SYNTHESIS AND CHARACTERIZATION OF SOME NEW MONOCYCLIC β- LACTAMS

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Abstract

Two compounds of 3-alkyl azetidine-2-one have been synthesized via Schiff bases in the presence of triethylamine with phosphorusoxychloride The active acid chloride react with triethylamine to generate corresponding ketene *in situ* which further react with Schiff's base to furnish the corresponding 3-alkyl azetidine-2-one in moderate yields. The structures of the newly synthesized compounds were confrmed by 2D NMR(HMQC, ^{1}H-^{13}C,COSY^{1}H-^{1}H) and mass spectroscopy,which showed the proposed stereochemistry of this derivatives

تخليق وتشخيص لبعض مركبات احاديه حلقه البيتالاكتام الجديده

محمود شاكر مكطوف التميمي

العراق ذي قار ناصريه جامعه ذي قاركليه العلوم قسم الكيمياء

الملخص

تضمنت الدراسه تخليق وتشخيص بعض مركبين احاديه حلقه البيتاكتام الرباعيه وهي 3- (3-بروبيل فنيل) ازيتيدين-2-ون التي تم تحضيرها من تفاعل حامض الفاليرك اسد مع بعض قواعد شف بوجود ثلاثي اثيل امين واوكسي كلوريد الفسفور في كلوريد الاثيلين الجاف عند درجه الصفر المئوي.حيث ينتج كيتين والذي يتفاعل مع قواعد شف ليعطي الناتج ازيتيدين-2-ون.شخصت المركبات باستخدام اطياف تحت الحمراء وطيف الكتله ومطيافيه الرنين النووي المغناطيسي البروتوني وكاربون 13 واقتران طيف الرنين البروتوني البروتوني والبروتوني وكاربون 13.

Introduction

The β -lactam skeleton is the key structural unit of the most widely employed class of antibacterial agents, the β -lactam antibiotics **1**. The constant need for new drugs displaying broader antibacterial activity and the necessity for newβ -lactam antibiotics to combat the microorganisms that have built up resistance against the most traditional drugs,**2** have maintained the interest of organic chemists in β -lactams for decades. The major cause of bacterial resistance to the antibiotics is a hydrolytic cleavage of the β -lactam ring byβ -lactamase enzyme. As a consequence, several stable new b-lactams as well asβ -lactamase inhibitors have been developed. Apart from the antibacterial agents,**1–3**β -lactams are also being increasingly used as synthons for the synthesis of a variety of pharmaceutically useful products.**4** An important class of compounds, which act as hydrolytic deactivators of b-lactamase enzyme, contains 3-alkylideneβ - lactam subunit (1). Also, the discovery of cholesterol absorption inhibition property associated with trans-3-alkylazetidin-2-ones **5** 2 and 3 (Fig. 1) renewed the interest in the synthesis of C-3-alkyl-substituted-b-lactams. Large number of β -lactams has been synthesized to study the structure activity relationship (SAR) in cholesterol absorption inhibitors. **6** In most of the synthesis, the azetidinone ring is constructed either by enolate–imine cyclocondensation**5,6,7** of appropriately substituted esters and imines or by a Staudinger ketene–imine cycloaddition reaction.**7,8** :

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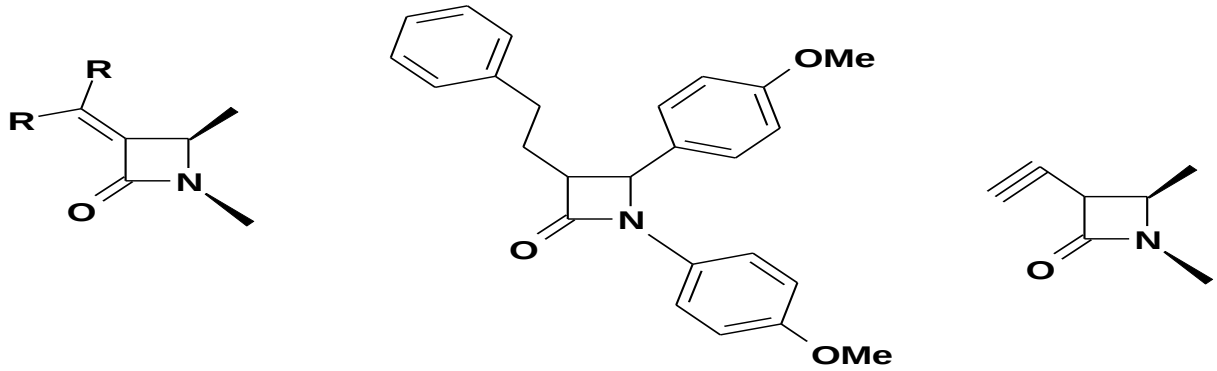


Fig 1

RESULTS AND DISCUTTION

Taking a lead from recent earlier studies **9,10,11,**12 The work here to cused on utilization of ketene-imine cyclization in the presence of triethylamine for the synthesis of 3-(3-phenylpropyl)azetidine-2-ones substituted of β- lactam (Fig 2) .

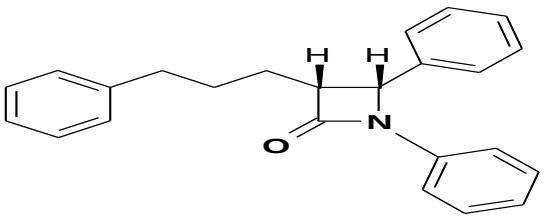
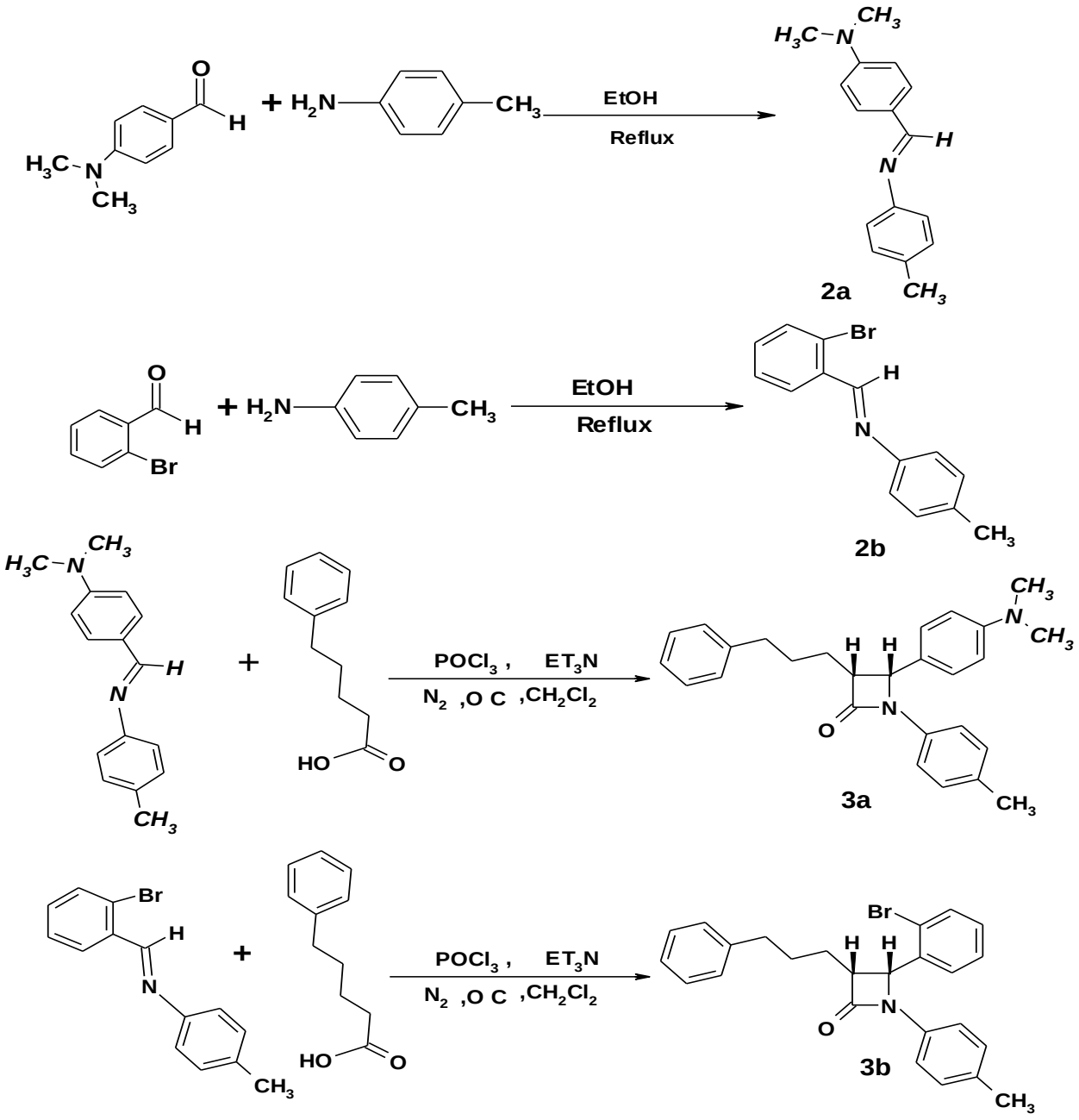


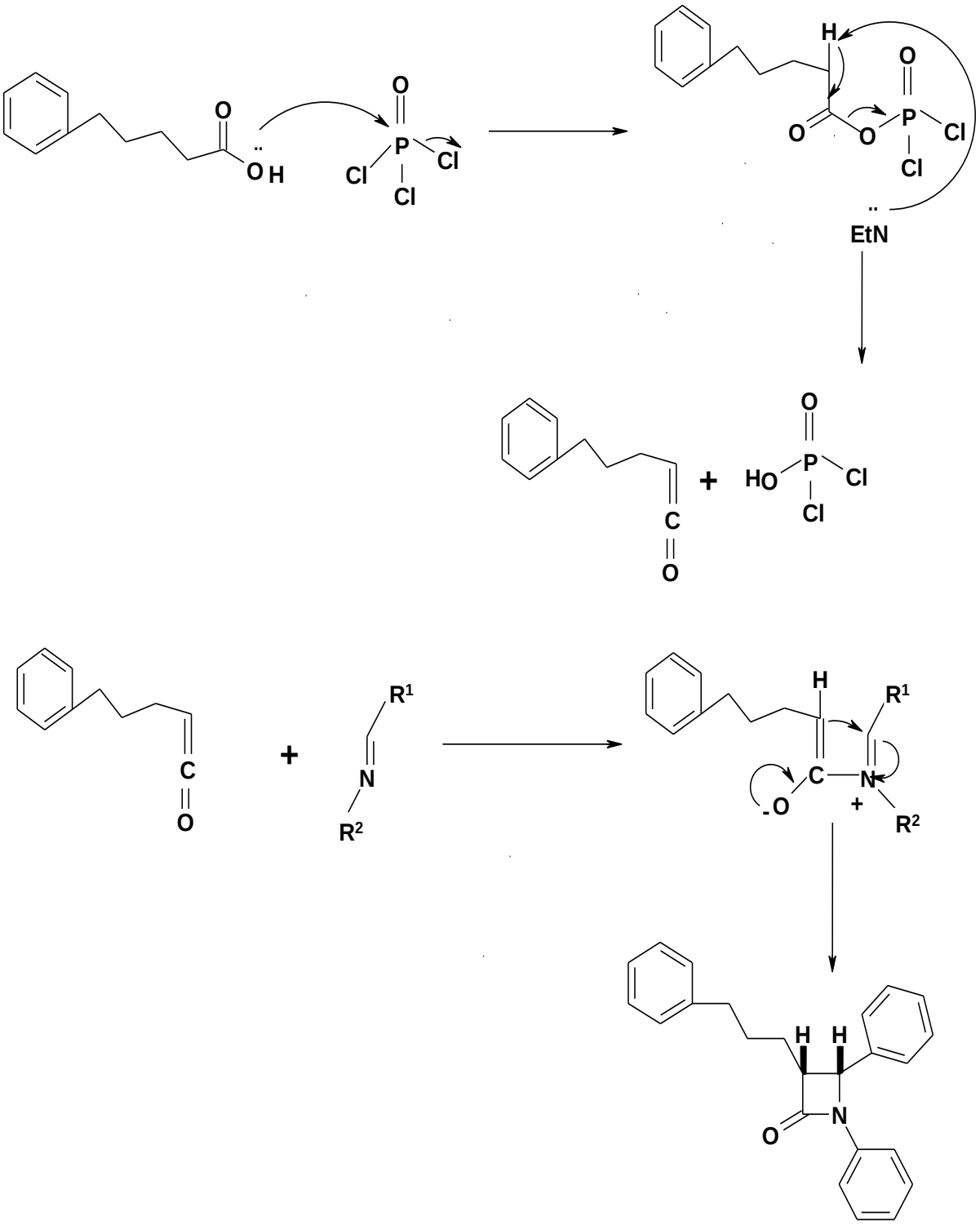
Fig 2

In view of the associated biological activity and utility in organic synthesis, the synthesis of 3-(3-phenylpropyl)azetidine-2-one performed. The key step involved the treatment of the imine with 5-phenylvaleric acid by using triethylamine in the presence of phosphorusoxychloride in dry methylenechloride under nitrogen to afford azetidine-2-one as shown in (scheme 1)



Scheme 1

The active acid chloride reacted with triethylamine to generate the corresponding ketene in *situ* which further reacted with Schiff's base to furnish the corresponding β-lactam in moderate yields (Scheme **2.**)



The IR spectra of the 3-(3-phenylpropyl)azetidine-2-one **3a and 3b** are characterized by the presence of appeared the carbonyl group,alkene and substituted ring which occurs within the ranges 3186-3025,2931- 2858,1653-1651,1600-1523 and 835-815 cm^{-1}, respectively **13**. The

substitution of the phenyl ring by electron-donating groups such as N,N-dimethyl group, decreased the absorption frequencies, whereas the substitution by an electron-withdrawing bromo group increased the absorption frequency at 1651 cm^{-1} and 1653 cm^{-1} ,respectively**.14**.

The ^{1}H-NMR of β-lactam **3a and 3b** showed two regions,an aliphatic region including two groups of signals at the region δ 1.69-1.81 ppm and δ 2.32-2.69 ppm ,corresponding to methylene , C_3-H, and C_4-H protons. In the ^{1}H-NMR spectra of the aromatic region ,these is close similarity of the electronic environment of the aromatic protons which led the line collapsd makes an arrow range of the chemical shift and in many cases the spectra lines are superimposed **15**upon each other. In spite of formula similarity, we can notice two doublet at the range of δ6.99-7.03 ppm and 7.11-7.47 ppm corresponding to 13H of β-lactam derivatives which are included (3-1) and(3-4).

The ^{13}C NMR spectra of the **3a and 3b** of the azetidine -2-ones showed a similar pattern .The resonance at δ172 for **3a** and171.14 for **3b** ppm were assigned to the carbonyl **11**groups,methylene group within the ra nge δ 24.1-33.71 ppm and methyl group within range δ 20.84-21.32 ppm.The chemical shift values of aromatic carbon atoms within the range 115.48-142.03 ppm are shown in (Figures (3-3)and,(3-5)) .

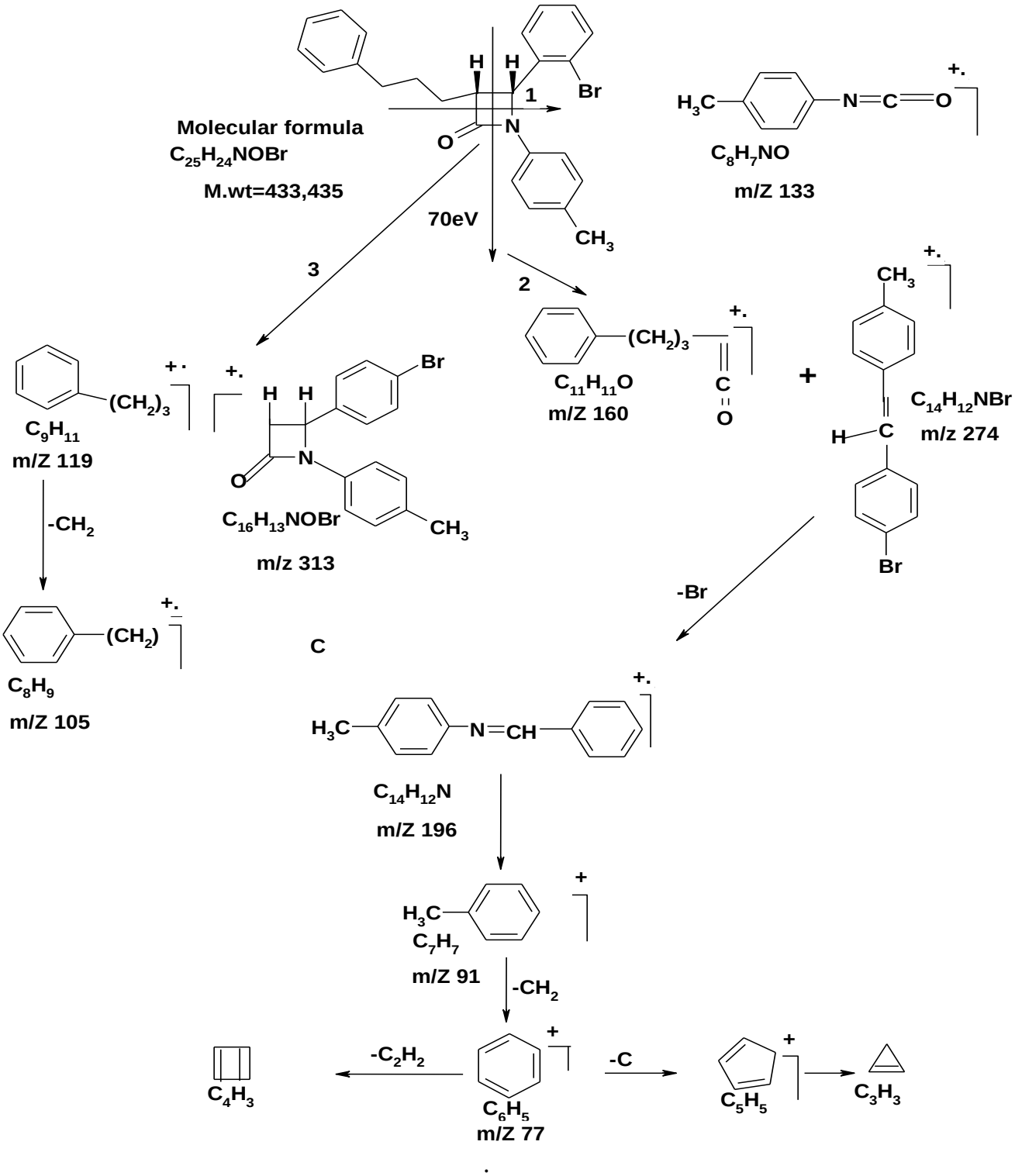
2D NMR HMQC ^{1}H-^{13}C spectra .

The 2D NMR HMQC ^{1}H-^{13}C spectra of the **3b** showed a correlation of the methyl protons signals of **3b** at δ 1.3 ppm with carbon at δ 25.32 ppm, which to the assignment of methyl group carbon.

The HMQC spectra showed a correlation between proton signals at 1.71-1.78 ppm ,2.35-2.38 and 2.65-2.68 ppm carbon signals at δ 25.1,30.9,35.6,37.6,37.5 ppm respectively

The aromatic protons from δ7.18,7.19,7.2,7.21,7.24,7.26, 7.27 ,7.28,7.29,7.30,7.45and7.46. ppm have been correlation with carbon aromatic signals at 121.0,125.8,129.1,136.4,142.0 ppm (Figures (3-7) and,(3-8)).

The mass spectra of the products are similar pattern. The fragmentation of the azetidine-2-one leads to ketene, isocyantes and imine. The fragmentation of **3a and 3b** showed peaks at m/z 231, 160,133,107,91, 77, 65, 51, 39 are attributed to the fragments ,imine $[C_{14}H_{12}NCl]^{+}$, ketene $[C_{11}H_{12}O]^{+}$, isocyanate $[C_8H_7NO]^{+}$,$[C_8H_9]^{+}$, $[C_7H_5]^{+}$, $[C_5H_5]^{+}$, $[C_4H_3]^{+}$, and $[C_3H_3]^{+}$ respectively , the fragmentation mechanism of compounds **3a,3b** is shown below **15**,**16,17** in Schemes 3 and 4**:.**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M.wt=433,435
70eV
1
2
3
C8H7NO
m/Z 133
C11H11O
m/Z 160
C9H11
m/Z 119
C16H13NOBr
m/z 313
C14H12NBr
m/z 274
-CH2
-Br
C8H9
m/Z 105
C14H12N
m/Z 196
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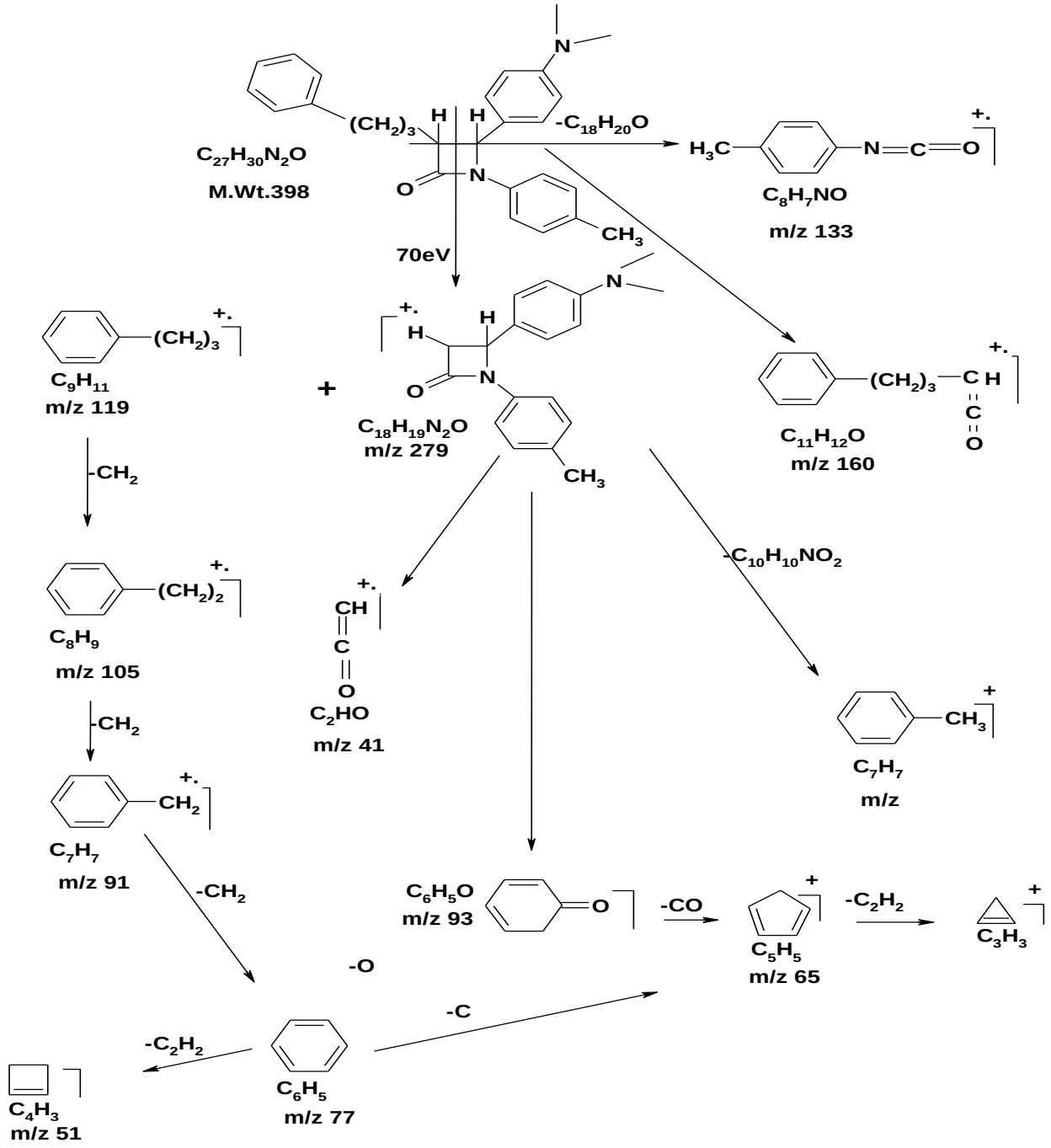
C4H3
C6H5
m/Z 77
C5H5
C3H3



Experimental

All the melting points (m.p.) are uncorrected and are expressed in degree centigrade (°C). Infrared spectra (IR) were recorded using Perkin-Elmer Model 1430 spectrophotometer using potassium bromide (KBr) cm^{-1}. ^{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). in the Department of Chemistry ,Sharif University, Tahran, Iran. The chemical shift values are expressed as δ (ppm) using tetramethylsilane (TMS) as internal standard Mass spectrum were recorded at 70 eV using AcqMethod DEFAULT Spectrum 5973 in the Department of

Chemistry,Tahran,university,tahran,iran .Thin layer chromatography (TLC) was performed using TLC grade silica gel 'G' (Acme Synthetic Chemicals). The spots were made visible by exposing plates to iodine vapours. Column chromatography was performed with silica gel (Acme Synthetic Chemicals, 60-120 mesh) and eluted with ethyl acetate : hexanes mixture unless otherwise stated. All solvents were distilled / dried prior to use, when this seemed necessary

Preparation of Schiff bases 2a ,2b 18,19

General procedure

A mixture of an appropriate aromatic amine (0.01 mole) and an aromatic aldehyde (0.01 mole) in 20 ml of absolute ethanol and one drop of glacial acetic acid was heated on water bath at (70-80C^0) for 30min.The progress of the reaction was checked by TLC.. The solvent was thenevaporated and recryastalized from a suitable solvent,to give the pure products as shown (Table 1-1.)

*4.1: N-(4-Methylphenyl)-4-N,N-dimethyl benzyldine **2a***

This compound was prepared from treatment of 4- methyl aniline (1.07g, 0.01mole,) and 4-(N,N-dimethylbenzaldehyde (1.192g ,0.01mole,).

*4.2: N-(4-Methylphenyl)-4-bromobenzylidine **2b***

The compound was prepared by the treatment of 4-methyl aniline (1.07g ,0.01mole,) and 4-bromobenzaldehyde (1.24g ,0.01mole,).

Table(1-1)physical data of Schiff's bases2a,2b

Schiff's bases	m.p°C	Yield %	Color	Solvent of recrystalization
2a	95-97	79	Yellowish	Ethanol
2b	85-87	70	Yellowish	Ethanol

5-Preparation of 3-(3-phenylpropyl)azetidine-2-one 3a,3b 20,21

5.1:1-(4-Methylphenyl**)-3-(3-phenylpropyl)-4-(4 N,N-dimethylphenyl)azetidine-2-one 3a**

To a mixture of 5-phenylvaleric acid (0.90g, 1.2 mmole), N-(4-methylphenyl)-4-N,N-dimethylbenzylidine**2a**(1.0g,1mmole)and triethylamine (1.27g,3 mmole,1.80mL) in dry dichloromethane 40mL at 0ºC under N_2 atmosphere,a solution of $POCl_3$ (0.95g,1.5 mmole,0.61mL) in dry dichloromethane 20mL was added as dropwise. The mixture was stirred over night at room temperature .There after, the contents were washed successively with 1N HCl 20mL ,5%$NaHCO_3$ 20mL and brine 20mL.The organic layer was separated and dried over anhydrous Na_2SO_4.The solvent was removed under reduced pressure and the crude product was column chrompotography silica gel using ethylacetate-hexane 3:7 as eleuent .The solvent was evaporated furnished pure –β-lactam 3a. Yield= 65. %, m.p °C (102-104); FT-IR (KBr disk): 1651 cm-1; ^{1}H (CDCl3) ppm:1.640 (m,2CH3,6H) 1.70-1.80(m, 2H CH2), 2.32-2.37 (m, 2H, CH2), 2.65-2.68 (m, 2H, CH2), 7.11-7.39 (m, 13H, aromatic protons), ^{13}**C** NMR (CDCl3) ppm:,
20.83,25.27,31.01,35.69,37.57,119.89,125.80,128.34,128.40,129.44,133.81,135.33,142.13,170.99

5:2:1-(4-Methylphenyl)-3-(3-phenylpropyl)-4(2-bromophenyl)azetidine-2-one 3b5555555

To a mixture of 5-phenylvalericacid (0.78g,1.2mmole), and

N-(4-methylphenyl)-4-2-bromobenzylidine2b (1.0g,1mmole) and triethyl-amine (1.10g,3mmole,1.58mL) in dry methylenechloride 40mL at 0ºC under N_2 atmosphere, a solution of $POCl_3$ (0.8g,1.5mmole,0.53mL) in dry methylenechloride 20mL was added drop wise .The reaction mixture after completion of reaction was worked up as usual. The cr ude product was column over silica gel using ethylacetate-hexane 3:7 as eluent and solvent evaporation furnished pure-β-lacatam 3b. Yield =68%, m.p. °C 104-106; FT-IR (KBr disk) : 1651 cm-1; 1H-NMR (CDCl3) ppm: 1.3(s,CH3,3H),1.71-1.78 (m, 2H,CH2) , 2.35-2.38 (m, 2H, CH2), 2.65-2.68 (m, 2H, , CH2), 7.18-7.46 (m, 13H, aromaticprotons); 13C-NMR (CDCl3) ppm: 25.13,30.94,35.65,37.59,37.54,121.02,125.86,128.97,129.16,136.44,142.01, 171.14.

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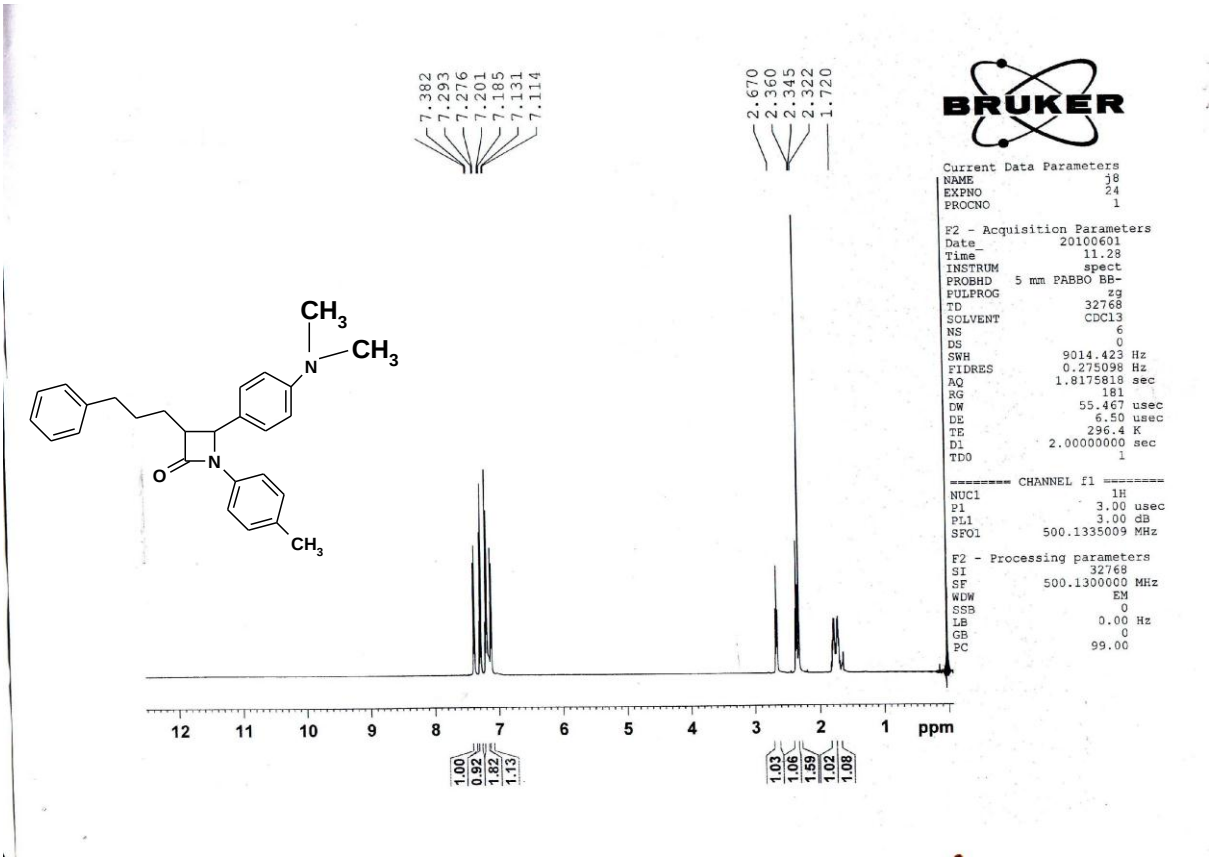

Figure (3-1)**^{1}H NMR** spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(N,N-dimethylphenyl)azetidine-2-one **2a.**

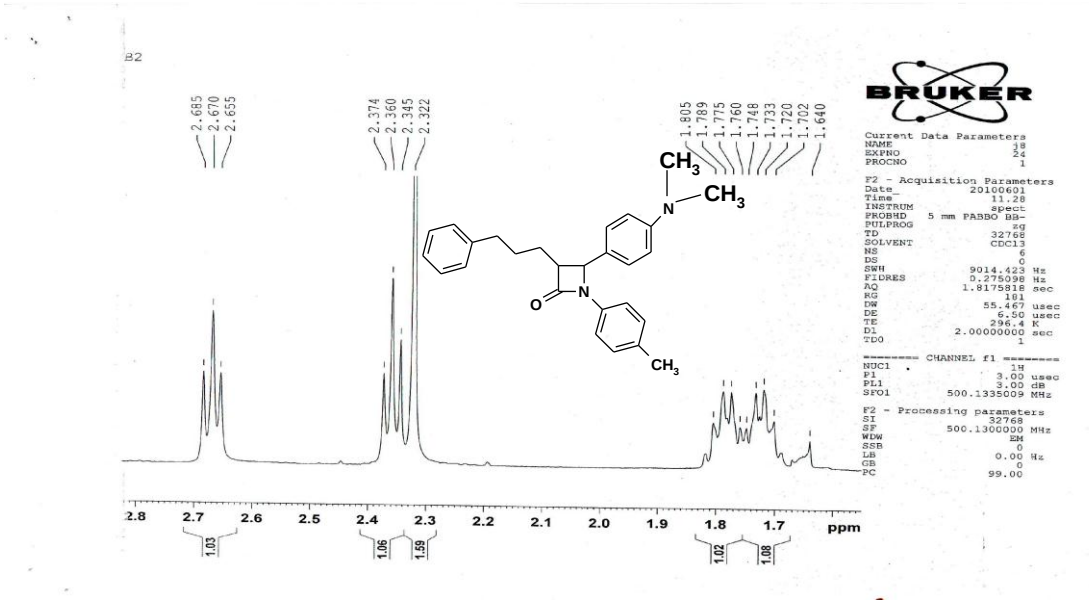

Figure (3-2)**^{1}H NMR broad** spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(N,N-dimethylphenyl)azetidine-2-one **2a.**

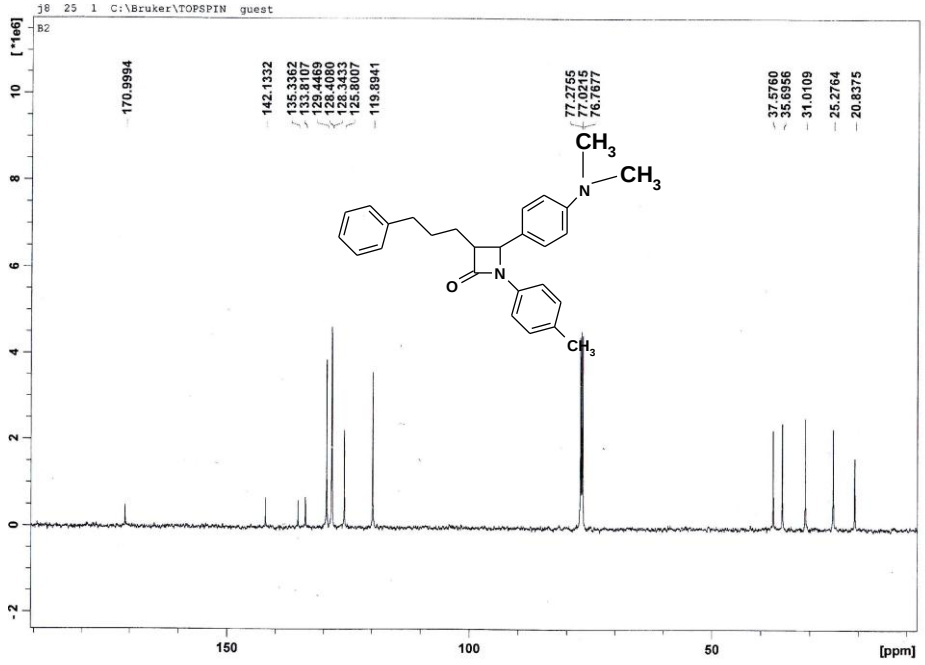

Figure (3-3)**^{13}C NMR** spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(N,N-dimethylphenyl)azetidine-2-one **3a**

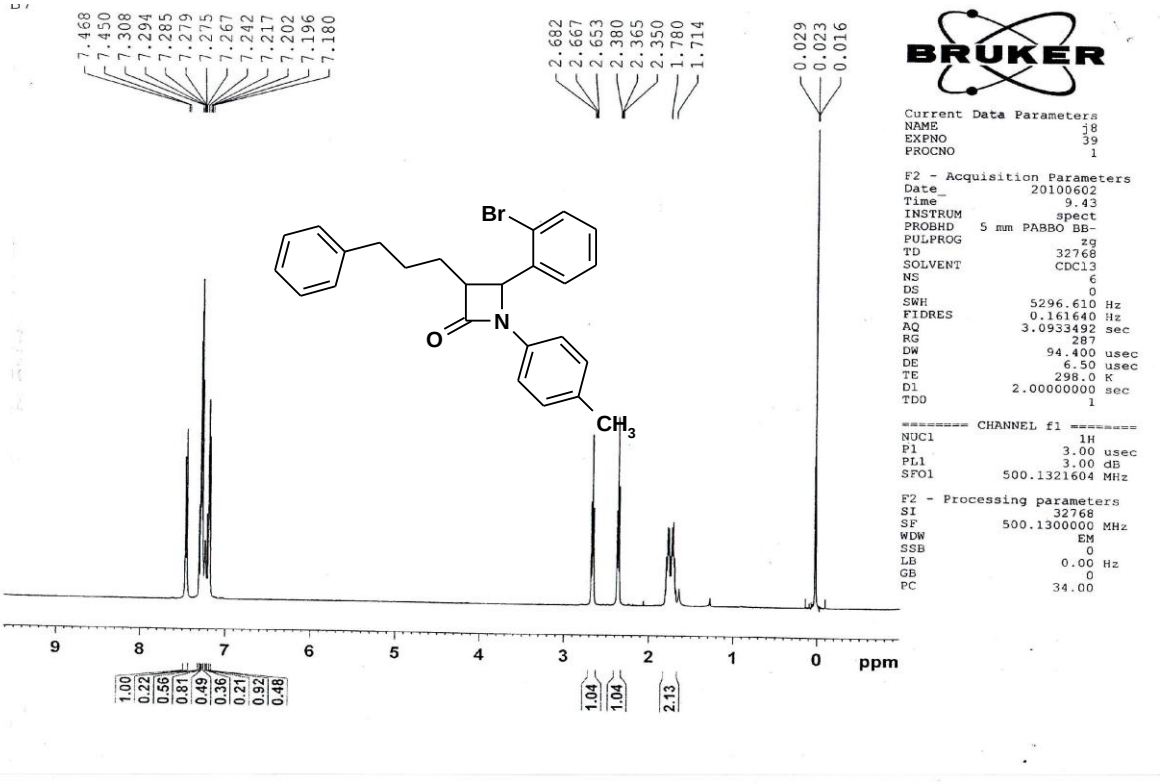

Figure (3-4)**^{1}H NMR** spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(2-bromophenyl)azetidine-2-one **2b.**

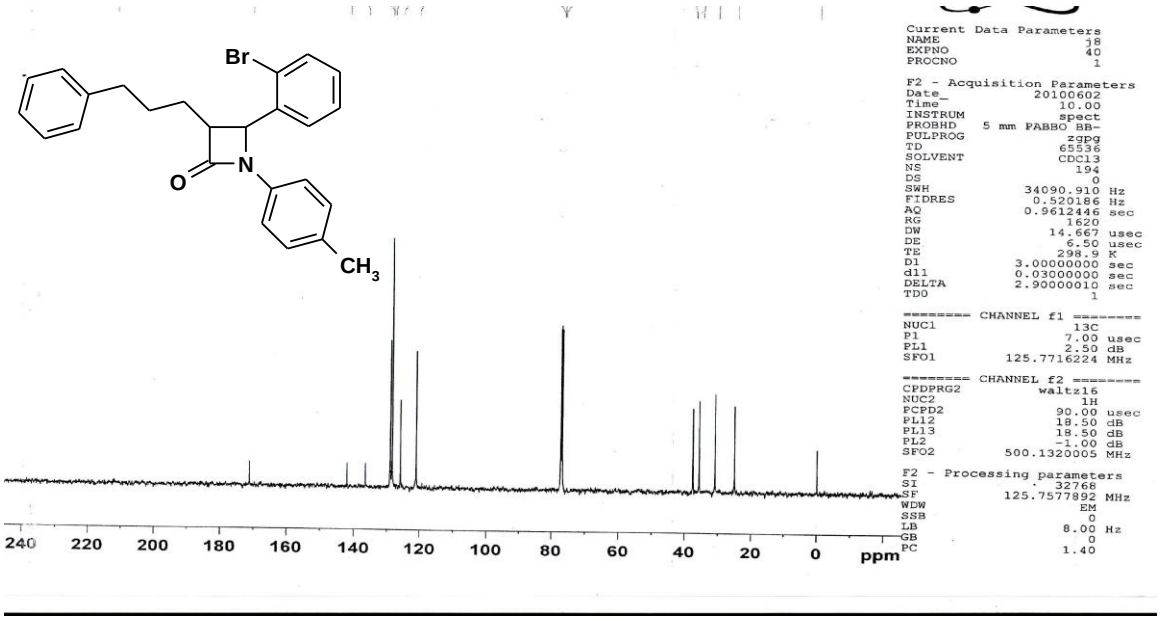

Figure (3-5)**^{13}C NMR** spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(2-bromophenyl)azetidine-2-one **3b,**

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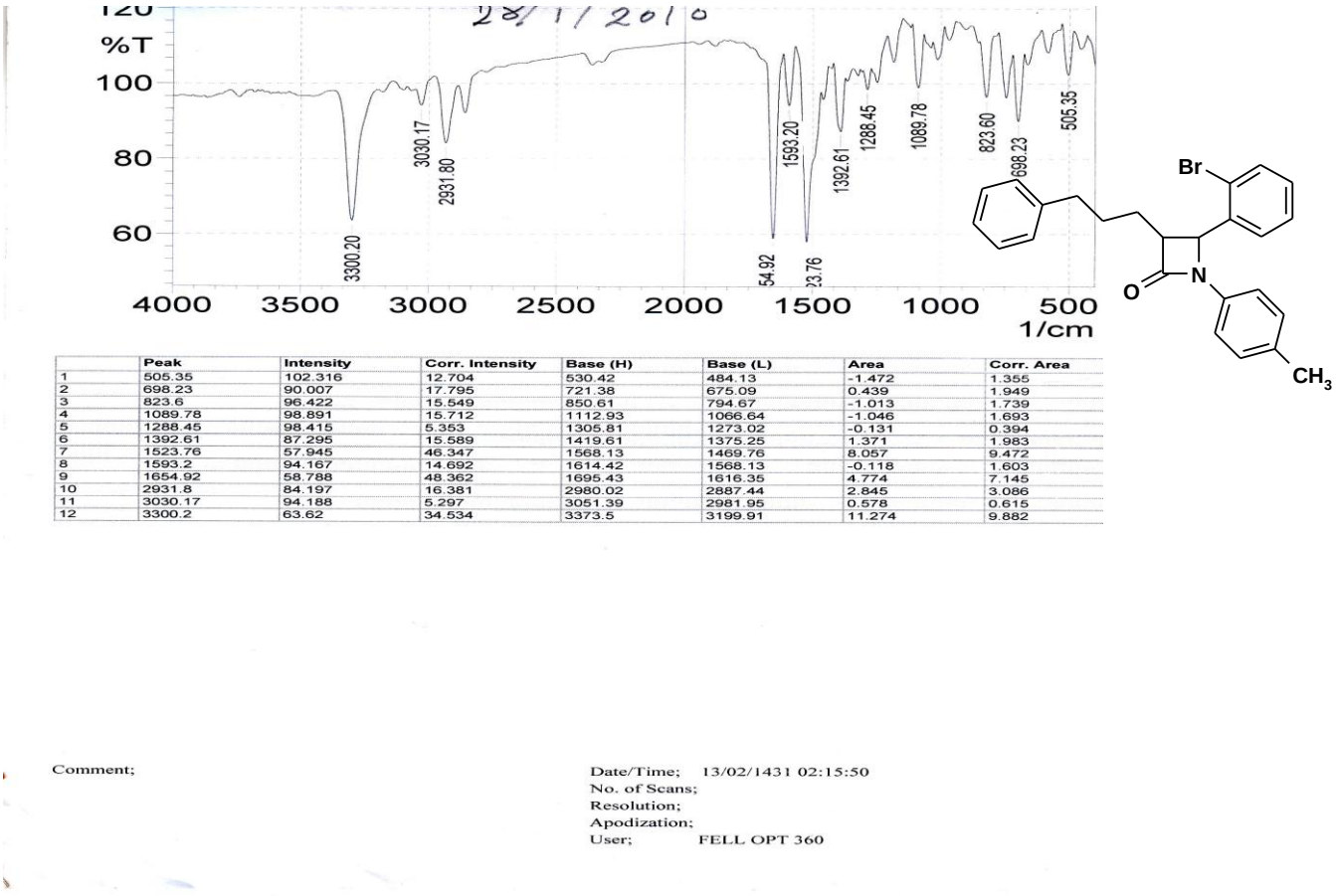

	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	505.35	102.316	12.704	530.42	484.13	-1.472	1.355
2	698.23	90.007	17.795	721.38	675.09	0.439	1.949
3	823.6	96.422	15.549	850.61	794.67	-1.013	1.739
4	1089.78	98.891	15.712	1112.93	1066.64	-1.046	1.693
5	1288.45	98.415	5.353	1305.81	1273.02	-0.131	0.394
6	1392.61	87.295	15.589	1419.61	1375.25	1.371	1.983
7	1523.76	57.945	46.347	1568.13	1469.76	8.057	9.472
8	1593.2	94.167	14.692	1614.42	1568.13	-0.118	1.603
9	1654.92	58.788	48.362	1695.43	1616.35	4.774	7.145
10	2931.8	84.197	16.381	2980.02	2887.44	2.845	3.086
11	3030.17	94.188	5.297	3051.39	2981.95	0.578	0.615
12	3300.2	63.62	34.534	3373.5	3199.91	11.274	9.882

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Figure (3-6): IR spectra of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(2-bromophenyl)azetidine-2-one **3b,**

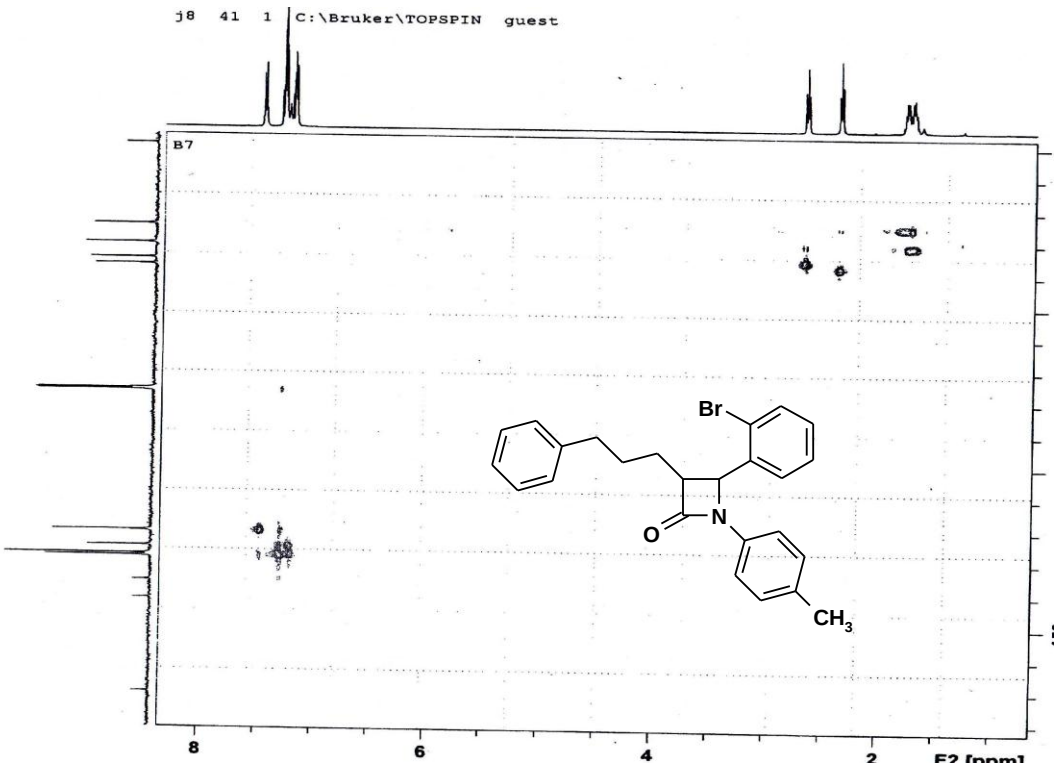


Figure (3-7)**^{1}H-^{13}C NMR** spectra of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(2-bromophenyl)azetidine-2-one **3b**

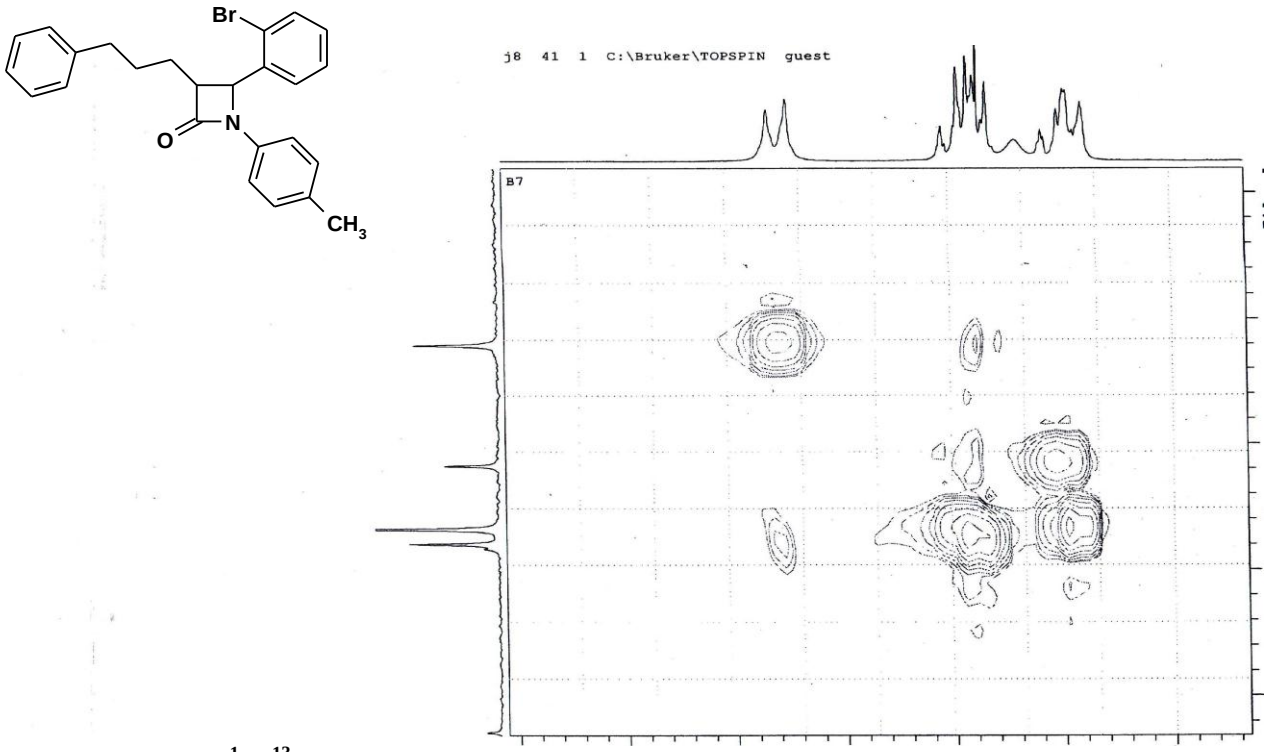
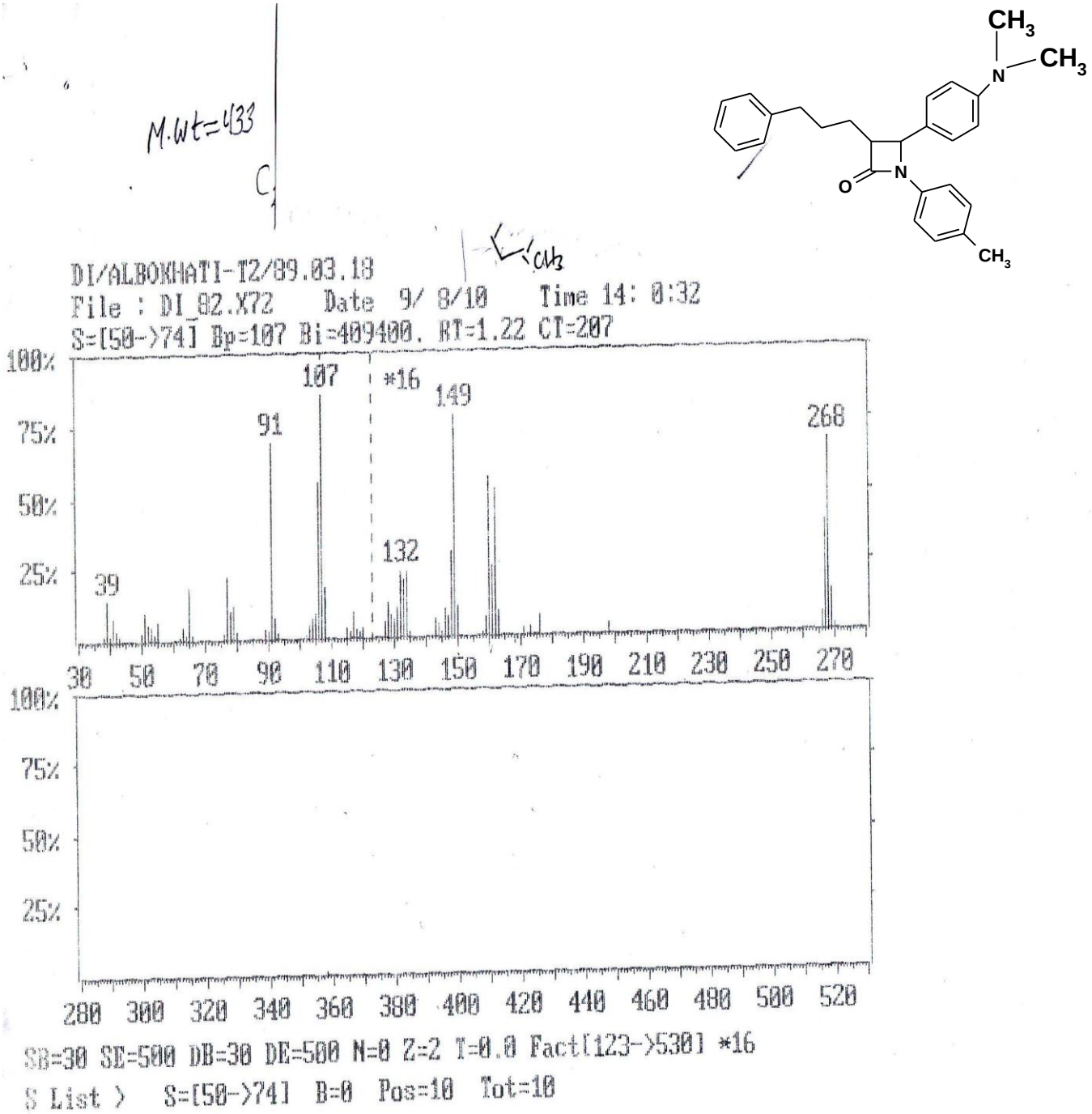


Figure (3-8)**^{1}H-^{13}C NMR** broad spectram of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(2-bromophenyl)azetidine-2-one **3b**



Figure(3-9)**Mass** spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(N,N-dimethyl phenyl)azetidine-2-one **3a**

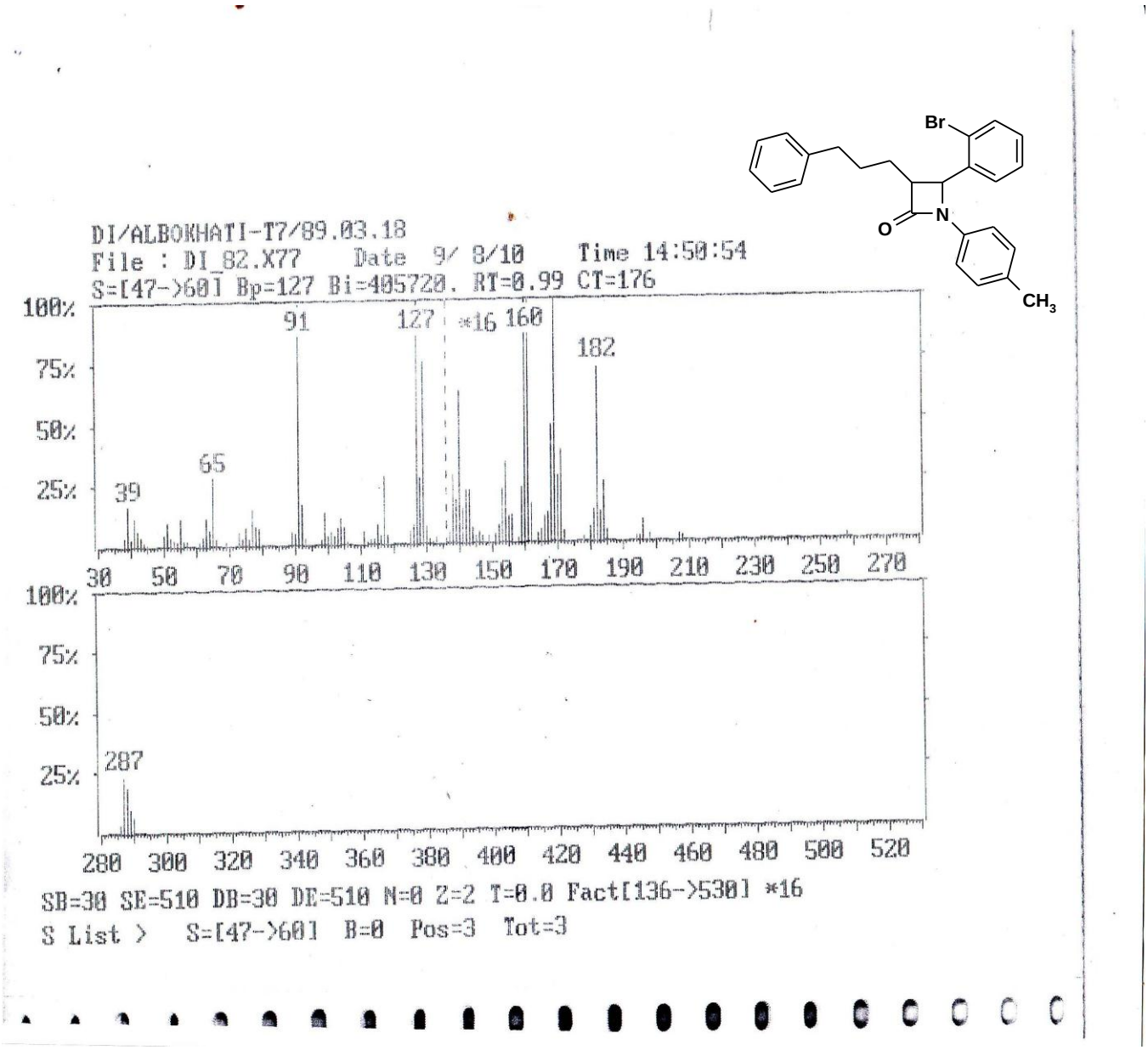


Figure (3-10)**Mass** spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(2-bromophenyl)azetidine-2-one **3a**