Journal of College of Education for pure sciences(JCEPS)
Web Site: http://eps.utq.edu.iq/ Email: com@eps.utq.edu.iq
Volume 7, Number 4, December 2017

Spectroscopy Study Of Mass Spectra For B -Lactams Mono , Dicarbonyl And Some Five Membered Ring

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Abstract

The mass fragmentation pattern of azetidine-2-one **3(c-e)** and azetidne-2,3-dione **5f,5g** in each case the molecular ion peaks were observed corresponding to molecular weight of the coupled products .The base peaks were observed also for each compounds.

the mass fragment □-lactam gave four ion in two directions, the first to give an olefin and isocyanate and the second to generate the original reactants that is ketene and phenyl . mercapto-5-phenyl -4*H*-1,2,4-triazoles **2a-b**. gave tropylium Cation at m/z as well as heterocyclic moiety were observed in the spectrum The mass fragmentation pattern of in each case the molecular ion peaks were observed corresponding to molecular weight of the coupled products .The base peaks were observed also for each compounds

Keywords: medicinal chemistry, β-lactam, Staudinger reaction ,1,3,4-Oxadiazoles,1,2,4-Triazoles ,Mass spectra

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دراسه مطيافيه الكتله لمركبات البيتالاكتام احاديه الكاربونيل و ثنائيه الكاربونيل وبعض المركبات الحلقيه الخماسيه الغير متجانسه

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(3) العراق ذي قار الشطره المعهدالتقني

الخلاصة

تضمن البحث دراسة جديده لأطياف الكتلة فقط لتشخيص انشطارات للمركبات الحلقية الغير متجانسه كمركبات البيتالكتام احاديه مجموعه الكاربونيل وثنائيه الكاربونيل حيث لوحظ من اطياف الكتلة ظهور حزم الايون الجزيئي وانشطار الحلقة الرباعية بشكل عمودي وافقي وتكوين اربعه ايونات هي الايزوسسينت والكيتين والايمين والاولفين اما المركبات الحلقية الخماسية الترايازول من طيف الكتلة لها ظهور حزمه الايون الجزيئي لهما وايضا ظهور حزم الاساس و تكوين حزمه التروبليوم عند 91 لكلا المركبين وظهور حزم اخرى.

Introdution

In this paper deals with the chemistry and biological importance of this different heterocyclic system. These heterocyclic system include substituted-1,2,4-triazole substituted-1,3,4-oxadiazole , azetidine-2-one and azetidine-2,3-dione.Due to wide variety of their biological importance,

Triazole

In the five-membered ring system the presence of three nitrogen atoms defines an interesting class of compounds, the triazoles.These may be of two structural, the 1,2,3- tiazoles or v-triazoles(1) and 1,2,4-triazoles or S-triazoles(2) .This name triazole was first given to the carbon nitrogen ring system $C_2H_3N_2$ bladin(1,2,3,4)

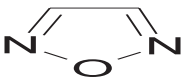
(1)

(2)

Oxadiazole:

Oxadiazole are cyclic compounds containing one oxygen and two nitrogen atoms in a five membered ring(**5,6,**)The sequence of these atoms may be different as 1,2,4-oxadiazole(3)and 1,3,5-oxadiazole(4),1,2,3-oxadiazole(5),1,3,4-oxadiazole(6)

(3)



(4)

(5)

(6)

-lactams Azetidin-2-ones, commonly known as -β- lactam constitute a famous class of heterocyclic compounds

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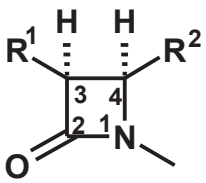


Since the discovery of new -lactam antibiotics such as mono bactams and nocardicins, a lot of interest has been aroused in the study of monocyclic -lactams [7,8]. The synthesis of functionalized monocyclic -lactams is have been shown to be biologically active as an important area of research. Recently, monocyclic -lactams cholesterol acyl transferase inhibitors [9,10], thrombin inhibitors

[11], and apoptosis inductors [12]. The first I was prepared by Staudinger through the reaction of diphenyl ketene with N-phenyl benzylidine

.

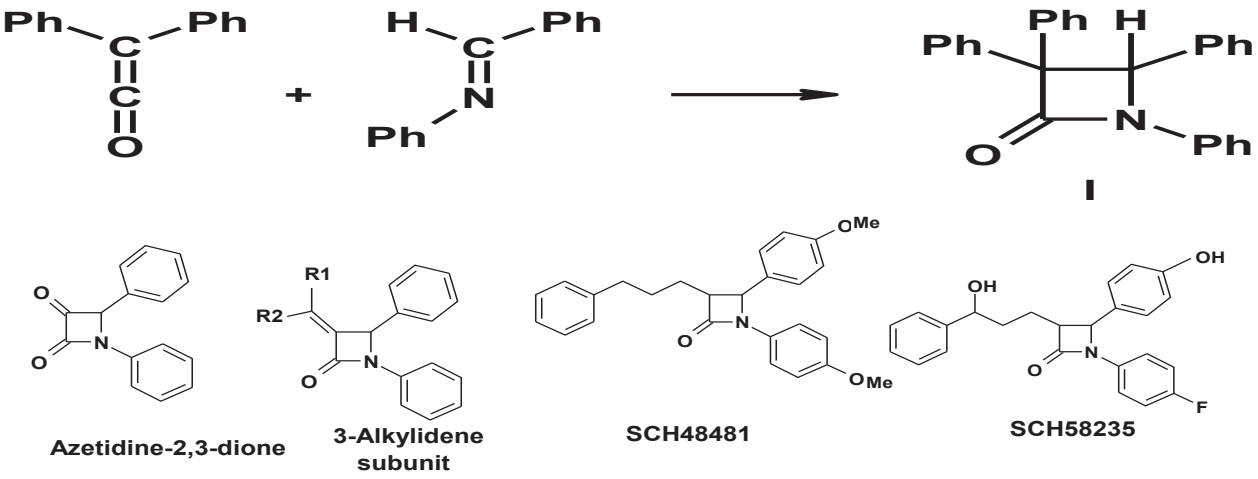
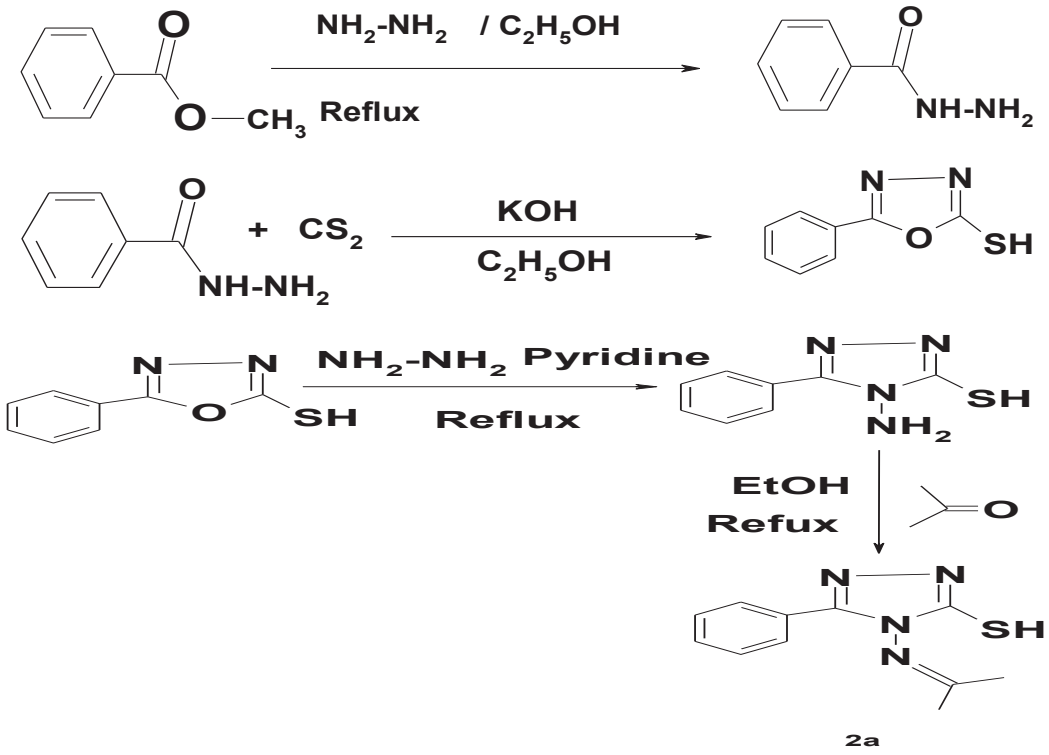
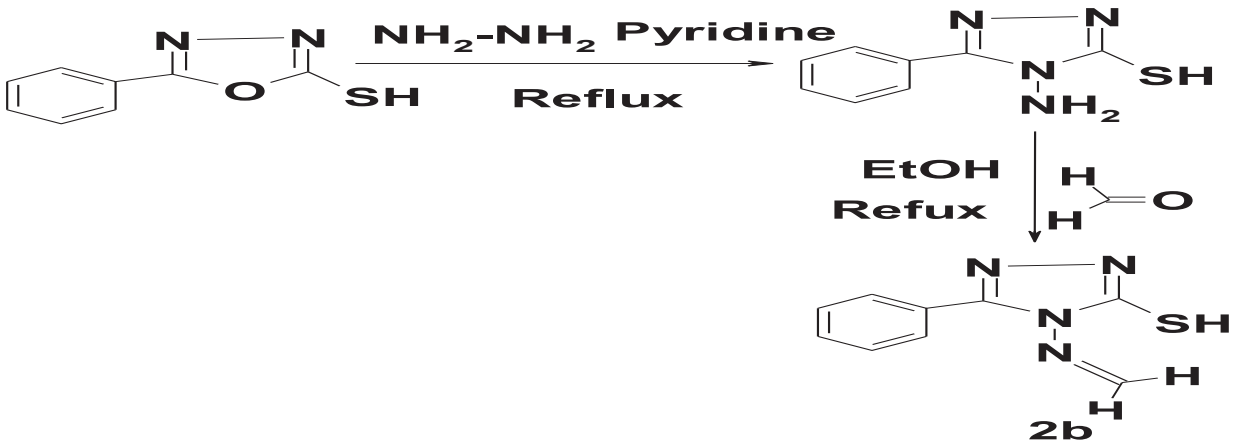


Figure 1:3-Alkylidene/ 3-Alkylazetidine-2-ones

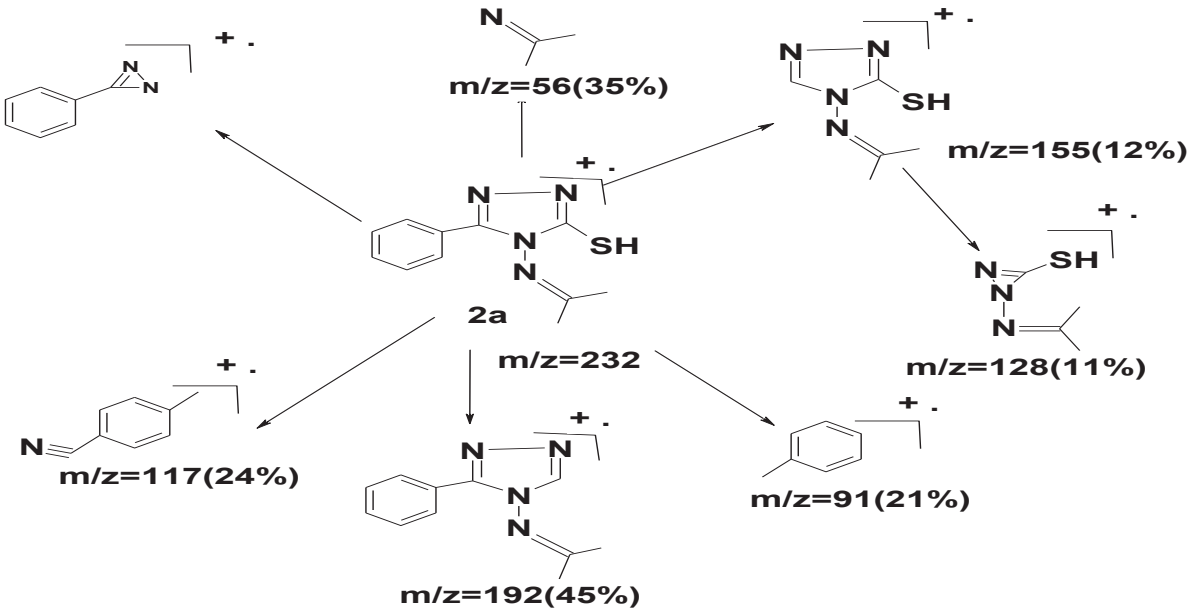
Results and Discussion

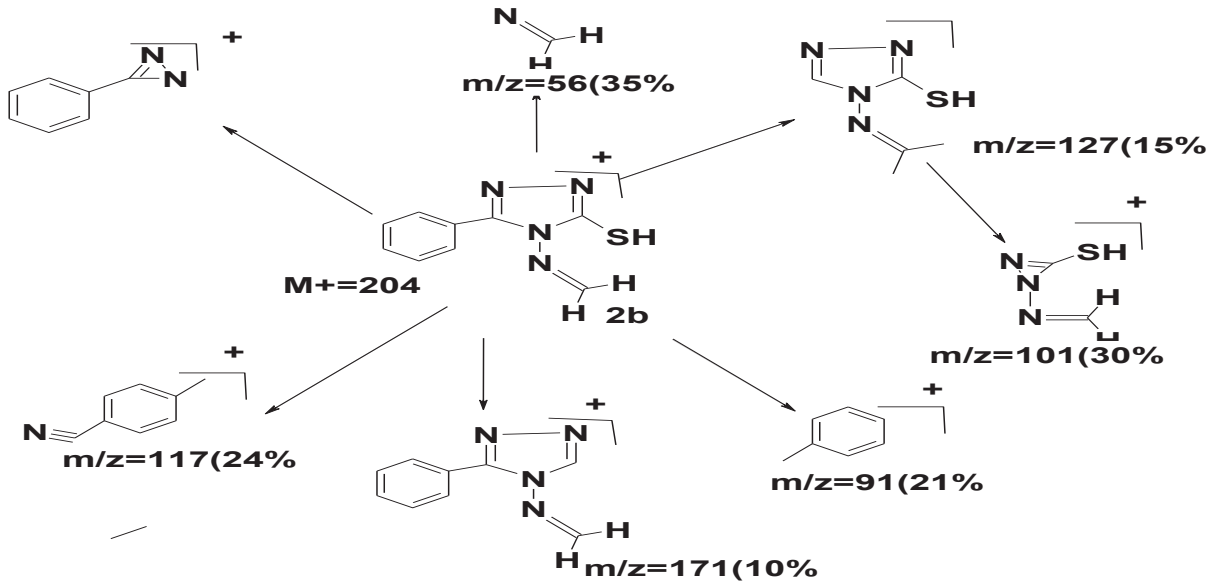
Substituted-1,2,4-Tiazole 2(a-b) were synthesized by the reaction of acid hydrazides with carbon disulfide in basic medium to gave 5-Substituted -2-mercapto-1,3,4- Oxadiazoles were reacted with hydrazine in pyridine to gave 3-mercapto triazole 2(a-b) under this(Scheme 1)(13)





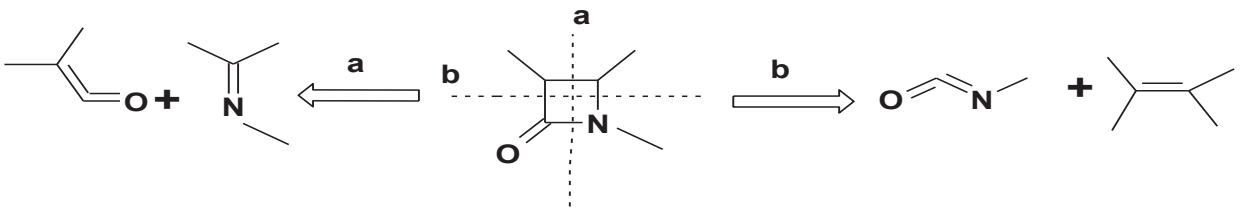
The mass spectra of 5-Substituted-1,2,4-Triazole 2(a-b) there compouds**2a and 2b** gave molecular ion of different intensities and the base peak which have been for this family e.g. tropylium ion m/z=91(C7H7)(14)..



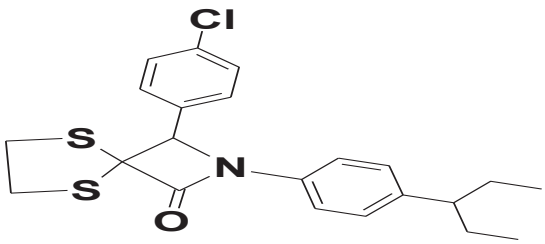


Azitidine-2-One

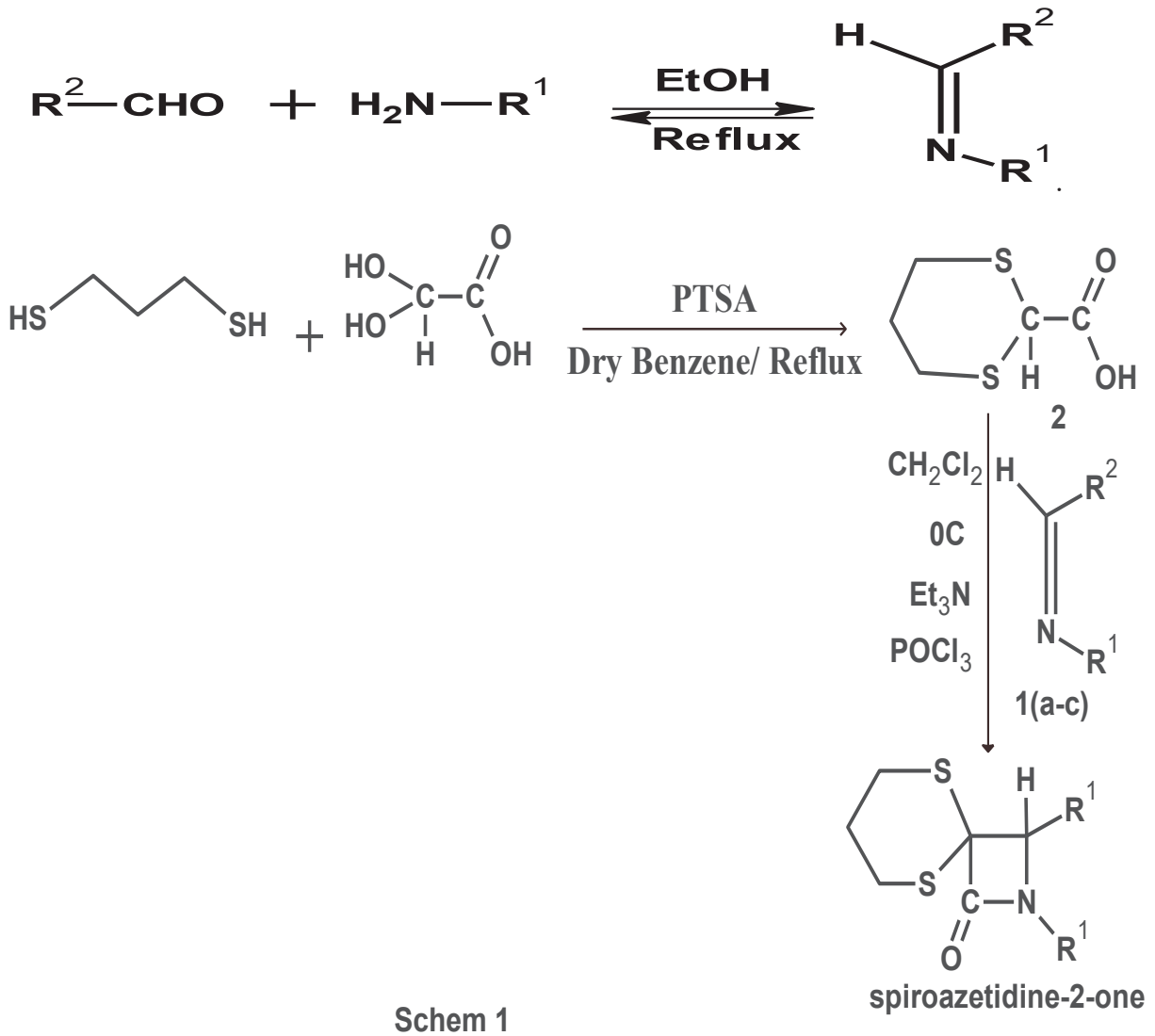
Two possible [2+2] cyclo additions can be envisaged for the synthesis of β - lactams (Scheme 1). One possibility consists of the [2+2] cyclo addition between ketenes and imines to yield β -lactams . This reaction has been explored experimentally and it is also known as the Staudinger reaction between ketenes and imines **(15,16)** In an alternative approach, the [2+2] cyclo addition between alkenes and isocyanate leads to β -lactams This reaction has been less extensively used, but it has proven to be useful in the chemical synthesis of interesting compounds



Taking a lead from recent earlier studies(**15-17**) we considered to utilize ketene-imine cyclization in the presence of triethylamine for the synthesis of 5,9-dithia-2-azaspiro(3,5)nonan-1-one substituted of β- lactam as shown in below in fig 2 .

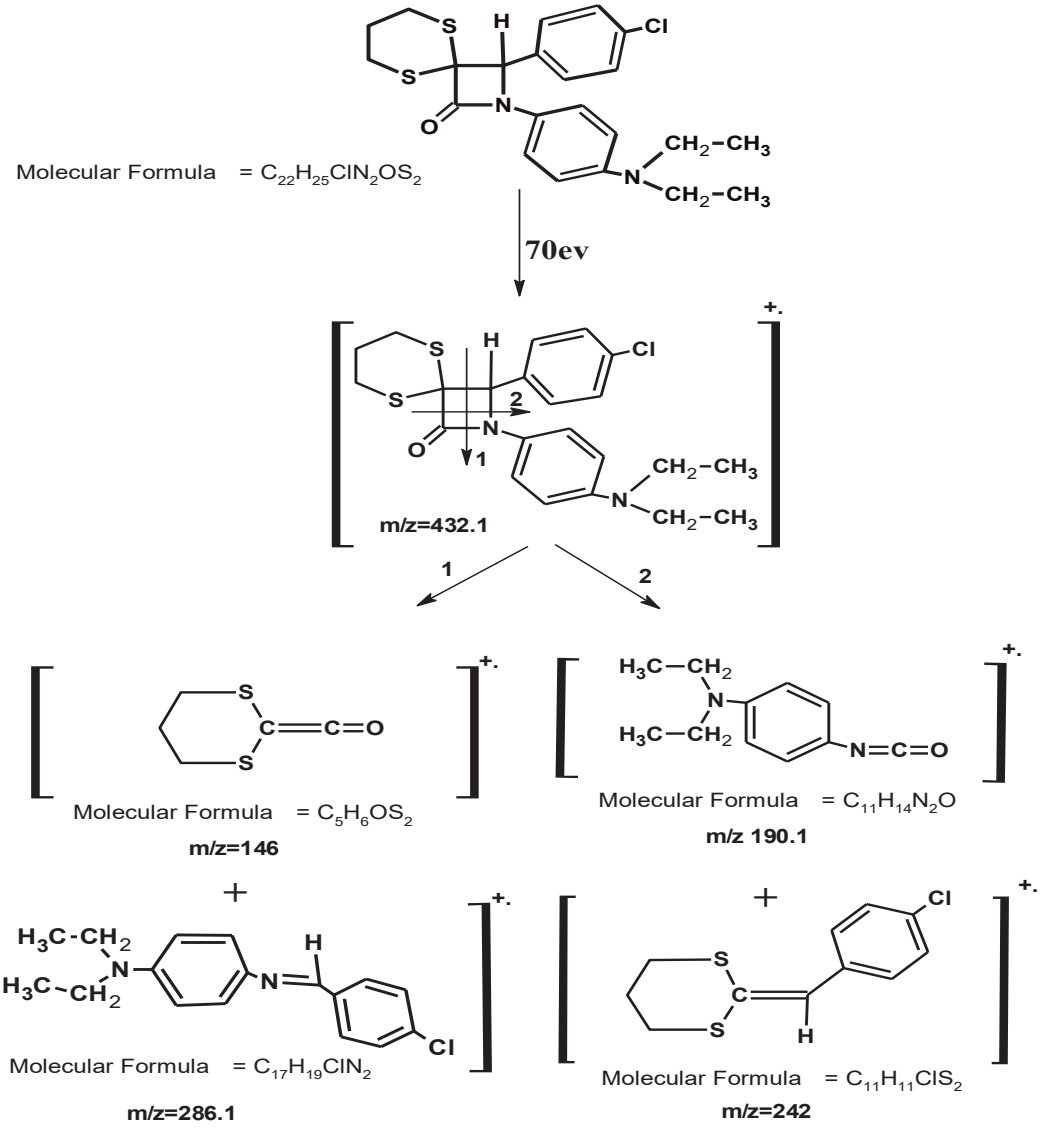


The **5,9-dithia-2- azaspiro[3.5]nonan-1-one 3c** was prepared by reacting 1,3-dithiane-2-carboxylic acid with the appropriate Schiff's base in the presence of triethylamine with phosphorus ox chloride in dry dichloromethane under nitrogen atmosphere **at 0°C.** The active acid chloride reacts with triethylamine to generate corresponding ketene in situ which further reacts with Schiff's base to furnish corresponding 5,9-dithia-2-azaspiro[3.5]nonan-1-one **3c** in moderate yields as shown



Schem 1

Mass spectra of the compound **3c** showed the molecular ion peak corresponding to the particular compound (M+,432.1,75%) .The fragmentation of the spiroazetidin-2-one leading to the imine (286.1,100%) base peak and the corresponding 1,3-dithiane ketene (146,8%) also the fragmentation of this compound showed the alkene peaks(242,20%) and isocyanates (190,33%). The fragmentation mechanism of compound **3c** was shown below [71] :.



taking a lead from earlier studies [**16,17**], it was considered important to utilize keteneimine cyclization in the presence of triethylamine using **C3–C4** bond formation of β-lactam.

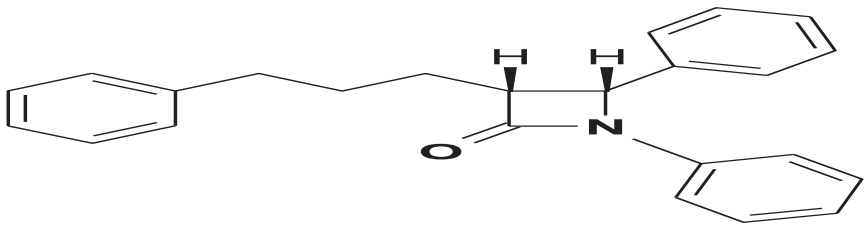
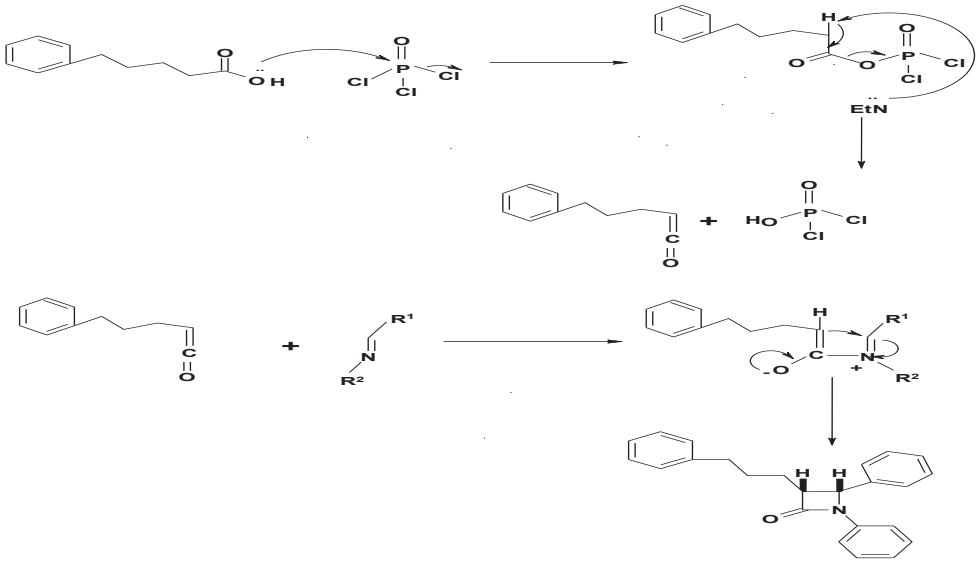
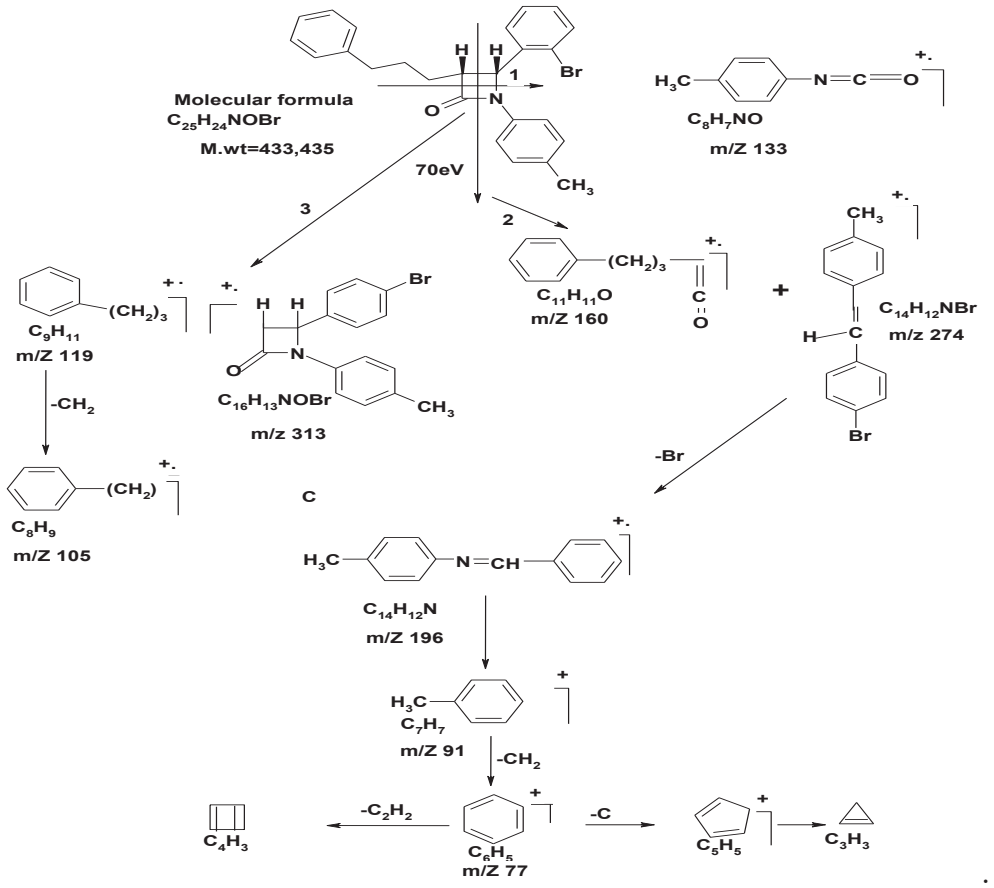


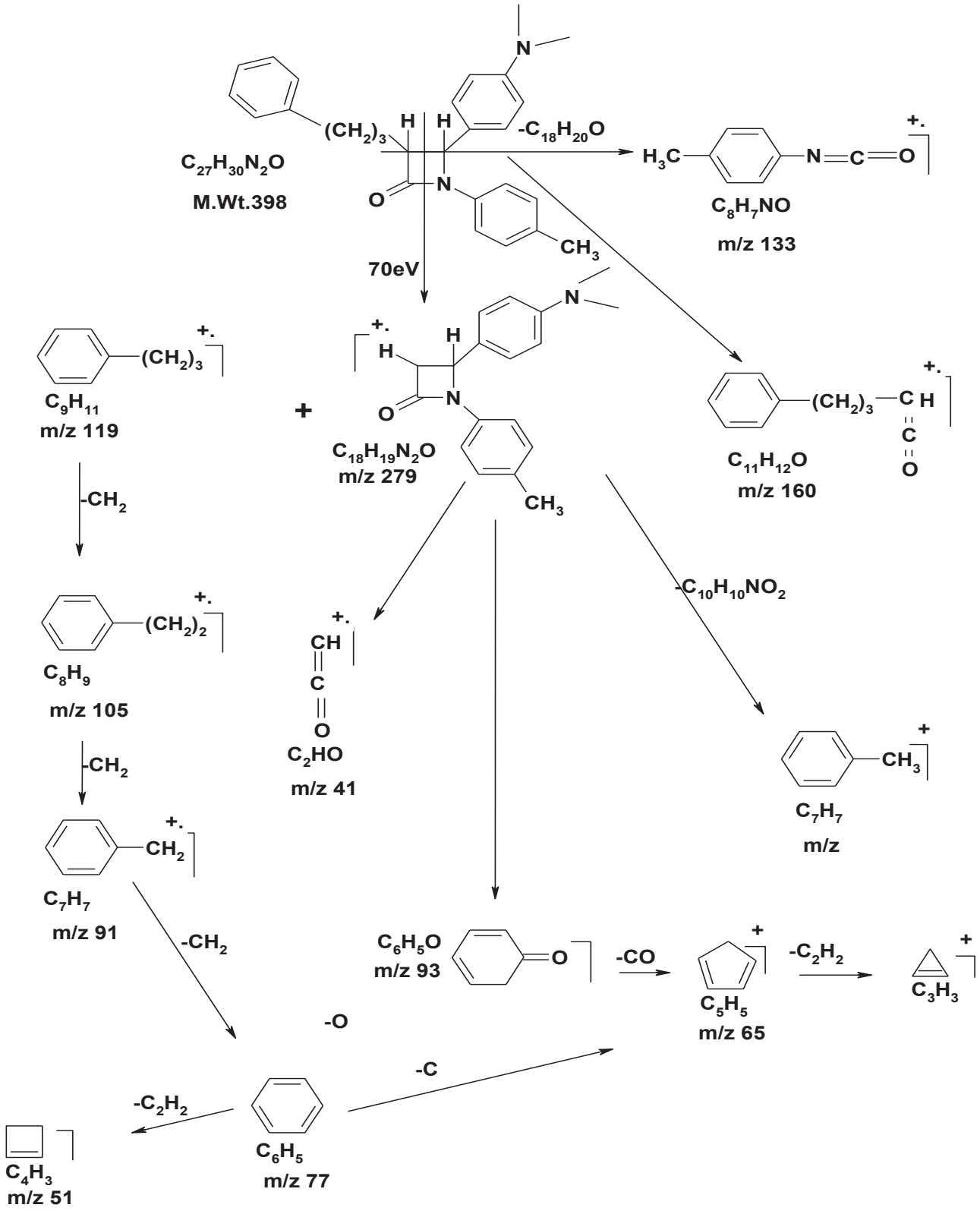
Fig 2

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 ,as shown in Scheme **2.**



The mass spectra of the products are similar. The fragmentation of the azetidine-2-one leads to ketene, isocyantes and imine. The fragmentation of **4d,4e** showed the peaks at 231m/z, 160 m/z ,133m/z 107m/z ,91m/z , 77m/z, 65m/z, 51m/z, 39m/z 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 **4(d-e)** is shown below **(15-17)** in Schemes 3 and 4**:.**

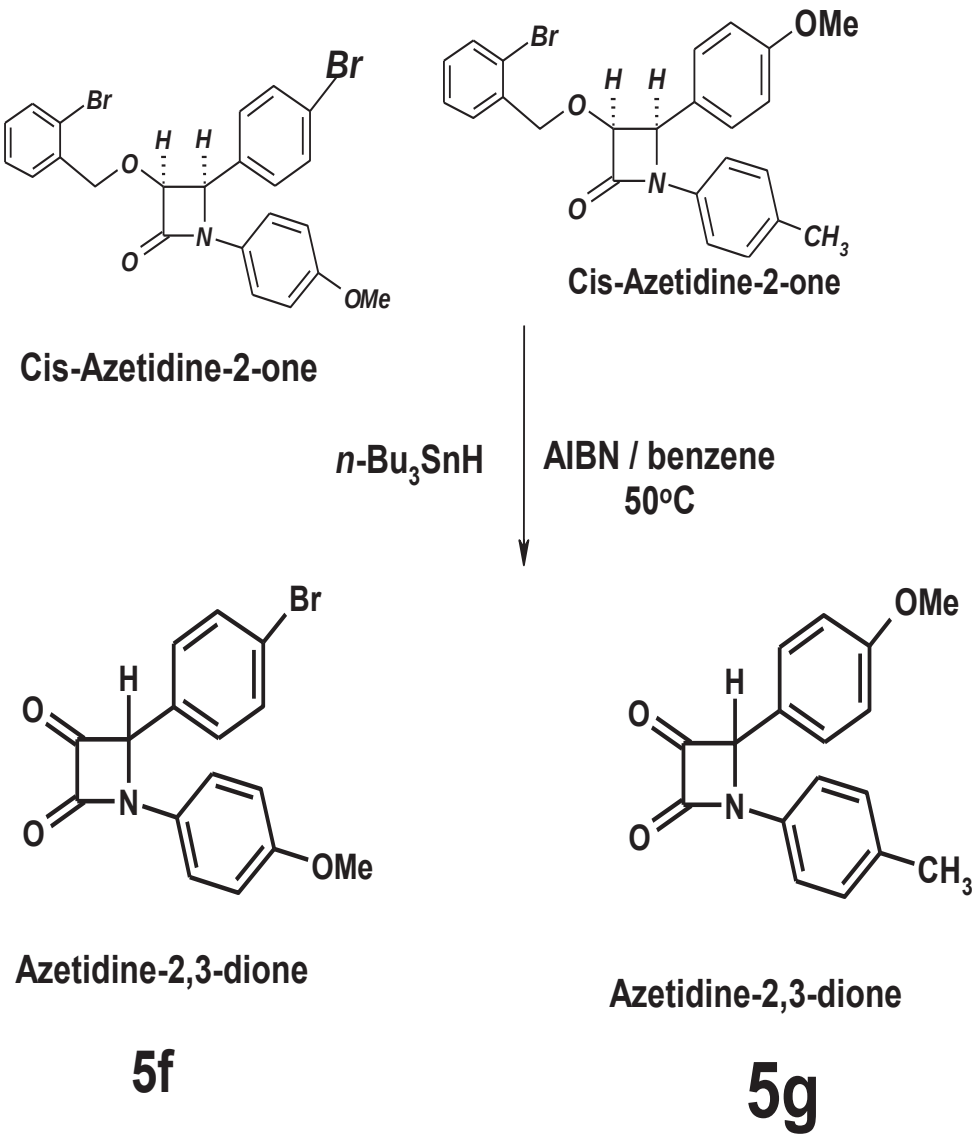




Azetidin-2,3-diones

The synthetic utility of these azetidin-2-ones, the 3-(2'-bromobenzyloxy)azetidin-2-ones were subjected to the radical initiated rearrangement. Thus, tri-*n*-butyltin hydride reduction of catalysed by

AIBN in benzene at 50°C led to formation of azetidin-2,3-diones **5f and 5g** in good yields as shown below in **scheme2** (**15-17**)



The Mass spectra of the compounds **5f** and **5g** showed the molecular ion peak corresponding to the particular compound (M+,345,10%,281,7%). The fragmentation of the **azetidine-2,3dione 5f** and **5g** leading to the imine (289,5%,225,5%) base peak and the corresponding ketene (198,10%,149,20%) also the fragmentation of this compound showed the alkene peaks (56,10%,56,25%) and isocyanates (134,15%,134,30%).The fragmentation mechanism of compounds were shown below (**18,,19**) fig(4-1),(4-5):

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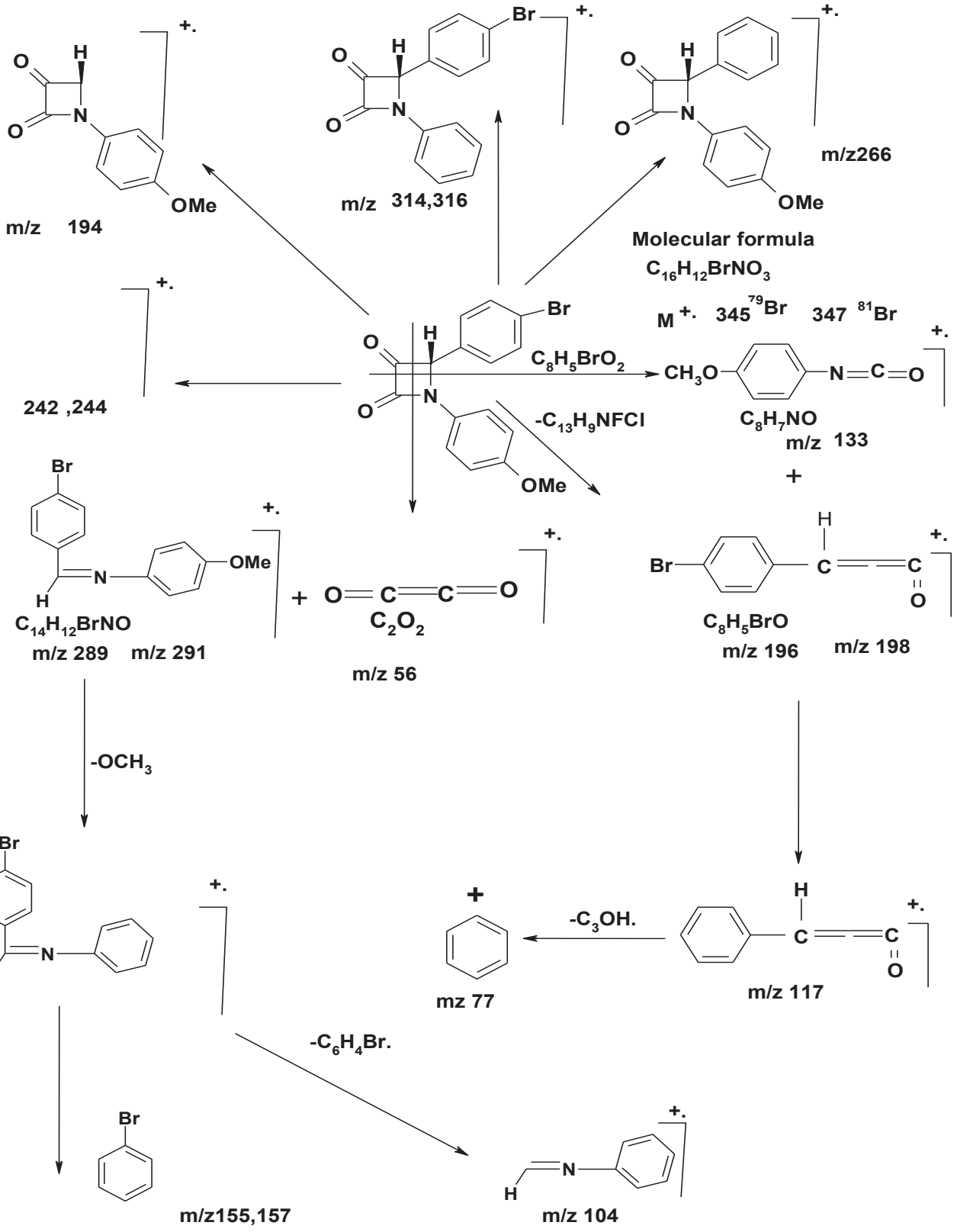
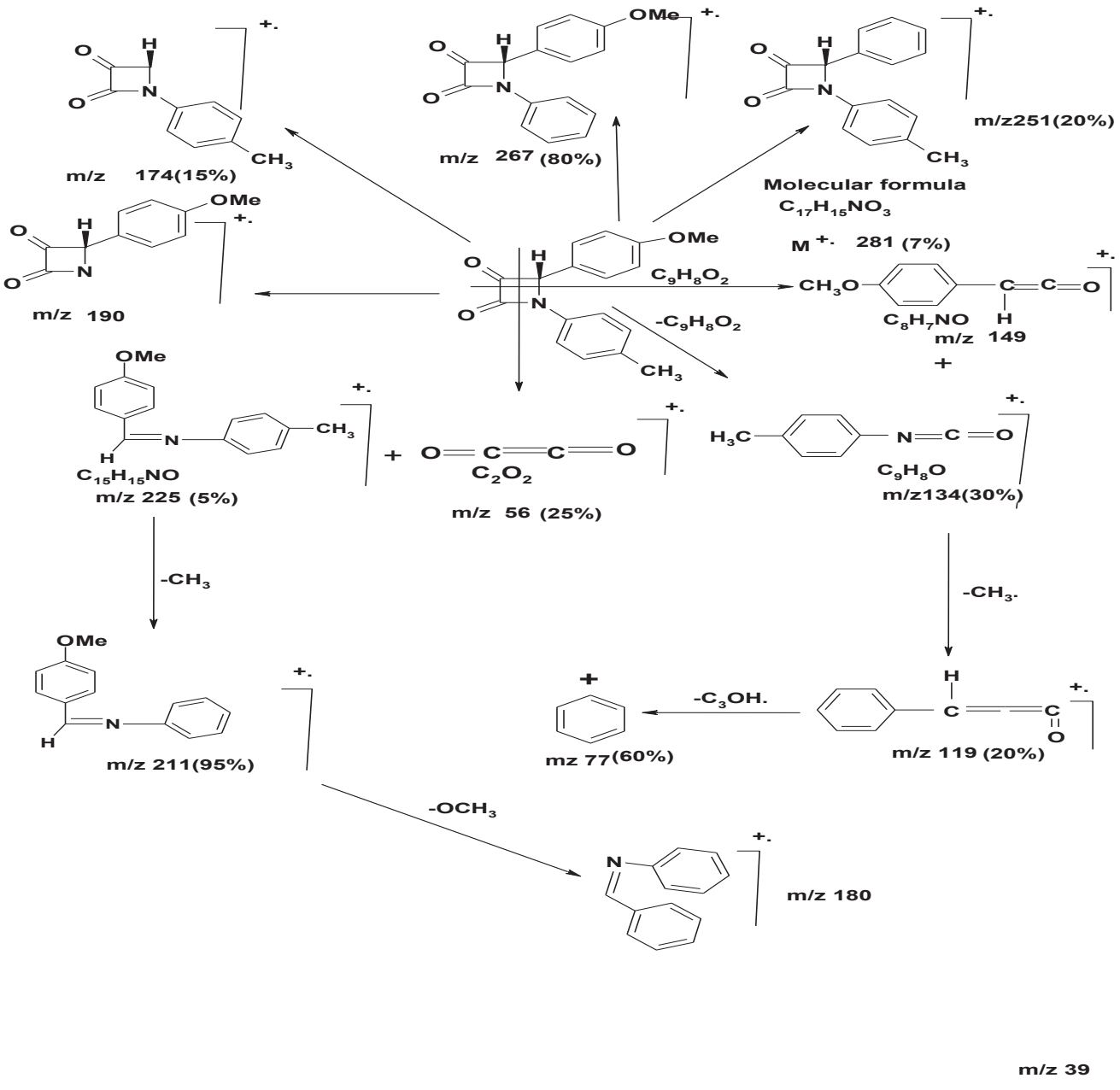




Experimental

Mass spectra were recorded at 70 ev using Acq Method 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 vapors. 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

General procedure

4-{[(1Z)-1-methyl ethylidene]amino }-5- phenyl– 4*H*-1,2,4-triazol -3- thiol 2(a—b).

Benzohydrazide

To mixture of 0.1mole of methyl benzoate with 0.2mole of hydrazine hydrate in 100Ml of absolute ethanol .The mixture was thoroughly stirred and heated under reflux for 5h,the reaction time was monitored through TLC technique after completion of reaction ,the solution was concentrated to a small volume and the residue was dissolved in water, this furnished a precipitate which was filtered, washed and recrystallized from aqueous ethanol Yield %80, m.p C0148-150.

5-Phenyl-1,3,4-oxadiazoles-2-thiol

To mixture of 0.1mole of hydrazide with 0.1mole of KOH in 100mLof absolute ethanol and add 0.1mole of carbon disulfide. The mixture was thoroughly stirred and heated under reflux for 5h,the reaction time was monitored through TLC technique after completion of reaction ,the solution was concentrated to a small volume and the residue was dissolved in water,this solution was acidified to pH 2-3 by addition of dihydrochloric acid and this furnished a precipitate which was filtered, washed and recrystallized from aqueous ethanol Yield %88, m.p C0 165

1-(3-mercapto-5-phenyl -4*H*-1,2,4-triazoles

To mixture of 01mole of5-Phenyl-1,3,4-oxadiazoles-2-thiol with 0.1mole of hydrazine hydrate in 25mL of pyridine .The mixture was thoroughly stirred and heated under reflux for 5h,the reaction time was monitored through TLC technique after completion of reaction ,the solution was concentrated to a small volume and the residue was dissolved in water and this furnished a precipitate which was filtered, and recrystallized from aqueous ethanol. Yield %70, m.p C0 203-205

4-{[(1Z)-1-methyl ethylidene]amino}-5- phenyl– 4*H*-1,2,4-triazol 3- thiol 2a.

To mixture of 0.02 mole of1-(3-mercapto-5-phenyl -4*H*-1,2,4-triazol**es** with 0.02mole of 2-acetone in 50mL of absolute ethanol .The mixture was thoroughly stirred and heated under reflux for 3h,the reaction time was monitored through TLC technique after completion of reaction ,the solution was concentrated to a small volume and the residue was dissolved in water and this furnished precipitate which was filtered, washed and recrystallized from aqueous ethanol. Yield %62.6, m.p C0 99-102.

4-{[(1Z)-1-methyl methylidene]amino}-5-phenyl–4*H*-1,2,4-triazol-3-thiol 2b.

To mixture of 0.02 mole of1-(3-mercapto-5-phenyl -4*H*-1,2,4-triazol**es** with 0.02mole of formaldehyde in 50mL of absolute ethanol .The mixture was thoroughly stirred and heated under reflux for 3h,the reaction time was monitored through TLC technique after completion of reaction ,the solution was concentrated to a small volume and the residue was dissolved in water and this furnished a precipitate which was filtered, washed and recrystallized from aqueous ethanol. Yield %70, m.p C0 90-92.

2-General procedure of(4-chloro phenyl) - 2-(4-diethyl amino)phenyl -5,9 –dithia-2-azaspiro[3.5]nonan-1-one 3b Schiff base

A mixture of 0l ethanol and drop of glacial acetic acid , was heated in water bath at (70-80) for 30 min .Then left to cool inbath of ice -water , whereby yellowish white crystals separated out . the crystals were filtered , washed with 2% HCl ,then with water and recrystallized from ethanol .Table 1 ,give M.P ,λ_{max} , and percent of yield . **m.p:101—102.**

3-General procedure for 3-(3-Phenylpropyl)azetidine-2-one 4d,4e(20,21)

1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(4N,N-dimethylphenyl)azetidine-2-one 4d.

To a mixture of 5-phenylvaleric acid (0.90g, 1.2 mmol), N-(4-methylphenyl)-4-N,N-dimethylbenzylidine**3d**(1.0g,1mmole)and triethylamine (1.27g,3mmole,) in dry dichloromethane 40mL at 0ºC under N_2 atmosphere, a solution of $POCl_3$ (0.95g,1.5mmole) in dry dichloromethane 20mL was added as drop wise. 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 Sodium sulphate Na_2SO_4.The solvent was removed under reduced pressure and the crude product was column chromphtographed over silica gel using ethyl acetate-hexane 3:7 as eluent and solvent evaporation furnished pure –β-lactam **4d**. Yield= 65. %, m.p °C (102-104);

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

mixture of 5-phenylvalericacid (0.78g,1.2mmole), and N-(4-methylphenyl)-4-2-bromobenzylidine3e (1.0g,1mmole) and triethyl-amine (1.10g,3mmole,1.58mL) in dry methylene chloride 40mL at 0ºC under N_2 atmosphere, a solution of $POCl_3$ (0.8g,1.5mmole,0.53mL) in dry methylene chloride 20mL was added drop wise .The reaction mixture after completion of reaction was worked up as usual. The crude product was column over silica gel using ethyl acetate-hexane 3:7 as eluent and solvent .

1,3-dithiane-2-carboxylic acid In 100 mL round bottom flask was placed (**0.01 mole 0.9205** g) of glyoxylic acid monohydrate in dry benzene **20mL ,**added amount of P-TSA as catalyst

was and gently refluxed. A solution of 1,3-dithaipropane (**0.01 mole ,1.0823 mL**) in dry benzene **25mL** was added in such away that the refluxing should not be vigorous.The reaction mixture was refluxed under stirring for 2hr .The progress of the reaction was monitored by TLC. After completion of the reaction ,the reaction mixture was filtered and the solvent was evaporated under reduced pressure , recrystalized from benzene to give acid **2**, white crystals **.** **Yield** 72% , **m.p** 112-114˚C ,

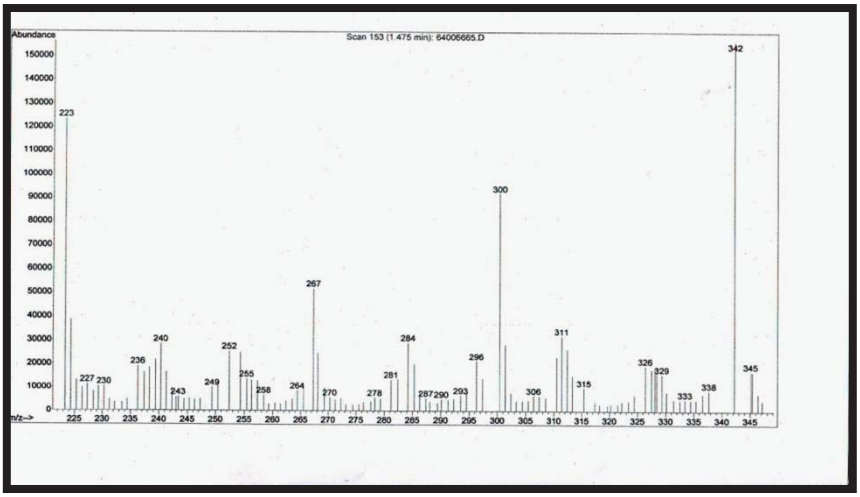
(4-chloro phenyl) - 2-(4-diethyl amino)phenyl 5,9 –dithia-2-azaspiro[3.5]nonan-1-one 3c. (15-20)

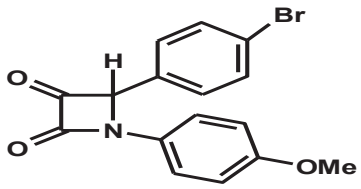
To a suspension of 1,3-dithiane-2-carboxylic acid **2** (**0.8563 gm, 0.0052213 mole**) ,N-(4-diethyl amino)phenyl -4-chloro benzylidine **2c** (**1.0gm, 0.0035 mole**) and triethyl amine (**1.0575916 gm** , **0.0104712 mole**) in 40 mL of dry dichloromethane ,was added drop wise ,under nitrogen atm at 0˚C , a solution of POCl3 (**0.8027749 gm ,0.0052306 mole**) in **20 mL** of dry methylene chloride with constant stirring .The reaction mixture after completion of reaction was worked up as usual . The product was column chromatographed over silica gel using 3:7 ethyl acetate – hexane as eluent solvent . Solvent evaporation furnished pure -β- lactam **3c** **Yield** 84% , **m.p** 144-146˚C ,

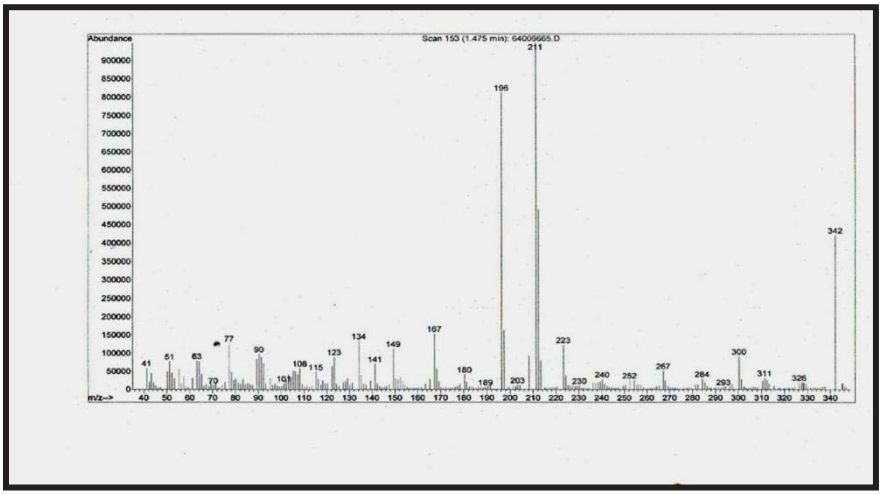
4 -General procedure of azetidin-2,3-diones 5f,5g(21,, 22,23)

It was worked up according to procedure as reported for(21-23) m.p:40-142°C

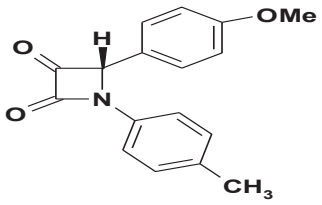
. 1-(4'-Methylphenyl)-4-(4'-methoxyphenyl)azetidin-2,3-dione 5g)It was worked up according to procedure as reported for(21-23) m.p. :136-138C

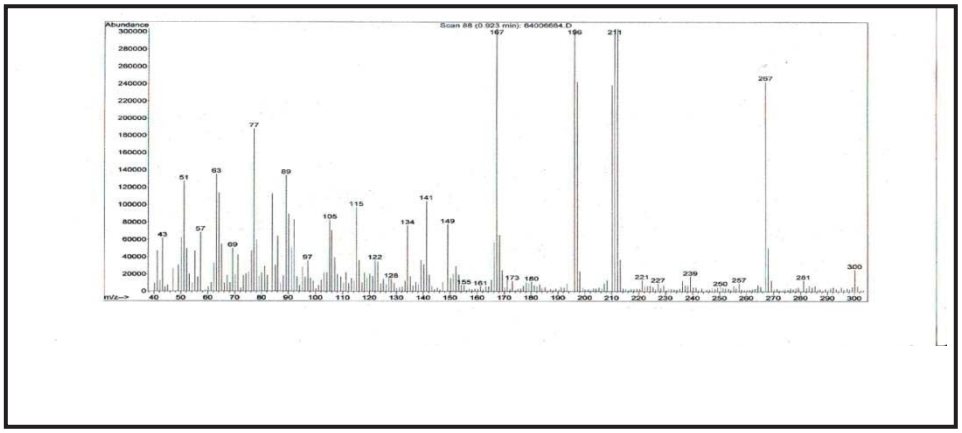




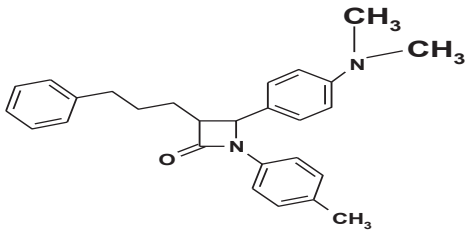


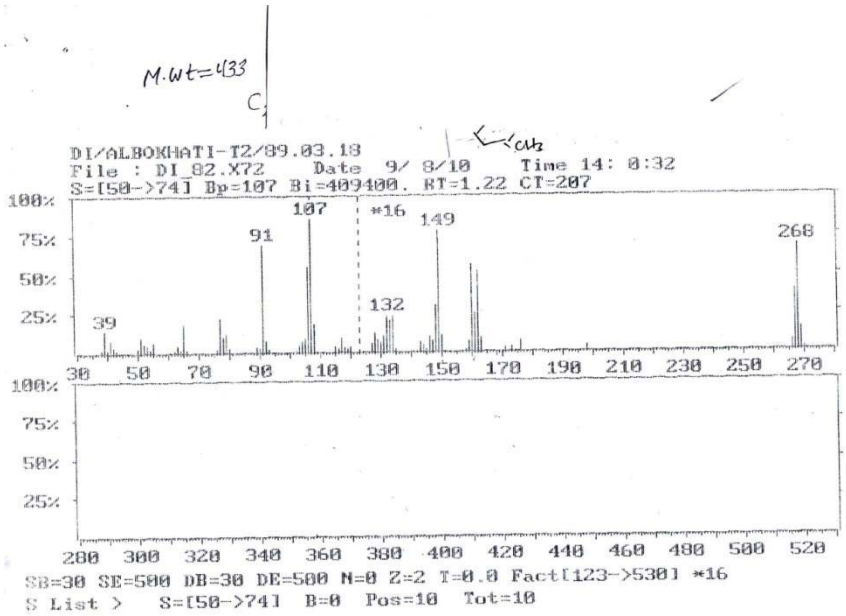
Fig(1-1): Mass spectra of 1-(4-Methoxyphenyl)-4-(4-bromophenyl)-azetidin-2,3-dione 4f



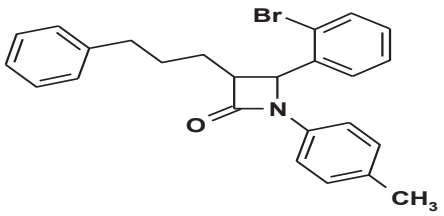


Fig(1-2): Mass spectra of 1-(4-Methylphenyl)-4-(4-Methoxyphenyl)-azetidin-2,3-dione 5g





Figure(1-3): Mass spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(N,N-dimethyl phenyl)azetidine-2-one 4d



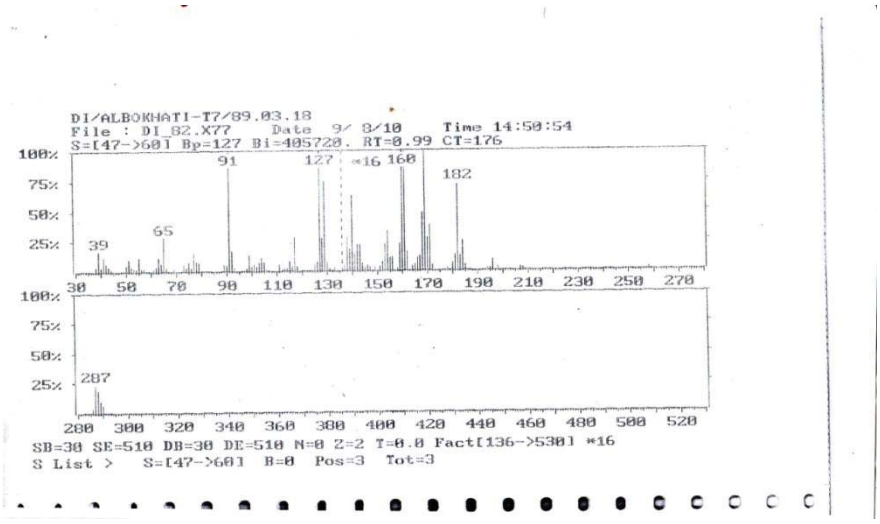
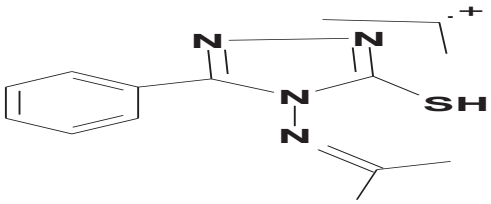
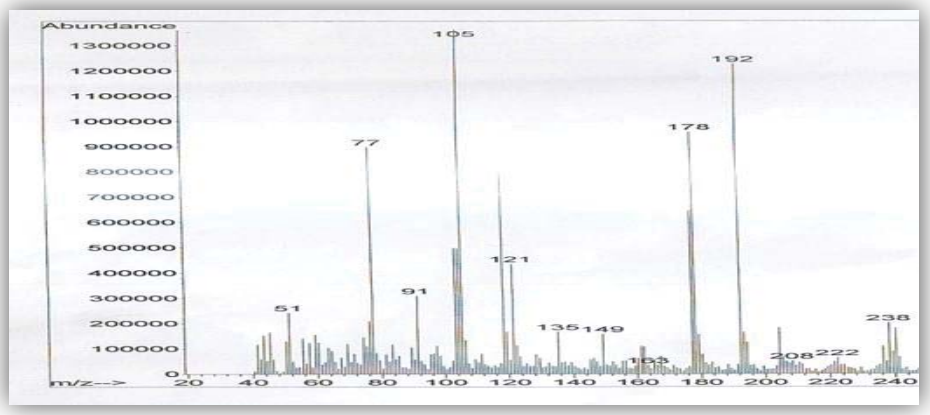
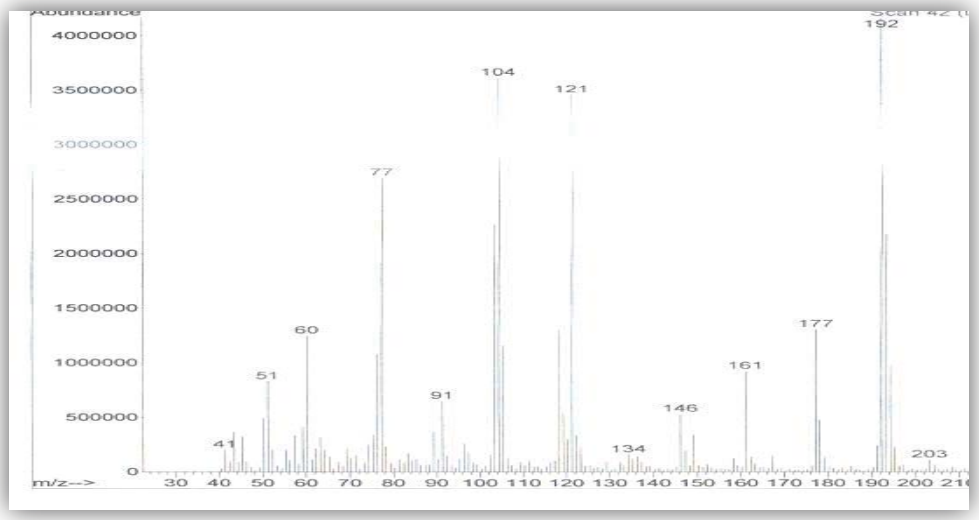


Figure (1-4): Mass spectrum of 1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(2-bromophenyl)azetidine-2-one 4e.

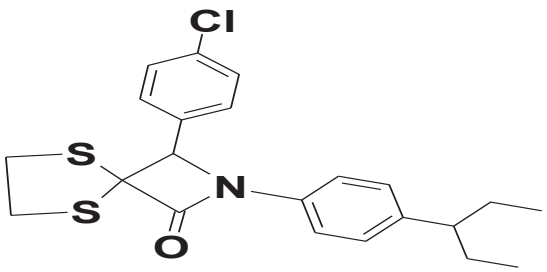


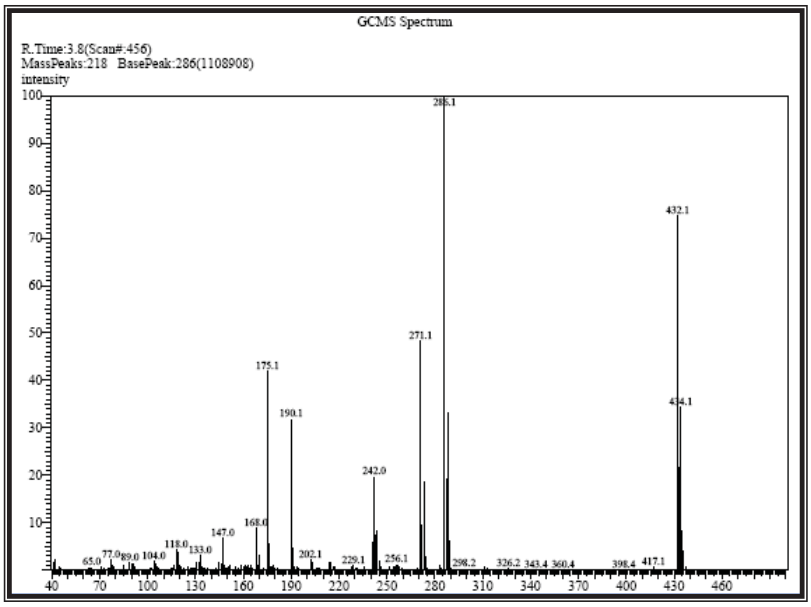


Fig(1-5): Mass spectra of 4-{[(1Z)-1-methyl ethylidene]amino }-5- phenyl – 4*H*-1,2,4-triazol -3-thiol2a**.**



Fig(1-6): Mass spectra of 4-{[(1Z)-1-methyl methylidine]amino }-5- phenyl – 4*H*-1,2,4-triazol -3-thiol 2b





Fig(1-7): Mass spectra of 5,9-dithia-2- azaspiro[3.5]nonan-1-one 3c

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