An Efficient Synthesis and Antibacterial Activity of Some Novel 2-Azetidinone Derivatives of 4H-1,2,4-Triazoles Under Mild Conditions

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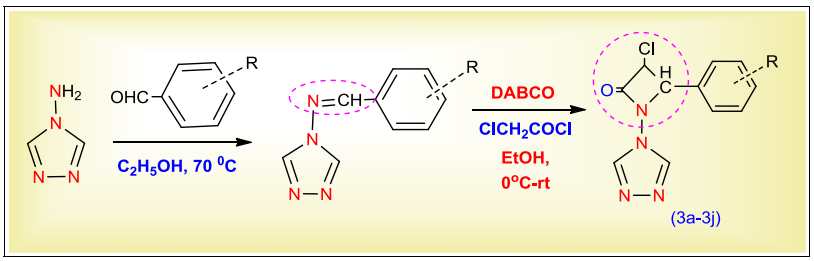

We have synthesized the novel 2-azetidinone derivatives by using Schiff bases of 1,2,4-triazoles via a single step protocol. We used DABCO as a good homogenous, ecofriendly, highly reactive, easy to handle, and nontoxic catalyst. In DABCO catalyzed synthesis of active 2-oxo-azetidine, a highly electrophilic ketene intermediate can react with weakly nucleophilic (N═CH) linkage, which is used as the precursor for the cycloaddition reaction to deliver the desired products in excellent yields with protic solvents. In addition, the DABCO as an economically viable and readily available catalyst is soluble in almost all solvents and their salts easily filtered off from the reaction medium. Moreover, this new synthetic protocol features high conversion in green solvents and a straightforward procedure.

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INTRODUCTION

β-Lactam antibiotics serve as one of the most important contributions of science to mankind. The 2-azetidinone (commonly known as β-lactam) ring system is the basic structural feature of a number of broad spectrum antibiotics, including penicillins, cephalosporins, carbapenems, nocardicins, mono-bactams, clavulanic acid, and sulbactams (Fig. 1), which have been widely used as therapeutic agents to treat bacterial infections and several others [1–4]. 2-Azetidinones exhibit a wide range of biological activities that includes anti-tubercular [5], anti-inflammatory [6], antitumor [7], anti-HIV [8], antimalarial [9], anti-hyperglycemic [10], and analgesic [11] activities. The biological activity of the β-lactams is generally believed to be associated with the chemical reactivity of the four-membered ring and on the substituents, especially at nitrogen of the 2-oxo-azetidine ring [12]. 1,2,4-Triazole and its derivatives possess a great importance in medicinal chemistry and can be used for the synthesis of numerous heterocyclic compounds with different biological activities that include anti-tubercular [13,14], antidepressant [15], anticonvulsant [16], anticancer [17], antioxidant [18], and antimicrobial activity [19]. A number of methods for the synthesis of 2-azetidinone derivatives have been reported [20–24]. Among them, Staudinger reaction [2 + 2] ketene-imine cycloaddition reaction is regarded as one of the most fundamental and versatile methods for the synthesis of structurally diverse 2-azetidinone derivatives [25].

This reaction has long been studied experimentally and theoretically to understand its mechanism and the rationale for the stereoselectivity. This reaction is carried out by two ways, one is photochemically and another is thermally using acid chlorides in the presence of triethylamine or α-diazoketones as a ketene precursors. However, in most of the methods, 2-azetidinone derivatives have been synthesized from the Schiff bases [26]. By dehydrative cyclo-addition of Schiff bases using chloroacetyl chloride and Et_3N as base catalyst; however, some problems in recovering the catalyst, solvents (dioxane), and purification of products have been encountered, so in place of Et_3N, DABCO (Diazabicyclooctane) catalyst has been the choice of our interest in 2-azetidinones synthesis due to their low cost and environment-friendly nature [27,28]. In continuation with our investigations into the synthesis of novel substituted 1,2,4-triazoles derivatives with biological activity, and due to several advantages of DABCO catalyst, here we report a new approach for the synthesis of 3-chloro-2-azetidinonyl-1,2,4-triazole derivatives using DABCO as a superior basic catalyst. To start with our study, Schiff

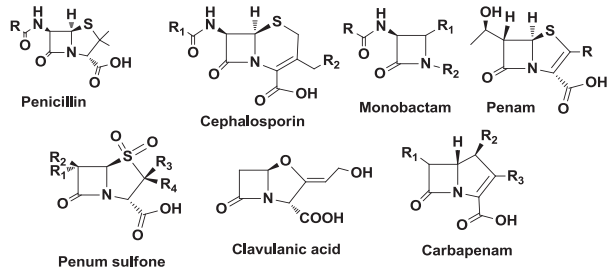


Figure 1. Some antibiotics containing 2-azetidinone moiety.

bases of 1,2,4-triazoles reacted with chloroacetyl chloride at room temp. using DABCO (diaza-bicyclooctane) as the base catalyst affording 2-azetidinone derivatives of 1,2,4-triazoles. Systematic study was then carried out using different solvents like methanol, ethanol, n-BuOH, acetonitrile, dioxane, benzene, chloroform, and THF; and at variable temperature and time to optimize the reaction conditions. These findings have provided justification to develop an efficient synthesis of 1,2,4-triazolyl-substituted β-lactams, based on the chemistry shown in Scheme 1. All the synthesized compounds have been screened for their antibacterial activity against bacteria; *Bacillus cereus*, *Escherichia coli*, and *Staphylcoccus aureus* using Ampicillin as standard drug.

RESULTS AND DISCUSSION

We presented DABCO as an efficient and eco-friendly base catalyst that catalyzes the dehydrative cycloaddition of chloroacetyl chloride with Schiff base. Herein, the catalyst is nontoxic, easy to handle, and can be easily filtered off from the reaction medium because it is soluble in water and other solvents. In this research, we aimed to develop a new green and efficient synthesis of 2-azetidinone derivatives at room temperature from various Schiff bases and chloroacetyl chloride in the presence of DABCO as a base catalyst with EtOH used as a green solvent (Scheme 1). Therefore, in order to optimize the reaction conditions, first, we performed the reaction between Schiff bases (20 mmol) and chloroacetyl chloride (20 mmol) under ethanol used as a solvent in the presence of Et_3N as catalyst at room temperature. The corresponding product yield was obtained in a very low percentage along with un-reacted starting materials after prolonged reaction times. After that, we carried out the same procedure by using EtOH/MeOH(20 mL) as a green solvent, with DABCO used as a homogeneous catalyst for the first time in the synthesis of 2-azetidinone derivatives at room temperature stirring for 2–7 h. The corresponding product was obtained in 83% yield (Table 1). The coupling of an activated nucleophilic derivatives is a key step in the addition of the tertiary amine catalyst to the nucleophilic center to form a stablished nucleophilic anion as shown in Scheme 2. *In situ* generated nucleophile that leads to cyclization and subsequent elimination of the catalyst and formation of azetidinone products in excellent yields. All the remaining reactions were carried out under these conditions. Moreover, the present protocol was screened with different solvent systems such as EtOH, MeOH, n-BuOH, $CHCl_3$, DCM, THF, CH_3CN, and dioxane at room temperature as shown in Table 1. After several experiments, EtOH/MeOH was proven to be the best choice, because the other solvents furnished low yields due to less solubility of Schiff base and stability of ketene intermediate in these solvents. All the synthesized compounds were characterized by FT-IR, ^1H NMR, and ^{13}C NMR. The FT-IR absoption band at 1710–1768 cm^{-1} shows the presence of C═O Stretching in 2-azetidinone ring.

Antimicrobial screening. The preliminary biological activity of the synthesized compounds (**3a**–**3j**) were evaluated against bacterial strains *S. aureus, B. cereus* (Gram-positive) and *E. coli* (Gram-negative). This

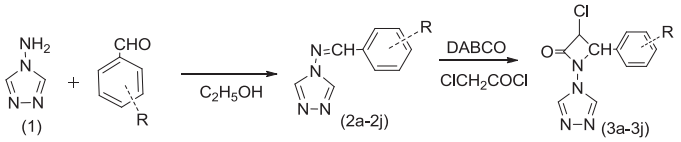
Table 1

Optimization of cyclization reaction condition[a].

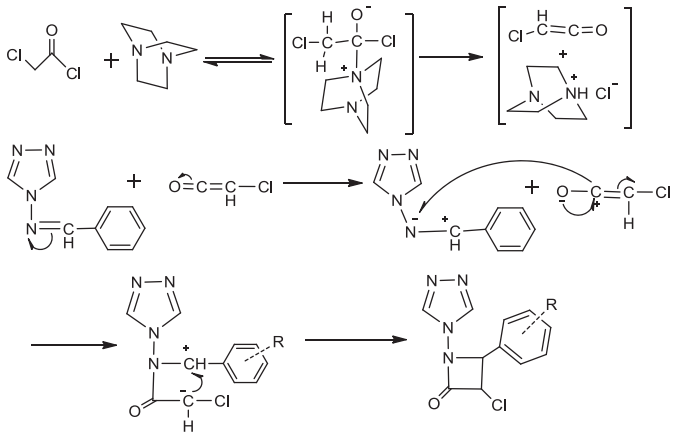
S. No.	Solvents	Time (h)	%Yield DABCO	%Yield Et_3N
1	Chloroform	5	59.4	30
2	MeOH	3	89.5	52
3	Ethanol	3	85.8	56
4	Dioxane	7	67.0	28
5	DCM	4.5	68.5	30
6	Acetonitrile	7	17.2	12
7	THF	6	29.9	18

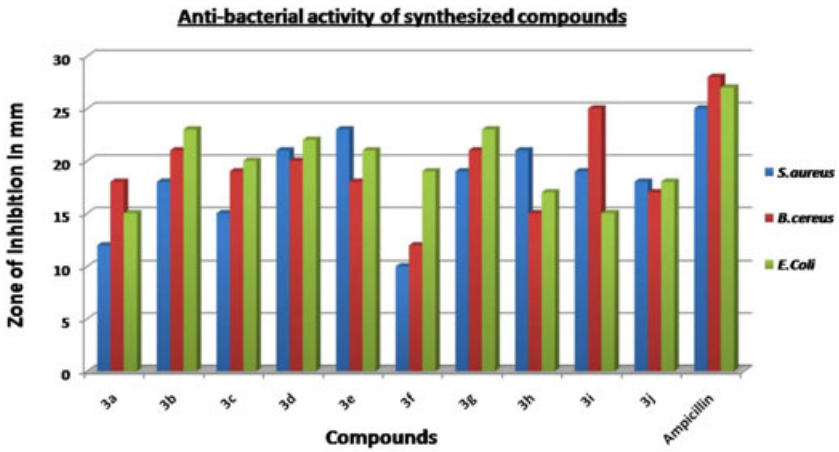
[a]Reaction conditions: 2B (20 mmol), Chloroacetyl chloride (20 mmol), catalyst (0.5-1 equiv.), solvent (20 mL), 0°C – room temp.

Scheme 1. Synthesis of 2-azetidinone derivatives from 4-amino-1,2,4-triazole.



Scheme 2. Plausible mechanism for dehydrative cyclization reaction.





Graph 1. Antibacterial activity of synthesized compounds (**3b**–**3j**). [Color figure can be viewed at wileyonlinelibrary.com]

activity was determined by disc diffusion method by measuring the zone of inhibition in millimeter. The compounds were dissolved in DMSO at a concentration of 200 ppm/mL. The antibacterial activity of each compound was compared with the standard drug Ampicillin. The results depicted in Graph 1 revealed that most of the tested compounds displayed variable inhibitory effects on the growth of tested Gram-positive and Gram negative bacterial strains. Compound **3b** showed better activity against *E. coli* (Gram-negative), while **3d** is impotent against *B. cereus* and *S. aureus* (Gram-positive). Compounds **3i** and **3b** showed an excellent activity against *B. cereus* (Gram-positive) bacterial strain.

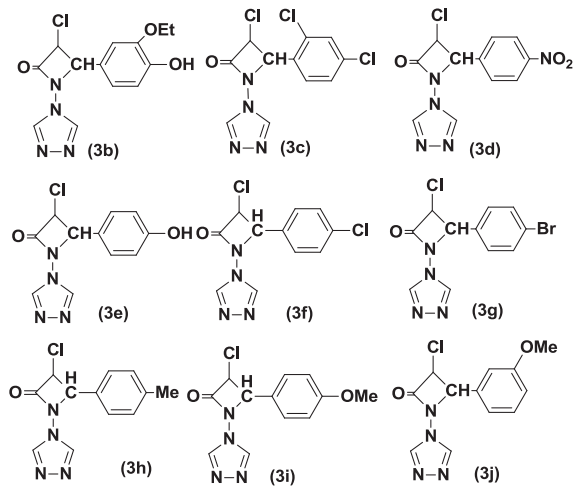


Figure 2. Structure of Synthesized Compounds (3b-3j)

CONCLUSIONS

In summary, we have reported an alternative catalyst for synthetic access to diverse 2-azetidinone derivatives of 1,2,4-triazoles in excellent yields via DABCO catalyzed dehydrative cyclization of functionalized Schiff bases with chloroacetyl chloride and evaluated their antibacterial activity. We have successfully accomplished

the synthesis of 2-azetidinone moieties (Fig. 2), for the first time promoted by DABCO as a base catalyst in EtOH used as green-solvent at low temperature. In addition, present protocol excludes toxic and hazardous solvents. This methodology involved shorter reaction times, good yields, besides being environmentally benign, inexpensive, and demanding mild reaction conditions.

EXPERIMENTAL SECTION

Methods and materials. High quality commercial reagents and anhydrous solvents were used for synthesis of all the compounds. The purity of the synthesized compounds was checked by ascending TLC on precoated silica-gel plates. Melting points were determined using an electrothermal melting point apparatus and are uncorrected. The FTIR spectra were taken on a SHIMADZU FTIR 8400 spectrophotometer in KBr. ^{1}H NMR and ^{13}C NMR spectra (data reported in δ-ppm) were recorded on Bruker Avance II-400 MHz, with TMS as internal reference in DMSO-d6. Mass of the synthesized compounds was identified by GC─MS.

General procedure for synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(substituted phenyl) azetidin-2-one (comp. 3a–3j). A solution of N-arylidene-4H-1,2,4-triazole-4-amine (0.02 mol) (Schiff bases) **2a**–**2j** in 20 mL ethanol, DABCO (0.01 mol) was added and stirred for half an hour at 0–5°C, and then chloroacetyl chloride (0.02 mol) was added drop-wise stirred the mixture for about 3-7 h. The completion of the reaction was monitored by TLC using Chloroform and MeOH (8:2) as eluent. After completion of the reaction, the solution were filtered. Filtrate was collected and solvent was evaporated. The product was washed with water, dried, and finally recrystallized from ethanol solvent. Residue contained DABCO. HCl salt was separated from the reaction mixture by simple filtration. Different 4-(4-aryl-2-azetidinonyl)-1,2,4-triazoles have synthesized using same procedure, and purified by column chromatography using chloroform: MeOH: ethylacetate (8:2:1) as eluent.

Synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(3,4,5-trimetho xyphenyl)azetidin-2-one (3a). Brownish solid, m.p. 172°C; Yield: 81%, FT─IR (KBr) 1730 cm^{-1} (>C═O stretch. of azetidinone), 3115 cm^{-1} (Ar, CH─ stretch.), 1590 cm^{-1} (C─N Stretch.) 791 cm^{-1} (CH─Cl stretch. of azetidinone), 1130 cm^{-1} (Ar─OCH_3). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.16(s, 2H, Ar─H), 3.75–3.85 (2s, 9H, ─OCH_3), 2.50 (t, 1H, HC─N), 9.02–9.10 (2s, 2H, triazole), 4.27 (d, 1H, ─CHCl) ppm; ^{13}C NMR (100 MHz, DMSO-d6, δ ppm) 127–158 (m, Ar─C), 55.9–60.2 (2s, 3C, ─OCH_3), 168.5(s,1C,C═O), 60.2 (s, 1C, CH─N), 153.8(s, 2C, C═N triazole). GC─MS for $C_{14}H_{15}N_4O_4Cl$ [M + H]$^+$, 338.04.

Synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(3-ethoxy-4-hydroxyphenyl)azetidin-2-one (3b). Light yellow solid, m.p.165°C; Yield: 72%, FT─IR (KBr) 1721 cm^{-1} (>C═O stretch. of azetidinone), 3050 cm^{-1} (Ar, CH─ stretch.), 1598 cm^{-1} (C─N Stretch.) 810 cm^{-1} (CH─Cl stretch. of azetidinone), 1080 cm^{-1} (Ar─OC_2H_5). ^{1}H NMR (400 MHz, DMSO, δ ppm): 6.6–6.9 (m, 3H, Ar─H), 1.5–4.65 (2s, 5H, ─OC_2H_5), 3.88 (m, 1H, HC─N), 9.02–9.10 (2 s, 2H, triazole), 4.27 (s, 1H, ─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 115–148 (m, 3Ar─C), 146(s, 1C, C─OEt) 147.8 (s, 1C, C─OH) 13.6, 64.5(2s, 2C, ─C_2H_5), 168.5 (s, 1C, C═O), 62.2 (s, 1C, CH─N), 153.5, 157 (2s, 2C, C═N triazole). GC–MS for $C_{13}H_{13}N_4O_3Cl$ [M + H]$^+$, 308.06.

Synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(2,4-dichlorophenyl)-azetidin-2-one (3c). Off white solid, m. p.162°C; Yield: 79%, FT─IR (KBr) 1710 cm^{-1} (>C═O stretch. of azetidinone), 3115 cm^{-1} (Ar, CH─ stretch.), 684 cm^{-1}(Ar─Cl Stretch.), 1585 cm^{-1} (C─N Stretch.), 789 cm^{-1} (CH─Cl stretch. of azetidinone). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.06–7.98(m, 3H, Ar─H), 3.85 (m, 1H, HC─N), 9.02–9.10 (2s, 2H, triazole), 4.25 (d, 1H,─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 126–154 (m, 4Ar─C), 133.6 (s, 2C, C─Cl), 168.5 (s, 1C, C═O), 62.3(s, 1C, CH─N), 68.5 (d, 1C, CH─Cl) 153.8 (s, 2C, C═N triazole). GC─MS for $C_{11}H_7N_4OCl_3$ [M + H]$^+$ 315.96.

Synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(4-nitrophenyl)-azetidin-2-one (3d). Yellow solid, m.p. 183°C; Yield: 76%, FT─IR (KBr) 1610 cm^{-1} (>C═O stretch. of azetidinone), 3137 cm^{-1} (Ar, CH─stretch.), 1575 cm^{-1} (C─N Stretch.) 808 cm^{-1} (CH─Cl stretching of azetidinone), 1397 cm^{-1} (Ar─NO_2). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.5–8.21 (2d, 4H, Ar─H), 3.85 (m, ^{1}H, HC─N), 9.02–9.10 (2s, 2H, triazole), 4.27(s, ^{1}H, ─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 120–150 (m, Ar─C), 147.95 (s, 1C, C─NO_2), 168.5(s, 1C, C═O), 62.2(s, 1C, CH─N), 72.3 (d, 1C, CHCl), 153.8 (s, 2C, C═N triazole). GC─MS for $C_{11}H_8N_5O_3Cl$ [M + H]$^+$, 293.06.

Synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(4-hydroxy phenyl)azetidin-2-one (3e). Off white solid, m.p. 190°C; Yield: 78%, FT─IR (KBr) 1729 cm^{-1} (>C═O stretch. of azetidinone), 3105 cm^{-1} (Ar, CH─stretch.), 1589 cm^{-1} (C─N Stretch.) 824 cm^{-1} (CH─Cl stretching of azetidinone), 1323 cm^{-1} (Ar─OH). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.1–7.9(2d, 4H, Ar─H), 5.26(Broard peak, 1H,-OH), 3.85 (m, 1H, HC─N), 9.02–9310 (2s, 2H, triazole), 4.27(d, 1H, ─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 115–153.8 (m, 5C, Ar─C), 158.9 (s, 1C, ─C─OH), 162.3(s, 1C, C═O), 62.2 (s, 1C, CH─N), 69.21 (s, 1C, CHCl), 152.9 (s, 2C, C═N triazole). GC─MS for $C_{11}H_9N_4O_2Cl$ [M + H]$^+$, 264.04.

Synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(4-chlorophenyl)-azetidin-2-one (3f). Yellow solid, m.p. 175°C; Yield: 80%, FT─IR (KBr) 1768 cm^{-1} (>C═O stretch. of azetidinone), 3080 cm^{-1} (Ar, CH─ stretch.), 1520 cm^{-1} (C─N Stretch.) 770 cm^{-1} (CH─Cl stretching of azetidinone), 680 cm^{-1} (Ar─Cl). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.06–7.8 (2d, 4H, Ar─H), 3.85 (m, 1H, HC─N), 9.02–9.10 (2s, 2H, triazole), 4.27(d, 1H, ─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 127–158.(m, Ar─C), 132.3 (s, 1C, ─C─Cl), 166.5 (s, 1C, C═O), 62.2(d, 1C, CH─N), 68.4 (d, 1C, CHCl), 158.4 (s, 2C, C═N triazole). GC─MS for $C_{11}H_8N_4OCl_2$ $[M + H]^+$, 282.05.

Synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(4-bromophenyl) azetidin-2-one (3g). Off white solid, m.p. 210°C; Yield: 76%, FT─IR (KBr) 1720 cm^{-1} (>C═O stretch. of azetidinone), 3115 cm^{-1} (Ar, CH─stretch.), 1590 cm^{-1} (C─N Stretch.), 791 cm^{-1} (CH─Cl stretching of azetidinone), 610 cm^{-1} (Ar─Br). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.3–7.9(2d, 4H, Ar─H), 3.85 (m, 1H, HC─N), 9.02–9.10 (2s, 2H, triazole), 4.27(d, 1H, ─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 127–138 (m,5Ar─C), 127.36 (s, 1C, ─C─Br), 168.4 (s, 1C, C═O), 62.3 (d, 1C, CH─N), 68.4 (d, 1C, CHCl), 157.3 (s, 2C, C═N triazole). GC─MS for $C_{11}H_8N_4OClBr$ $[M + H]^+$, 325.95.

Synthesis of 3-chloro-1-(4H-1,2,4-triazol-4-yl)-4-(4-methylphenyl) azetidin-2-one (3h). Off white solid, m.p.122°C; Yield: 82%, FT─IR (KBr) 1654 cm^{-1} (>C═O stretch. of azetidinone), 3129 cm^{-1} (Ar, CH─stretch.), 1596 cm^{-1} (C─N Stretch.) 805 cm^{-1} (CH─Cl stretching of azetidinone), 2937 cm^{-1} (Ar─CH_3). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.2–8.3 (2d, 4H, Ar─H), 2.58(s, 3H, ─CH_3), 3.85 (m, 1H, HC─N), 9.02–9.10 (2s, 2H, triazole), 4.27(d, 1H, ─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 126–139. (m, 5Ar─C), 20.45 (s, 1C, ─CH_3), 166.6(s, 1C, C═O), 45.8 (s, 1C, CH─N), 63.2 (d, 1C, CHCl) 144.2 (d, 2C, C═N triazole). GC─MS for $C_{12}H_{11}N_4OCl$ $[M + H]^+$, 262.06.

Synthesis of 3-chloro-1-(4H-1,2,4-triazolyl)-4-(4-methoxyphenyl) azetidin-2-one (3i). Brown solid, m.p.165°C; Yield: 72%, FT─IR (KBr) 1712 cm^{-1} (>C═O stretch. of azetidinone), 3115 cm^{-1} (Ar, CH─ stretch.), 1590 cm^{-1} (C─N Stretch.) 791 cm^{-1} (CH─Cl stretching of azetidinone), 1130 cm^{-1} (Ar─OCH_3). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.0–7.6 (2d, 4H, Ar─H), 3.83 (s, 3H, ─OCH3), 3.85 (m, 1H, HC─N), 9.02–9.10 (2s, 2H, triazole), 4.27 (d, 1H, ─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 127–160 (m, 6C, Ar─C), 55.84 (s, 3C, ─OCH_3), 161.8 (s, 1C, C═O), 153.0 (s, 2C, C═N triazole). GC─MS for $C_{12}H_{11}N_4O_2Cl$ $[M + H]^+$ 278.08.

Synthesis of 3-chloro-1-(4H-1,2,4-triazol-4-yl)-4-(3-metho xyphenyl) azetidin-2-one (3j). White solid, m.p.122°C; Yield: 75% FT─IR (KBr) 1680 cm^{-1} (>C═O stretch. of azetidinone), 3125 cm^{-1} (Ar, CH─ stretch.), 1596 cm^{-1} (C─N Stretch.) 793 cm^{-1} (CH─Cl stretching of azetidinone), 1133 cm^{-1} (Ar─OCH_3). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.0–7.6(m, 4H, Ar─H), 3.81(s, 3H, ─OCH_3), 3.85 (m, 1H, HC─N), 9.02–9.10 (2s, 2H, triazole), 4.27(d, 1H, ─CHCl) ppm; ^{13}C NMR (100 MHz, δ ppm) 117–158 (m, 6C, Ar─C), 53.27 (s, 3C, ─OCH_3), 168.8 (s, 1C, C═O), 65.7 (d, 1C, CHCl), 153.8 (s, 2C, C═N triazole). GC─MS for $C_{12}H_{11}N_4O_2Cl$ $[M + H]^+$, 278.08.

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SUPPORTING INFORMATION

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