<200)	32(25)
2i	32(15.5)	24(<10.5)	25(25)	22(25)
2j	08(<200)	12(<200)	20(25)	10(<200)
2k	18(<150)	10(<200)	14(<200)	18(<200)
2l	12(<200)	08(<200)	14(<200)	12(<200)
2m	30(<15.5)	26(<10.5)	30(25)	26(25.5)
2n	32(15.5)	30(12.5)	28(25.5)	26(25.5)
2o	24(100)	06(<200)	16(50)	10(50)
2p	26(100)	24(100)	14(50)	18(50)
2q	20(100)	22(100)	20(50)	18(50)
# #	22(100)	26(12.5)	-------	-------
¶¶	-------	-------	28(25)	24(25)

Ofloxacin ¶¶ Ketoconazole

3. Material and Methods

The chemicals and solvents used were of laboratory grade and were purified. Melting points

were determined in an open capillary tube and are uncorrected. Purification of the compound was indicated using TLC (ethyl acetate / hexane, 0.25 mL: 0.25 mL, and petroleum ether / hexane, v/v as the mobile phase). FT-IR spectra were recorded in KBr pellets on a Perkin-Elmer (8201) spectrometer. ^{1}H-NMR spectra were recorded on a Gemini 300-MHz instrument in DMSO-d6 as the solvent and TMS was used as an internal standard. The mass spectra were recorded on SHIMADZU (GCMS-QP 1000 EX) GC-EI-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. The reactions were carried out in 2-methoxyethanol (10mL: 10mL, v/v) as reaction medium in QPro-M modified microwave oven, at 200 watts and 2450 MHz frequency.

General procedure for synthesis of 2-azetidinones (2a-q)

Conventional method A

A solution of corresponding imines **1a-q** (0.001 mole) in 2-methoxyethanol (20mL, v/v) containing chloroacetyl chloride (0.01 g) was refluxed for 6-8 hrs. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered under reduced pressure and recrystallized from ethanol to yield pure 2-azetidinone derivatives **2a-q** as light yellow solid crystals.

Microwave method B

A mixture of corresponding imines **1a-q** (0.001 mole) in 2-methoxyethanol (20mL, v/v) chloroacetyl chloride (0.01 g) was irradiated in QPro-M microwave oven for about intermittently at 30 sec. interval for 4-6 minutes. Then reaction mixture was diluted with ice-cold water. The solid product thus formed was collected under reduced pressure, dried over $MgSO_4$ and recrystallized from ethanol to yield pure 2-azetidnone derivatives **2a-q** as light yellow solid crystals.

2a. *3-Chloro-1-(4-chloro-2-iodo-phenyl)-4-(1-hydroxy-4-iodo-naphthalen-2-yl)-4-methyl-azetidin-2-one*: 3370 (OH), 2910 (C-H), 1678 (C=O), 1568, 1537, 1429 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.3-8.2 (m, 8H, Aromatic proton); ^{13}C NMR: 29.69 (CH_3), 72.54 (C-Cl of 2-azetidinone ring), 102-148 (C of Aromatic ring), 165 (CO); EIMS (*m/z*): 623 (M+); Anal. Calcd. For $C_{20}H_{13}O_2NI_2Cl_2$: C, 38.52; H, 2.08; N, 2.24; X (I, Cl); 52.00; Found: C, 38.48; H, 2.12; N, 2.27; X (I, Cl); 52.18.

2b. *4-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-chloro-1-(4-chloro-2-iodo-phenyl)-4-methyl-azetidin-2-one*: 3372 (OH), 2918 (C-H), 1675 (C=O), 1573, 1532, 1442 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.3-8.3 (m, 8H, Aromatic proton); ^{13}C NMR: 29.73 (CH_3), 72.57 (C-Cl of 2-azetidinone ring), 105-143 (C of Aromatic ring), 165.17 (CO); EIMS (*m/z*): 576 (M+); Anal. Calcd. For $C_{20}H_{13}O_2NIBrCl_2$: C, 41.66; H, 2.25; N, 2.43; X (I, Br,Cl); 42.10; Found: C, 41.58; H, 2.31; N, 2.46; X (I, Br,Cl); 42.18.

2c. *3-Chloro-4-(4-chloro-1-hydroxy-naphthalen-2-yl)-1-(4-chloro-2-iodo-phenyl)-4-methyl-azetidin-2-one:* 3372 (OH), 2912 (C-H), 1674 (C=O), 1567, 1537, 1445 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.6 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.2 (m, 8H, Aromatic proton); ^{13}C NMR: 29.79 (CH_3), 72.47(C-Cl of 2-azetidinone ring), 103-147 (C of Aromatic ring), 165.18 (CO); EIMS (*m/z*): 531 (M+); Anal. Calcd. For $C_{20}H_{13}O_2NICl_3$: C, 45.19; H, 2.44; N, 2.63; X (I, Cl); 43.69; Found: C, 45.24; H, 2.45; N, 2.68; X (I, Cl); 43.73.

2d. *3-Chloro-4-(1-hydroxy-4-iodo-naphthalen-2-yl)-1-(4-iodo-2-nitro-phenyl)-4-methyl-azetidin-2-one:* 3375 (OH), 2927 (C-H), 1670 (C=O), 1548, 1540, 1449 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.4-8.4 (m, 8H, Aromatic proton); ^{13}C NMR: 29.75 (CH_3), 72.51(C-Cl of 2-azetidinone ring), 102-145 (C of Aromatic ring), 165.11 (CO); EIMS (*m/z*): 634 (M+); Anal. Calcd. For $C_{20}H_{13}O_4N_2I_2Cl$: C, 37.85; H, 2.05; N, 2.20; X (I, Cl); 45.58; Found: C, 37.89; H, 2.08; N, 2.16; X (I, Cl); 45.64.

2e. *4-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-chloro-1-(4-iodo-2-nitro-phenyl)-4-methyl-azetidin-2-one:* 3371 (OH), 2941(C-H), 1673 (C=O), 1543, 1537, 1445 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.3 (m, 8H, Aromatic proton); ^{13}C NMR: 29.69 (CH_3), 72.48(C-Cl of 2-azetidinone ring), 102-147 (C of Aromatic ring), 165.16 (CO); EIMS (*m/z*): 587.5 (M+); Anal. Calcd. For $C_{20}H_{13}O_4N_2IBrCl$: C, 40.85; H, 2.21; N, 4.76; X

(I,Br,Cl); 41.27; Found: C, 40.89; H, 2.25; N, 4.70; X (I,Br,Cl); 41.35.

2f. *3-Chloro-4-(4-chloro-1-hydroxy-naphthalen-2-yl)-1-(4-iodo-2-nitro-phenyl)-4-methyl-azetidin-2-one:* 3374 (OH), 2945 (C-H), 1675 (C=O), 1545, 1540, 1447 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.3 (m, 8H, Aromatic proton); ^{13}C NMR: 29.62 (CH_3), 72.53 (C-Cl of 2-azetidinone ring), 105-142 (C of Aromatic ring), 165.21 (CO); EIMS (*m/z*): 542 (M+); Anal. Calcd. For $C_{20}H_{13}O_4N_2ICl_2$: C, 44.28; H, 2.39; N, 5.16; X (I,Cl); 36.34; Found: C, 44.35; H, 2.35; N, 5.19; X (I,Cl); 36.40.

2g. *3-Chloro-1-(2-chloro-4-iodo-phenyl)-4-(1-hydroxy-4-iodo-naphthalen-2-yl)-4-methyl-azetidin-2-one*: 3373 (OH), 2945 (C-H), 1676 (C=O), 1547, 1539, 1442 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.6 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.4 (m, 8H, Aromatic proton); ^{13}C NMR: 29.73 (CH_3), 72.42 (C-Cl of 2-azetidinone ring), 102-145 (C of Aromatic ring), 165.20 (CO); EIMS (*m/z*): 623 (M+); Anal. Calcd. For $C_{20}H_{13}O_2NI_2Cl_2$: C, 38.52; H, 2.08; N, 2.24; X (I,Cl); 52.0; Found: C, 38.56; H, 2.07; N, 2.26; X (I,Cl); 52.15.

2h. *4-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-chloro-1-(2-chloro-4-iodo-phenyl)-4-methyl-azetidin-2-one*: 3374 (OH), 2945 (C-H), 1669 (C=O), 1532, 1523, 1441 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.3 (m, 8H, Aromatic proton); ^{13}C NMR: 29.75 (CH_3), 72.60 (C-Cl of 2-azetidinone ring), 104-146 (C of Aromatic ring), 165.20 (CO); EIMS (*m/z*): 576 (M+); Anal. Calcd. For $C_{20}H_{13}O_2NIBrCl_2$: C, 41.66; H, 2.25; N, 2.43; X (I,Br,Cl); 48.09; Found: C, 41.68; H, 2.23; N, 2.45; X (I,Br,Cl); 48.12.

2i. *3-Chloro-4-(4-chloro-1-hydroxy-naphthalen-2-yl)-1-(2-chloro-4-iodo-phenyl)-4-methyl-azetidin-2-one:* 3376 (OH), 2948 (C-H), 1676 (C=O), 1552, 1539, 1447 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.3 (m, 8H, Aromatic proton); ^{13}C NMR: 29.73 (CH_3), 72.52 (C-Cl of 2-azetidinone ring), 105-151 (C of Aromatic ring), 165.21 (CO); EIMS (*m/z*): 531 (M+); Anal. Calcd. For $C_{20}H_{13}O_2NICl_3$: C, 45.19; H, 2.44; N, 2.63; X (I,Cl); 43.69; Found: C, 45.23; H, 2.47; N, 2.65; X (I,Cl); 43.75.

2j. *3-Chloro-4-(1-hydroxy-4-iodo-naphthalen-2-yl)-1-(2-iodo-4-nitro-phenyl)-4-methyl-azetidin-2-one*: 3370 (OH), 2941(C-H), 1676 (C=O), 1548, 1534, 1449 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.4 (m, 8H, Aromatic proton); ^{13}C NMR: 29.75 (CH_3), 72.53 (C-Cl of 2-azetidinone ring), 104-143 (C of Aromatic ring), 165.12 (CO); EIMS (*m/z*): 634 (M+); Anal. Calcd. For $C_{20}H_{13}O_4N_2I_2Cl$: C, 37.85; H, 2.05; N, 4.41; X (I,Cl); 45.58; Found: C, 37.91; H, 2.11; N, 4.44; X (I,Cl); 45.63.

2k. *4-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-chloro-1-(2-iodo-4-nitro-phenyl)-4-methyl-azetidin-2-one*: 3374 (OH), 2948 (C-H), 1676 (C=O), 1547, 1533, 1440 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.3 (m, 8H, Aromatic proton); ^{13}C NMR: 29.69 (CH_3), 72.48 (C-Cl of 2-azetidinone ring), 103-147 (C of Aromatic ring), 165.16 (CO); EIMS (*m/z*): 587 (M+); Anal. Calcd. For $C_{20}H_{13}O_4N_2IBrCl$: C, 40.88; H, 2.21; N, 4.47; X (I,BrCl); 41.22; Found: C, 40.94; H, 2.22; N, 4.49; X (I,BrCl); 41.28.

2l. *3-Chloro-4-(4-chloro-1-hydroxy-naphthalen-2-yl)-1-(2-iodo-4-nitro-phenyl)-4-methyl-azetidin-2-one*: 3371 (OH), 2945 (C-H), 1670 (C=O), 1549, 1531, 1439 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.4 (m, 8H, Aromatic proton); ^{13}C NMR: 29.73 (CH_3), 72.55 (C-Cl of 2-azetidinone ring), 103-144 (C of Aromatic ring), 165.20 (CO); EIMS (*m/z*): 542 (M+); Anal. Calcd. For $C_{20}H_{13}O_4N_2ICl_2$: C, 44.28; H, 2.39; N, 5.16; X (I,BrCl); 44.64; Found: C, 44.33; H, 2.41; N, 5.18; X (I,Br,Cl); 44.68.

2m. *3-Chloro-4-(4-chloro-1-hydroxy-naphthalen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-azetidin-2-one*: 3374 (OH), 2943 (C-H), 1675 (C=O), 1547, 1526, 1437 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.3 (m, 8H, Aromatic proton); ^{13}C NMR: 29.69 (CH_3), 72.56 (C-Cl of 2-azetidinone ring), 103-147 (C of Aromatic ring), 165.18 (CO); EIMS (*m/z*): 439 (M+); Anal. Calcd. For $C_{20}H_{13}O_2NCl_4$: C, 54.66; H, 2.96; N, 3.18; X (Cl); 31.89; Found: C, 54.72; H, 2.98; N, 3.16; X (Cl); 31.86.

2n. *1-(4-Bromo-2-chloro-phenyl)-4-(4-bromo-1-hydroxy-naphthalen-2-yl)-3-chloro-4-methyl-azetidin-2-one*: 3378 (OH), 2943 (C-H), 1677 (C=O), 1548, 1540, 1443 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H,OH), 1.5 (s, 3H, CH_3), 7.2-8.3 (m, 8H, Aromatic proton); ^{13}C NMR: 29.75 (CH_3), 72.52 (C-Cl of 2-azetidinone

ring), 103-147 (C of Aromatic ring), 165.15 (CO); EIMS (*m/z*): 529 (M+); Anal. Calcd. For $C_{20}H_{13}O_2NBr_2Cl_2$: C, 45.36; H, 2.45; N, 2.64; X (Br,Cl); 47.25; Found: C, 45.42; H, 2.46; N, 2.67; X (Br,Cl); 47.28;

2o. *4-[2-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-chloro-2-methyl-4-oxo-azetidin-1-yl]-3,5-diiodo-benzoic acid*: 3375 (OH), 2943 (C-H), 1675 (C=O), 1545, 1535, 1442 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 12.2 (1H, COOH), 5.8 (s, 1H,OH), 1.6 (s, 3H, CH_3), 7.3-8.4 (m, 7H, Aromatic proton); ^{13}C NMR: 29.74 (CH_3), 72.52 (C-Cl of 2-azetidinone ring), 102-149 (C of Aromatic ring), 165.20 (CO); EIMS (*m/z*): 712 (M+); Anal. Calcd. For $C_{21}H_{13}O_4NI_2BrCl$: C, 35.39; H, 1.82; N, 1.96; X (I,Br,Cl); 33.98; Found: C, 35.42; H, 1.85; N, 1.98; X (I,Br,Cl); 34.05.

2p. *4-[3-Chloro-2-(1-hydroxy-4-iodo-naphthalen-2-yl)-2-methyl-4-oxo-azetidin-1-yl]-3,5-diiodo-benzoic acid*: 3375 (OH), 2948 (C-H), 1674 (C=O), 1547, 1537, 1441 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 12.2 (1H, COOH), 5.8 (s, 1H,OH), 1.6 (s, 3H, CH_3), 7.3-8.4 (m, 7H, Aromatic proton); ^{13}C NMR: 29.77 (CH_3), 72.52 (C-Cl of 2-azetidinone ring), 102-147 (C of Aromatic ring), 165.19 (CO); EIMS (*m/z*): 759 (M+); Anal. Calcd. For $C_{21}H_{13}O_4NI_3Cl$: C, 33.20; H, 1.71; N, 1.84; X (I,Cl); 54.80; Found: C, 33.25; H, 1.73; N, 1.87; X (I,Cl); 54.85.

2q. *4-[3-Chloro-2-(4-chloro-1-hydroxy-naphthalen-2-yl)-2-methyl-4-oxo-azetidin-1-yl]-3,5-diiodo-benzoic acid*: 3377 (OH), 2949 (C-H), 1675 (C=O), 1542, 1539, 1445 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 12.2 (1H, COOH), 5.8 (s, 1H,OH), 1.6 (s, 3H, CH_3), 7.2-8.4 (m, 7H, Aromatic proton); ^{13}C NMR: 29.72 (CH_3), 72.50 (C-Cl of 2-azetidinone ring), 102-148 (C of Aromatic ring), 165.18 (CO); EIMS (*m/z*): 667 (M+); Anal. Calcd. For $C_{21}H_{13}O_4NI_2Cl_2$: C, 37.78; H, 1.94; N, 2.09; X (I,Cl); 48.57; Found: C, 37.80; H, 1.96; N, 2.11; X (I,Cl); 48.61

4. Conclusions

In summary, halogenohydroxy substituted 2-azetidinone derivatives have been synthesized from corresponding imines **1a-q** using 2-methoxyethanol solvent in Q-Pro-M modified microwave oven. The method is highly efficient and convenient in terms of simple reaction procedure, short reaction time, increasing the purity of resulting products with high yields in comparison with classical procedure. Further preliminary *in vitro a*ntimicrobial study of newly synthesized compounds reveals that, presence of halo group (Cl, Br and I) in basic nucleus of 2-azetidinones enhances the pharmacological activity. The electronic effect also plays an important role in further increasing pharmacological activity, as can be seen from compounds **2d, 2e, 2f, 2j, 2k** and **2l** which possess -NO_2 group has more electronic withdrawing character shows sharp decrease in antimicrobial activity. Owing to these results, the synthesized compounds **2o** and **2q** have broader value than standard drug used for screening of bacterial and fungal strains. Therefore, the present study is useful for drugs in medicinal investigation against bacterial and fungal diseases.

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