Synthesis and characterization of 3-phenylthio/3-phenoxy-azetidine-2-one: Application of two dimensional NMR HMQC 1H-13C, COSY 1H–1H and mass spectroscopy

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ABSTRACT

A series of *cis* and *trans* 3–phenylthio/3-phenoxyazetidine-2-one **(3a-e)** have been synthesized via Schiff bases **(2a-d)** in the presence of triethylamine with phosphorusoxychloride using dry methylene chloride under nitrogen atmosphere at 0°C. The active acid chloride reacts with triethylamine to generate corresponding ketene *in situ* which further react with Schiff's base to furnish the corresponding *cis* and *trans* 3–phenylthio/3-phenoxyazetidine-2-one **(3a-e)** in moderate yields. The calculated and the found values of Carbon, Hydrogen, and Nitrogen percentage in the elemental analysis were in agreement with each other. The mass spectroscopy confirms the molecular weight of the prepared compound. Furthermore, the two dimensional NMR HMQC 1H-13C, COSY 1H–1H was used to confirm the proposed structure and the stereochemistry of the synthesized compound.
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INTRODUCTION

Nitrogen heterocyclic compounds are the basis of many essential pharmaceuticals and physiologically active natural products. The 2-azetidinone (β-lactam) ring system is the common structural feature of broad spectrum β-lactam antibiotics, including penicillins, cephalosporins, carbapenems, nocardicins and monobactams, which have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases[1]. These molecules operate by forming a covalent adduct with membrane-bound bacterial transpeptidases, which are also known as penicillin binding proteins (PBPs), involved in the biosynthesis of cell walls[2,3]. These mechanism-based inhibitors prevent the construction of cell wall and eventually lead to cell lysis and death. Moreover, due to their β-lactamase inhibitory action, 2-azetidinone-based heterocycles represent an attractive target of contemporary organic synthesis[4]. However, the efficacy of β-lactam antibiotics has been overshadowed in the last 20 years by the emergence of drug-resistant bacterial strains resulting from evolutionary responses to the widespread overuse and abuse of antibiotics in clinical traits[5].

Consequently, strategies to address this challenge lead to the design of improved versions of β-lactams with novel

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modes of action. It has been reported that introduction of different substituent's to four-membered β-lactam nucleus tends to exert profound influence in conferring promising biological activities in these molecules[6,7].

The recent discoveries of some 1,3,4-trisubstituted-β-lactams as new potent cholesterol absorption inhibitors[8], human cytomegalovirus protease inhibitors[9], and thrombin inhibitors[10], justify a renewed interest in these compounds[11,12]. Furthermore, interest in the chemistry, synthesis and biology of the 2-azetidinone pharmacophore continues to be fuelled by their wide range of biological properties such as antibacterial[13,14] antihyperglycemic[15], anti-tumour[16], anti-HIV[17], anti-inflammatory and analgesic activities[18]. In addition, 2-azetidinones also display a broad range of enzyme-inhibitory activities[19-23].

Looking at the promising antimicrobial activity of 2-azetidinone[24,25] as well as 1,3-diketoamino analogues[26], it was thought of interest to combine 2-azetidinone and 1,3-diketoamino analogues together in a molecular framework of hydrazones and imines. Such a combination was the chief success of the present study. The biological activity of the synthesized compounds is in progress in our laboratory.

EXPERIMENTAL

Sample characterization

All solvents were distilled / dried prior to use, when this seemed necessary by standard methods. All solvent extracts were dried over anhydrous sodium sulphate unless otherwise specified. All the melting points are uncorrected and are expressed in degree (°C), using melting point \SMP$_3$1. The FT-IR spectra were recorded on shimadzu FT-IR affinity 1 spectra. The ^{13}C NMR; ^{1}H-^{13}C Heteronuclear 2D Correlation Spectroscopy (Cosy), HETCOR; ^{1}H-^{1}H Homonuclear 2D Correlation Spectroscopy (Cosy) were recorded using Bruker DRX system AL 500 (500 MHz). The mass spectrums were recorded at 70 eV using agalint technologes Spectrum 5973.

Preparation of schiff base (2a-d)

General procedure

A mixture of an equimolar amount (0.01 mol) of appropriate aromatic amine and an aromatic aldehyde

in 10 mL of absolute ethanol and one drop of glacial acetic acid was heated in water bath at (70-80°C) for 30 min. The progress of the reaction was checked by thin layer chromatography (TLC). After completion the solvent was evaporated then the product was recryastalized from a suitable solvent.

Preparation of 3-phenylthio/3-phenoxyazetidine-2-one (3a-e)

Trans-1-(4-*N*,*N*-diethylamino)phenyl-3-phenyl-thio-4-(4-methoxyphenyl) azetidine-2-one (3a)

To a mixture of phenylthioacetic acid (0.89 g, 1.5 mmol), imine **(2a)** (1 g, 1.0 mmol) and triethylamine (1.07 g, 3 mmol) in dry dichloromethane 40 mL at 0°C under N$_2$ atmosphere, a solution of POCl$_3$ (0.81g, 1.5 mmol) in dry dichloromethane 20 mL was added dropwise. The mixture was stirred overnight at room temperature. Thereafter, the contents were washed successively with 1N HCl (30 mL), water (3×30 mL), 5 % NaHCO$_3$ 30 mL and finally with brine 30 mL. The organic layer was separated and dried over anhydrous sodium sulphate (Na$_2$SO$_4$). The solvent was removed under reduced pressure and the crude product was column chromatographed over silica gel using ethyl acetate-hexane (3:7) as eluent. The solvent evaporation furnished pure β-lactam **(3a)**. Yield 70%, m.p:120-122°C, FT-IR (KBr disk): 1741 cm^{-1} ; MS, M$^+$ 432 :+44%; ^{1}H NMR(CDCl$_3$) ppm: 0.9(t, 6H, -CH$_2$CH$_3$), 3.73 (s, 3H, -OCH$_3$), 3.20 (q, 4H, - CH$_2$CH$_3$), 4.94 (d, 1H, J = 2.4 Hz C$_3$-H), 4.59 (d, 1H, J = 2.2Hz C$_4$-H), 6.52-7.46 (*m*, 13H, aromatic). ^{13}C NMR (CDCl$_3$/DMSO) ppm: 162.35, 160.36, 145.44, 133.42, 131.73, 130.07, 129.16, 128.99, 128.34, 126.35, 119.81, 115.18, 112.59, 62.71, 60.19, 55.99, 44.47, 31.20. Elemental analysis (C.H.N): (C$_{26}$H$_{28}$N$_2$O$_2$S) Calculation: C, 72.22 %; H, 6.48 %; N, 6.48 %; Found: C, 72.18 %; H, 6.45 %; N, 6.41 %.

Cis-1-(4-*N*,*N*-diethylamino)phenyl-3-phenoxy-4-(4-chlorophenyl) azetidine-2-one (3b)

To a mixture of phenoxyacetic acid (0.79 g, 1.5 mmol), Imine **(2b)** (1.0 g, 1.0 mmol) and triethylamine (1.05 g, 3.0 mmol) in dry dichloromethane (40 mL) at 0°C under N$_2$ atmosphere, a solution of POCl$_3$ (0.80 g, 1.5 mmol) in dry dichloromethane (20 mL) was added dropwise. The reaction mixture after comple-

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tion of reaction was worked up as usual. The crude product was column chromatographed over silica gel using ethyl acetate – hexane (3:7) as eluent, a solvent evaporation furnished pure β-lactam **(3b)**. Yield = 64.75 %, m.p °C (140-142), FT-IR (KBr disk) : 1743 cm^{-1} ; MS,M$^+$ 420 :+48 %; ^{1}H NMR (CDCl3): 1.01 (*t*, 6H, -CH$_2$CH$_3$) 3.20(*q*, 4H, -CH$_2$CH$_3$), 5.61 (*d*, 1H, *J* = 4.8 Hz,, C$_4$-H), 5.72 (*d*, 1H, *J* = 4.8 Hz, C$_3$-H), 6.60-7.51 (*m*, 13H, aromatic), ^{13}C NMR (CDCl$_3$ / DMSO) ppm: 162.02, 158.33, 145.65, 133.03, 131.77, 131.03, 129.05, 127.03, 123.43, 120.01, 115.04, 112.82, 81.02, 61.02, 42.10, 12.20. Elemental analysis (C.H.N): C$_{25}$H$_{25}$O$_2$N$_2$Cl Calculation: C, 71.34 &; H, 5.94 %; N, 6.65 %; Found: C, 71.23 %; H, 5.87 %; N, 6.61 %.

Cis-1-(4-*N*,*N*-diethylamino)phenyl-3-phenoxy-4-(4-methoxy phenyl) azetidine-2-one (3c)

To a mixture of phenoxyacetic acid (0.80 g, 1.5 mmol), Imine **(2a)** (1.0 g, 1.0 mmol), and triethylamine (1.07 g, 3.0 mmol) in dry dichloromethane 40 mL at 0°C under N$_2$ atmosphere, a solution of POCl$_3$ (0.81 g, 1.5 mmol) in dry dichloromethane (20 mL was added dropwise. The reaction of the mixture after completion of reaction was worked up as usual. The crude product was column chromatographed over silica gel using ethyl acetate – hexane (3:7) as eluent, solvent evaporation furnished pure β-lactam **3c**. Yield= 68.0 %, m.p °C (119-120), FT-IR (KBr disk) : 1741 cm^{-1}; ^{1}H NMR (CDCl3) ppm: 0.99 (*t*, 6H, -CH$_2$CH$_3$), 3.72 (*s*, 3H, -OCH3), 3.30 (*q*, 4H, -CH$_2$CH$_3$), 5.72 (*d*, *J* = 2.7 Hz, 1H, C$_3$-H), 5.61 (*d*, 1H, *J* = 2.7 Hz, C$_4$-H), 6.60-7.40(*m*, 13H, aromatic), ^{13}C NMR (CDCl$_3$ / DMSO) ppm: 162.06, 160.09, 158.55, 145.08, 131.44, 128.82, 128.04, 122.05, 120.01, 116.04, 115.02, 113.45, 81.20, 61.10, 55.60, 43.80, 12.03. Elemental analysis (C.H.N): C$_{26}$H$_{28}$N$_2$O$_2$S Calculation: C, 72.22 %; H, 6.48 %; N, 6.48 %; Found: C, 72.18 %; H, 6.45 %; N, 6.41 %.

Cis-1-(4-methylphenyl)-3-phenoxy-4-(4-*N*,*N*-dimethylamino)phenylazetidine-2-one (3d)

To a mixture of phenoxyacetic acid (0.95 g, 1.5 mmol), imine **(2c)** (1.0 g, 1.0mmol) and triethylamine (1.27g, 3mmol) in dry dichloromethane 40 mL at 0°C under N$_2$ atmosphere, a solution of POCl$_3$ (0.96 g, 1.5

mmol) in dry dichloromethane 40 mL was added dropwise. The reaction of the mixture after completion of reaction was worked up as usual. The crude product was separated by column chromatograph over silica gel, using ethyl acetate – hexane (3:7) as eluent, solvent evaporation furnished pure β-lactam **(3d)**. Yield = 50. %, m.p °C (116-118); FT-IR (KBr disk): 1753 cm^{-1}; ^{1}H (CDCl$_3$) ppm: 3.35 (*s*, 3H, CH$_3$), 2.25 (*d*, 6H, CH3), 6.95-7.54 (*m*, 13H, aromatic), ^{13}C NMR (CDCl$_3$ / DMSO) ppm: 167.18, 158.70, 136.74, 133.51, 130.37, 129.95, 122.03, 120.61, 115.55, 68.02, 21.31. Elemental analysis (C.H.N): C$_{27}$H$_{28}$N$_2$O$_2$ Calculation: C, 78.64 %; H, 6.79%; N, 6.79%; Found: C, 72.58 %; H, 6.74 %, N, 6.71 %.

Trans-1-(4-*N*,*N*-diethylamino)phenyl-3-phenylthio-4-(4-chloro phenyl) azetidine-2-one (3e)

This was prepared from phenylthioacetic acid (0.87 g, 1.5 mmol), imine **(2c)** (1.0 g, 1.0 mmol), triethylamine (1.46 mL, 3.0 mmol) and POCl$_3$ (0.48 mL, 1.5 mmol). Following the procedure reported in section 2.3.1. The residue obtained after usual workup and chromatographic purification furnished the desired β-lactam **(3e)** (1.24 g, 65.0 %) as a crystalline solid and its structure was confirmed on the basis of the following data: Yield = 65%, m.p. °C (124-126); FT-IR (KBr disk) : 1753 cm^{-1}; ^{1}H-NMR (CDCl$_3$) ppm: 1.1 (t, 6H, 2×CH$_3$), 3.3 (q, 4H, 2×CH$_2$), 4.1 (d, 1H, *J* = 2.19 Hz, C$_4$-H), 4.7 (d, 1H, *J* = 2.11 Hz, C$_3$-H), 6.7-7.6 (m, 13H, aromatic); ^{13}C-NMR (CDCl$_3$) ppm: 12.4, 44.4, 61.3, 63.4, 112.2, 119.2, 126.1, 126.3, 127.1, 128.1, 129.1, 132.9, 132.4, 135.6, 144.1, 162.6; Elemental analysis (C.H.N): C$_{25}$H$_{25}$N$_2$OSCl Calculation: C, 68.72 %; H, 5.72 %; N, 6.41 %; Found: C, 68.59 %; H, 5.69 %; N, 6.35 %.

RESULTS AND DISCUSSION

The β-lactam synthesis

Taking a lead from earlier studies[27], it was considered important to utilize ketene-imine cyclization in the presence of triethylamine using C$_3$–C$_4$ bond formation of β-lactam. The key steps for the synthesis of 3-phenylthio/3-Phenoxy substituted β-lactams of type **A** and B are shown in scheme 1, while R^1 and R^2 are shown in TABLE 1.

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The key step for the synthesis of 3-phenylthio/3-phenoxyazetidine-2-ones **(3a-e)** involves the treatment of imines **(2a-d)** with phenylthioacetic acid/phenoxyacetic acid. This reaction was done in presence of triethylamine and phosphorusoxychloride using dichloromethane as a solvent under dry N_2 atmosphere as shown in scheme 2. The R, R^1, and R^3 are shown in TABLE 2.
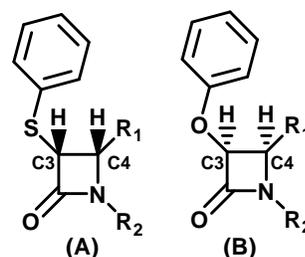
TABLE 2 shows the various type of Schiff's bases **(2a-d)** used in the β-lactam formation **(3a-e)**. It was prepared by reacting equimolar amounts of appropriate aromatic aldehydes and aromatic amines either in dry methylene chloride in the presence of molecular sieves (4A°) or under refluxed condition in ethanol, as shown in scheme 3.

FT-IR spectroscopy

In general the FT-IR spectra of these compounds **(3a-e)** showed strong stretching absorption band at 1743-1658 cm^{-1} for (C=O) as shown figure 1. The FT-IR absorption frequencies of carbonyl groups (C=O) depended upon the nature of substituent's at adjacent nitrogen atom .So the substitution of the phenyl ring by electron-donating groups such as *N,N*-dimethylamino, methoxy or *N,N*-diethylamino group lowered the absorption frequencies where as the substitution by an electron-withdrawing chloro group increased the absorption frequency. A similar trend in FT-IR absorption frequency is reported[28-30].

Scheme 1 : The general structure of synthesized β-lactams. (A) 3-phenylthio substituted β-lactam. (B) 3-Phenoxy substituted β-lactam. The C_3–C_4 bond formation of β-lactam is also shown R^1 and R^2 are shown in TABLE 1
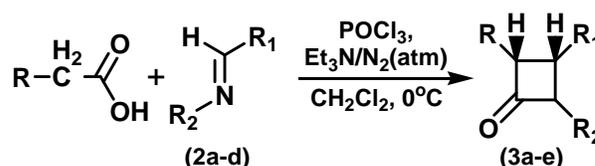
Scheme 2 : The reaction of acid derivatives with schiff bases to produce azetidine-2-ones (β-lactam) ring. The *cis* structure was shown only
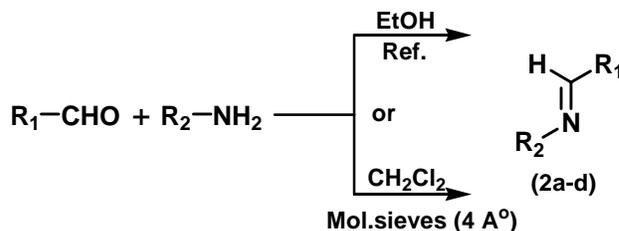
Scheme 3 : The two strategies for the synthesis of Schiff's bases (2a-d). In both strategies equimolar amounts of appropriate aromatic aldehydes and amines were used

TABLE 1 : The physical properties of phenylthio/3-Phenoxy substituted β-lactams (3a-e). The R, R^1, and R^3 are shown. Melting point (m. p. °C) and the percentage of yield with the stereo chemistry of the derivatives are also shown

Entry	R	R^1	R^2	Yield (%)	m.p. (°C)	Stereo chemistry
3a	Ph–S—	—(C₆H₄)—OCH₃	—(C₆H₄)—N(CH₃)(CH₃)	70	122–122	*trans*
3b	Ph–O—	—(C₆H₄)—Cl	—(C₆H₄)—N(CH₃)(CH₃)	64.75	140–142	*cis*
3c	Ph–O—	—(C₆H₄)—OCH₃	—(C₆H₄)—N(CH₃)(CH₃)	68	119–120	*cis*
3d	Ph–O—	—(C₆H₄)—N(CH₃)(CH₃)	—(C₆H₄)—CH₃	50	116–118	*cis*
3e	Ph–S—	—(C₆H₄)—Cl	—(C₆H₄)—N(CH₃)(CH₃)	65	124–126	*trans*

TABLE 2 : The R^1 and R^2 structures of aromatic Schiff's bases (2a-d) are shown. The percentage of yield, m.p. °C, and the stereo chemistry of the derivatives are also shown

No.	Schiff's base	Yield %	m. p. °C	R^1	R^2
1	2a	103-105	80	⬡—OCH$_3$	⬡—N(CH$_3$)(CH$_3$)
2	2b	101-103	75.2	⬡—Cl	⬡—N(CH$_3$)(CH$_3$)
3	2c	124-126	75.6	⬡—N(CH$_3$)(CH$_3$)	⬡—CH$_3$
4	2d	127-129	87.14	⬡—Cl	⬡—CH$_3$

Figure 1 : The FT-IR spectra of 1-(4-*N,N*-diethylamino)phenyl-3-phenoxy-4-(4-chloro-phenyl) azetidine-2-one (3b). The structure of the compound is shown inside
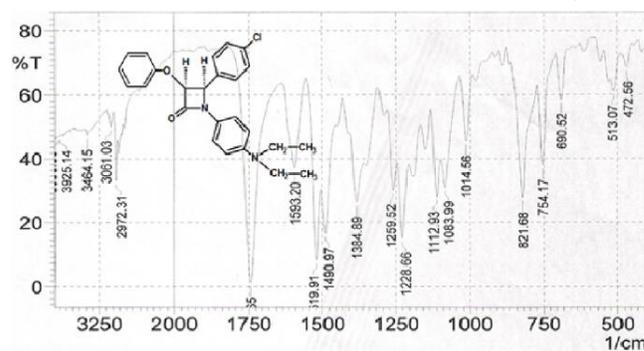
^{1}H-NMR spectroscopy

The protons at C$_3$-H and C$_4$-H positions (Scheme 1) of the ring have been observed to resonate from 4.93 to 5.61 ppm[31]. The ^{1}H-NMR spectroscopy is the most powerful tool for the determination of relative stereochemistry at C$_3$-H and C$_4$-H positions of 3-phenylthio/3-phenoxyazetidine-2-ones. The coupling constant for vicinal protons at C$_3$-H and C$_4$-H is 4.5-6.0 Hz for *cis* derivatives and 2.0-2.5 Hz for *trans*
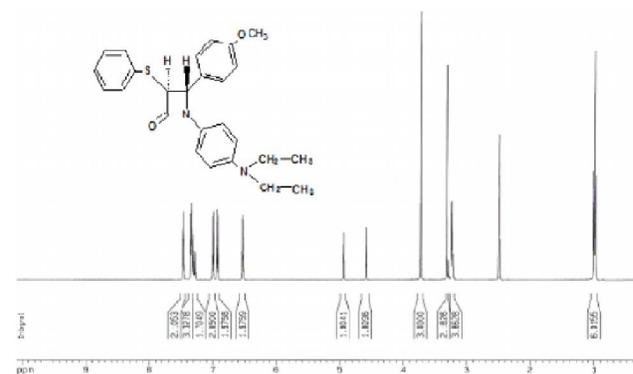

Figure 2 : The ^{1}H-NMR spectra ^{1}H NMR spectra of 1-(4-*N,N*-diethylamino)phenyl-3-phenylthio-4-(4-methoxyphenyl) azetidine-2-one (3a). The structure of the compound is shown inside

TABLE 3 : The chemical shifts of ^{1}H NMR and ^{13}C NMR spectral for 3-phenylthio/3-phenoxy azetidine-2-one in CDCl$_3$/DMSO (ppm)

Comp.	Chemical shifts (ppm) (CDCl$_3$/DMSO)	
	^{1}H NMR	^{13}C NMR
3a	6.52-7.46 (*m*,13H,aromatic), 4.94(*d*,1H,C$_3$-H), 4.59 (*d*,1H, C$_4$-H), 3.73 (*s*,3H, -OCH$_3$), 3.20 (q,4H,-CH$_2$CH$_3$) 0.9 (*t*,6H,-CH$_2$CH$_3$)	162.35, 160.36, 145.44, 133.42, 131.73, 130.07, 129.16, 128.99, 128.34, 126.35, 119.81, 115.18, 112.59, 62.71, 60.19, 55.99, 44.47, 31.20
3b	6.60-7.51(*m*,13H,aromatic), 5.72 (*d*, 1H, C$_3$-H), 5.61 (*d*, 1H, C$_4$-H), 3.20 (*q*,4H, -CH$_2$CH$_3$), 1.01 (*t*, 6H, -CH$_2$CH$_3$)	162.02,158.33,145.65,133.03,131.77,131.03,129.05,127.0 3,123.43,120.01,115.04,112.82,81.02,61.02,42.10,12.20
3c	6.60-7.40 (*m*, 13H, aromatic), 5.72 (*d*, 1H, C$_3$-H), 5.61 (*d*, 1H, C$_4$-H), 3.72 (*s*, 3H, -OCH3) 3.30 (*q*, 4H, -CH$_2$CH$_3$) 0.99 (*t*, 6H, -CH$_2$CH$_3$)	162.06, 160.09, 158.55, 145.08, 131.44, 128.82, 128.04, 122.05, 120.01, 116.04, 115.02, 113.45, 81.20, 61.10, 55.60, 43.80, 12.03
3d	6.95-7.54 (*m*, 13H, aromatic), 3.35 (*s*, 3H, CH$_3$), 2.25 (*d*, 6H, CH3)	167.18, 158.70, 136.74, 133.51, 130.37, 29.95, 122.03, 120.61 115.55, 68.02,21.31
3e	7.09-7.44 (*m*, 13H, aromatic), 2.24 (*s*, 3H, CH$_3$)	167.40, 137.21, 136.81, 133.30, 130.01, 129.87, 128.94, 126.85, 120.05, 38.33, 21.30

derivatives, the stereochemistry of compound (**3a**) was found to be *trans*, while the compound (**3b**) was *cis*. The ^{1}H-NMR spectra of these compounds (**3a-e**) showed two singlets around δ 4.93-5.72 and 4.58-5.61 ppm, corresponding to C$_3$-H and C$_4$-H positions of the β-lactam ring .The ^{1}H-NMR spectra of the compounds showed 13 aromatic protons at 6.52-7.54 ppm as shown in figure 2 and TABLE 3.

The ^{13}C NMR spectroscopy study

The ^{13}C-NMR spectra of azetidine-2-ones showed the typical carbonyl resonance at chemical shifts 162.02-167.40 ppm. However, the values outside this range are possible if strong electron withdrawing or electron donating groups are present on the adjacent carbon atoms. For example, the ^{13}C-NMR spectra of 4-(4-chlorophenyl) azetidine-2-one (**3e**) (not shown) showed

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the carbonyl carbon signal at chemical shifts 167.40 ppm where as the carbonyl group in 1-(4-*N*,*N*-diethylamino)phenylazetidine-2-one **(3a)** (Figure 3, TABLE 3) resonated at chemical shifts of 162.35 ppm[32].

The 2D NMR spectroscopy study

The 2D NMR COSY [1]H-^{1}H studies led to assignment of signals to protons and protons in the azetidine-2-ones **(3a-e)**.The application of COSY using ^{1}H-^{1}H COSY NMR spectra in characterization of such compounds is discussed in succeeding paragraphs by taking representative examples of **(3a)**, **(3b)**, and **(3c)**.

As stated in the ^{1}H and ^{1}H NMR subsections, the characterization of **(3a)** (Figure 4a, 4b) required assignment of proton signals at chemical shifts 4.94 and 4.58 ppm, which showed a correlation with the proton signals at 4.58, 4.59, 4.93, 4,94 ppm; thus the signal could be assigned to the C_3-H and C_4-H positions of azetidine-2-ones.
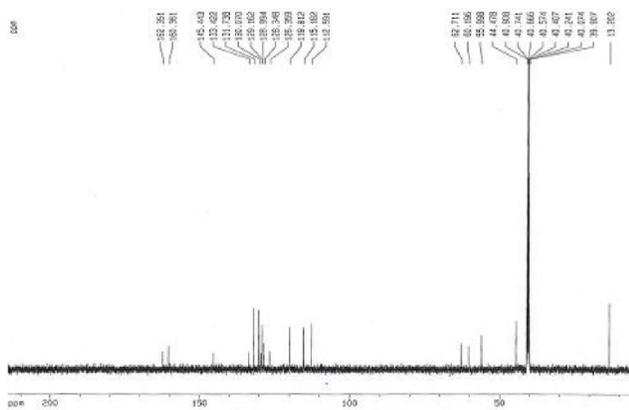
Also, the COSY [1]H-^{1}H spectrum of **(3a)** showed the correlation for each aromatic proton signal at 6.52-7.46 ppm with chemical shifts 6.52, 6.54, 6.91, 6.93, 6.99, 7.00, 7.26, 7.27, 7.28, 7.29, 7.30, 7.32, 7.33, 7.34, 7.44, 7.46 ppm. This led to the assignment of this

Figure 4 : COSY [1]H-^{1}H spectra of 1-(4-*N*,*N*-diethylamino) phenyl-3-phenylthio-4-(4-methoxyphenyl)azetidine-2-one (3a). The structure of the compound is shown inside

Figure 3 : The ^{13}C NMR spectra of 1-(4-*N*,*N*-diethylamino)phenyl-3- phenylthio-4-(4-methoxyphenyl) azetidine-2 one (3a)
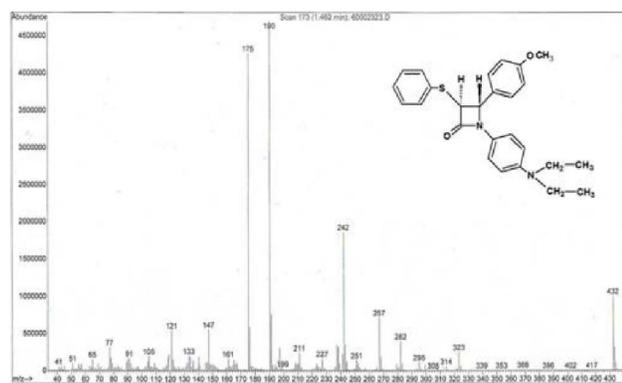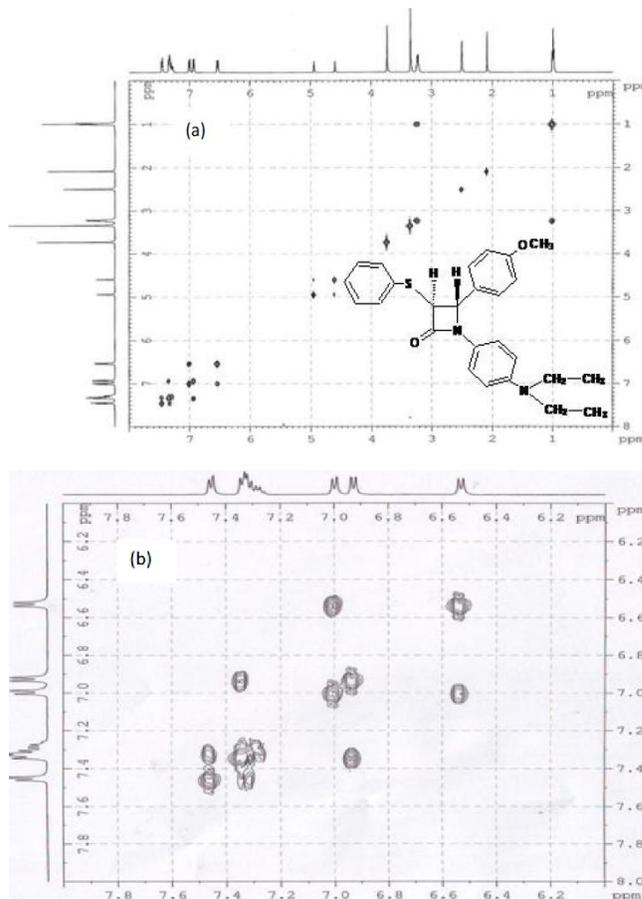

Figure 5 : The mass spectra of 1-(4-*N*,*N*-diethylamino) phenyl-3-phenylthio-4-(4-methoxyphenyl) azetidine-2-one (3a). The structure of the compound is shown inside
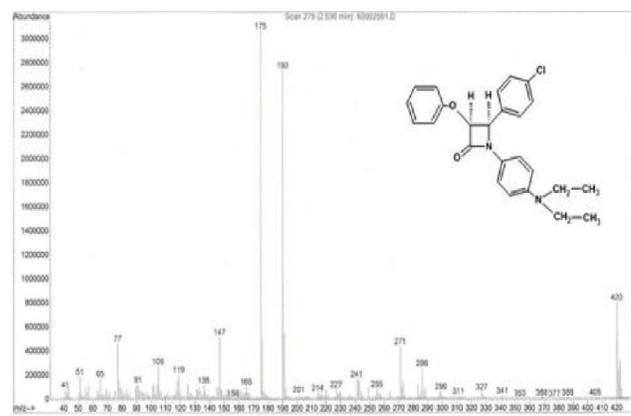

Figure 6 : The mass spectra of 1-(4-*N*,*N*-diethylamino)phenyl-3-phenoxy-4-(4-chloro-phenyl) azetidine-2-one (3b). The structure of the compound is shown inside

signal to the aromatic protons.

The 2D NMR HMQC ^{1}H-^{13}C spectroscopic study

The 2D NMR HMQC ^{1}H-^{13}C spectra of **(3c)** shows the correlation of the methoxy proton in compound **(3c)** signal at chemical shifts 3.72 ppm with carbon signal at chemical shifts 55.60 ppm, which led to the assignment of this signal to the methoxy group carbon. The HMQC spectrum showed the correlation of proton signals at chemical shifts 5.60-5.61 and 5.71-5.72 ppm with carbon signals at chemical shifts 61.02 and 81.02, respectively[33,34].

The chemical shifts of aromatic protons from 6.60 to 7.40 ppm correlated with carbon aromatic signals at 112.06, 113.05, 114.02, 118.72, 122.84, 125.22, 125.75, 130.22, and 143.02 ppm (see supplementary data 1, 2, 3, 4, and 5). All these correlation are shown in scheme 4.
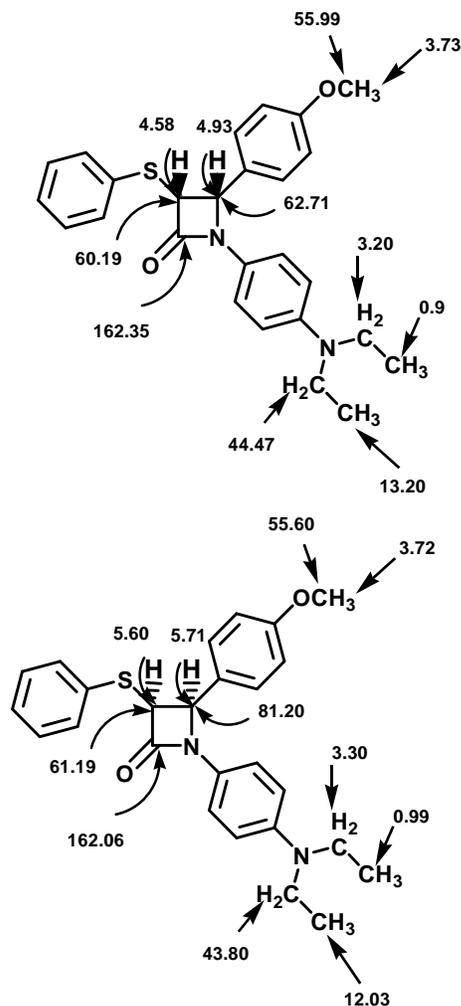
Scheme 4 : The ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY of compounds (3a) and (3c). The values of the chemical shifts are also shown
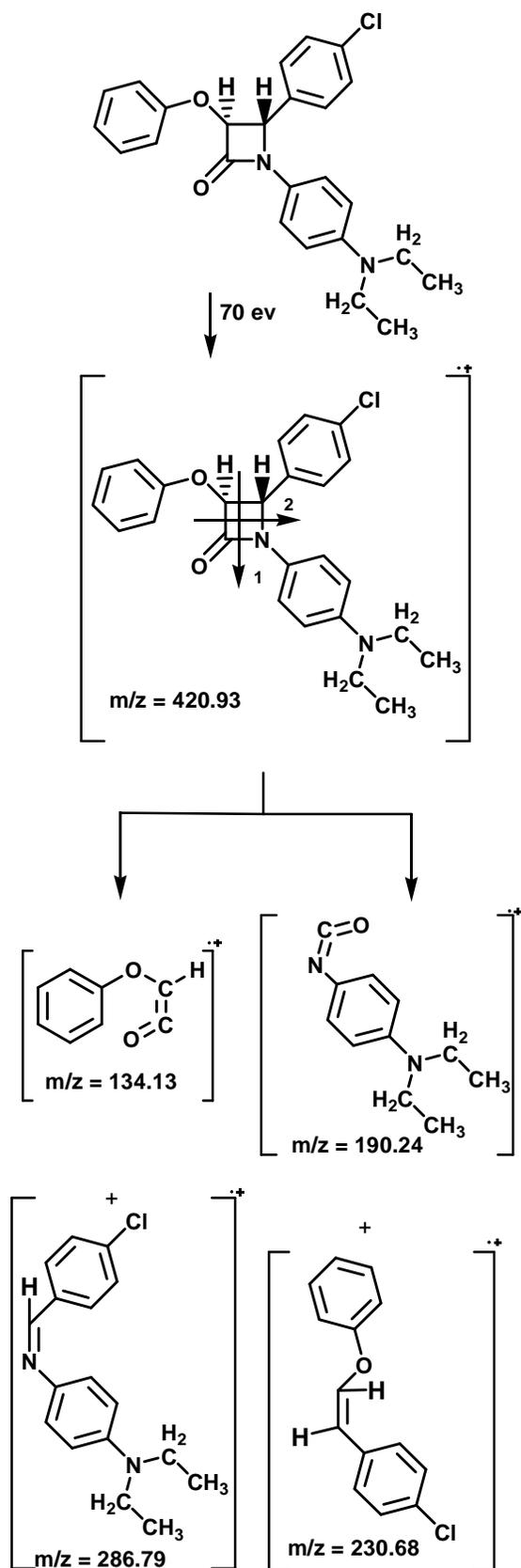
The mass spectroscopic study

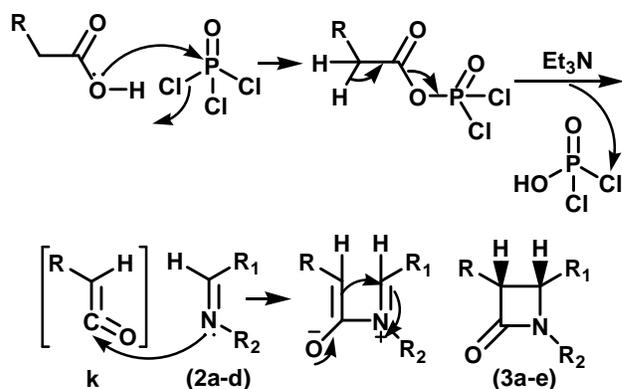The mass spectra of the compounds **(3a)** and **(3b)**
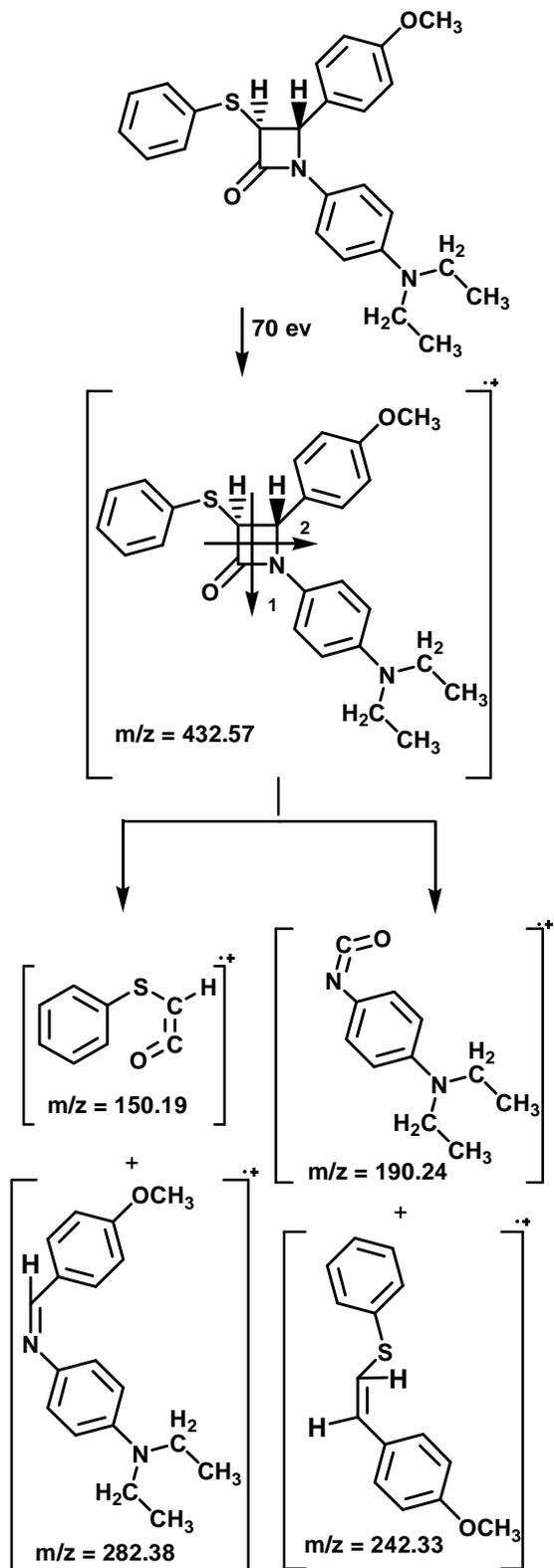
Scheme 5 : The fragmentation mechanism of compounds (3a) which show the fragment of ketene

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Scheme 6 : The fragmentation mechanism of compounds (3b) which show the fragment of ketene

Scheme 7 : The proposed mechanism suggested the formation of ketene (k) *in situ* which attack by corresponding Schiff's base (2a-d) yielding corresponding β-lactam (3a-e). The R, R¹ and R³ are shown in TABLE 1

showed a molecular ion peak corresponding to the particular compound (M+, 432, 18%, 420, and 21%). The fragmentation of the 3-phenylthio/3-phenoxy azetidine-2-one leading to the imine (282, 7%, 286, 6.6%) base peak and the corresponding ketene (150, 1.5%, 134, 2%), also the fragmentation of this compound showed the alkene peaks (242, 34%, 230, 1.4%) and isocyanates (190, 100%, 190, 72%). The fragmentation mechanism of compounds **(3a)** (Figure 5) and **(3b)** (Figure 6) were shown in scheme 5 and 6 respectively[35].

The proposed mechanism

To synthesize 3-phenylthio/3-phenoxyazetidine-2-ones **(3a-e)**, it is believed that the active acid chloride formed from an appropriate acid with $POCl_3$, reacted with triethylamine to give the corresponding ketene (k) *in situ*. This ketene (k) was subsequently reacted with various Schiff bases **(2a-d)** and afforded the corresponding β-lactam **(3a-e)** in moderate yields. The proposed mechanism for their formations was shown in scheme 7.

CONCLUSION

A new series of 3–phenylthio/3-phenoxyazetidine-2-one have been synthesized via Schiff bases. The reaction was done in the presence of $POCl_3$ and triethylamine both have assisted to generate a ketene *in situ*. The mass spectroscopy confirms the molecular weight of the β-lactam compounds. The FT-IR shows the presence of the lactam carbonyl group, while the ¹H-NMR

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spectroscopy was determined the stereochemistry at C_3-H and C_4-H positions of 3-phenylthio/3-phenoxyazetidine-2-ones, at *cis* and *trans* position. The 2D NMR HMQC ^{1}H-^{13}C spectra of **3c** had shown the correlation between the methoxy protons.

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