Synthesis and Characterization of Some New Azetidines and Azetidine-2-Ones

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Abstract

This study is concerned with the synthesis and characterization of azitidiane derivatives. These compounds were prepared by reacting alkyl halides with (imines) by heating at 70-60°C in ethanol with moderate yields (51-75%).Also prepared azetidine-2- from Schiff base with ketene in Et3N in ethenol Spectroscopic studies using IR, 1H-NMR, 13C-NMR, and Mass spectra.

Keywords: Azetidine ; imines; synthesis; NMR spectroscopy ,Azetidine-2-one

1. Introduction

One of the most significant substructures in pharmaceuticals is the azetidine motif, which can be found in a variety of approved medications including antibiotics1, kinases2 (such as baricitinib, cobimetinib, and itacitinib), and other compound classes3 (such as thrombin inhibitors like ximelagatran/melagatran and Cachannel blockers like azelnidipine.

The azetidine group can rigidify an acyclic counterpart, restrict its conformation4, and produce compounds with improved pharmacokinetic or toxicity profiles5. Studies have also shown that incorporating azetidines into pharmaceutically applicable scaffolds can enhance pharmacokinetic properties and metabolic stability6-7.

Given that they are widely used in numerous chemistry-related sectors, nitrogen heterocycles are valuable and of significant interest (Figure 1).

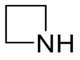

Figure 1. Azetidine ring

A cyclic amide is a lactam[8].It is so named because, in relation to the carbonyl, the nitrogen atom is connected to the -carbon atom..The most straightforward -lactam is 2-azetidinone.

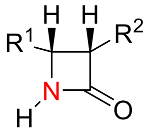

Figure 2. azetidine-2-one

The term "beta-lactam antibiotics" refers to a class of antibiotics that comprises all chemical structures such as penicillin, penams, cephalosporins, cephems, monobactams, and carbapenems 9.

Experimental part

The1H-NMR spectra were recorded using VARIAN spectrophotometer (500 MHz), the 13C-NMR spectra were recorded using VARIAN spectrophotometer (75 MHz).The chemical shift values are expressed in δ(ppm), using tetramethylsilane (TMS) as internal standard and d6-DMSO as the solvent.

General Procedure for preparation of azetidine from the reaction of the amine with the alkyl halide

The general method for preparing azetidine is to mix the elemental amin with an alkyl halide (1.3- dibromo propane) in an ethanol solvent in the presence of sodium carbonate. Set the machine's hotplate with the agitator to 70-80 ° C. Followed by TLC with eluent: (3: 7 ethyl acetate / hexane). Next, the contents. They were washed successively with hot (10 mL) water, and hot methanol .The organic layer was dried with Na2SO4.After completing From the reaction, the solvent was evaporated and recrystallized from ethanol.

1-tritylazetidine (1a)

It is prepared by reacting triphenylmethanamine 1g with 1,3-dibromopropane (0. 78 g , 0.39 mL) Sodium carbonate 0.41g R$_f$ =0.7, yield = 76.6%, m.p = 109-111°C Color :White . IR (KBr disk): 3054-3022cm^{-1}Ar-H , 2995cm^{-1}C-Haliphatic, 1620cm^{-1}C=Carm.^{1}H-NMR(500 MHz, DMSO-d$_6$) δ= 1.95 (m. 2H, CH$_2$); 2.94(t,2H,CH$_2$) ; 7.22-7.25 (m, Ar-H). ^{13}C-NMR (75MHz, DMSO-d$_6$) δ = 21.15, 42.68, 68.65, 128.81-151.92 . Mass spectra : 299 m/z(4%),271 m/z (2%) , 243 m/z (10%).

1-benzhydrylazetidine (1b)

It is prepared by reacting benzhydryl amine (1g , 0.94 mL) with 1,3-dibromopropane (1.1g , 0.55mL) , Sodium carbonate 0.58 g Rf =0.81, yield =36 m.p = 118-120°C. Colour :White . IR (KBr disk): 3051-3015cm-1Ar-H; 2957-2909cm-1C-Haliphatic ; 1591cm-1C=C arm. 1H-NMR(500 MHz, DMSO-d6) δ= 1.95 (m ,2H,CH2); 3.1 (t,2H, CH2) ; 4.36 (s,1H, C-H) ; 7.15-7.25-7.41(m,Ar-H) . 13C-NMR (75MHz, DMSO-d6) δ= 16.80 , 53.85, 77.57, 127.32-143.09 . Mass spectra: 223 m/z (46%) , 195 m/z(10%) , 119 m/z(14%) , 78 m/z (25%).

1-(4-Triylphenyl)azetidine (1c)

It is prepared by reacting 4-Triylaniline 1g with 1,3-dibromopropane (0.6g , 0.3mL) , Sodium carbonate 0.32g R$_f$=0.84, yield =44 m.p=263-265°C.Colour:White. IR (KBr disk): 3054-3022cm^{-1}Ar-H; 2958-2915-2842cm^{-1}C-Haliphatic; 1612cm^{-}

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^{1}C=Carm.^{1}H-NMR(500 MHz, DMSO-d_6) δ= 2.28 (m ,2H,CH_2); 3.1 (t,2H, CH_2) ; 3.76 (t,2H, CH) ; 7.25-7.17-6.89-6.78(m,Ar-H) . ^{13}C-NMR (75MHz, DMSO-d_6) δ = 16.23, 54.55, 73.60, 112.94- 149.72. Mass spectra : 375m/z (88%) , 347 m/z (2%) , 271 m/z (10%) ,168 m/z (20%) ,117 m/z (6%) ,78 m/z (10%) .

2-(azetidin-1-yl)benzo[d]thiazole (1d)

It is prepared by reacting 2-Benzothiazolamine 1g with 1,3-dibromopropane (1.35 g , 0.68 mL) , Sodium carbonate 0.71g R_f=0.53, yield =38 m.p = 119-121°C. Colour :White Yellow . IR (KBr disk):3058cm^{-1}Ar-H,2928cm^{-1}C-Haliphatic,1530cm^{-1}C=Carm,1640cm^{-1}C=N.^{1}H-NMR(500 MHz, DMSO-d_6)δ=1.96 (m ,2H,CH_2); 4.15 (t,2H, CH_2) ; 7.68-7.49-7.38-7.32 (m,Ar-H) . ^{13}C-NMR (75MHz, DMSO-d_6) δ = 20.87 ,57.92, 120.33- 155.38, 169.08. Mass spectra: 190 m/z (2%) , 162 m/z (2%) , 86 m/z (2%) , 78 m/z (8%) .

General Procedure for preparation of azetidin-2-ones 2(a-d)

3-chloro-1-((3-((4-nitrophenyl)amino)propyl)amino)-4-phenylazetidin-2-one (2a)

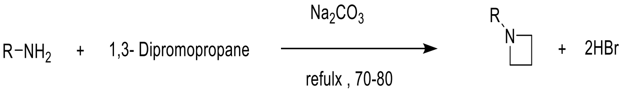
Compound 1a , it is prepared by reacting 4-Nitroaniline 5g with 1,3- di bromo propane (7.3g , 3.7mL). compound 1a ,it is prepared by reacting compound 1a (3.5 g) with hydrazine hydrate (0.63g , 0.64 mL) . compound 2a , it is prepared by reacting compound 2a (3g) with benzaldehyde (1.51 g , 1.45 mL) . R_f =0.66, yield =55%, m.p. =200-202 °C. IR (KBr disk): 1631cm -1 (C=N). compound 3a , it is prepared by reacting compound 3a (0.18 g) with Et_3N(triethylamine),(0.06 g , 0.25 mL) , and chloroacetyl chloride (0.07 g , 0.07 mL) . R_f =0.66 ,Yield =52, m.p. =186-188 ^{0}C , Colour: Yellow. IR (KBr disk) 3280cm^{-1}N-H, 3164-3108cm^{-1}Ar-H,2942-2924-2853cm^{-1}C-Haliphatic,1598cm^{-1}C=Carm,1640cm^{-1} C=N,1683cm^{-1}O=C-N . ^{1}H-NMR(500 MHz, DMSO-d_6) δ= 1.21 (m,CH_2), 4.16(s, C_4-H), 4.39 (d, C_3-H),7.70-8.25 (m,Ar-H) 11.18(N-H, isatin amide) .^{13}C-NMR (75MHz, DMSO-d_6) δ =29, 37, 42, 46- 76, 78, 121- 147, 168.

4-(4-aminophenyl)-3-chloro-4-methyl-1-((3-(tritylamino)propyl)amino)azetidin-2-one(2b)

Compound 1a , it is prepared by reacting triphenylmethylamine (1.2g) with 1,3-dibromo propane (0.94g , 0.47 mL). Compound 1 ,it is prepared by reacting compound 1a (0.95 g) with hydrazine hydrate (0.13g , 0.13 mL) Compound 2a , it is prepared by reacting compound 2a (1.3 g) with 4-aminoacetophenone(0.53 g).Rf= 0.61, yield = 58%, m.p. =175-177°C.IR(KBr disk): 1645cm-1C=N. compound 3a , it is prepared by reacting compound 3a (0.35 g) with Et3N(trietheylamine),(0.08 g , 0.33 mL) , and chloroacetyl chloride (0.09 g , 0.1 mL) . Rf =0.73 ,Yield =50, m.p.= 138-140 0C , Colour :Yellow.IR(KBr disk), 3315cm-1N-H,3184-1Ar-H,2947-2922cm-1C-Haliphatic,1604-1562cm-1C=Carm,1678cm-1O=C-N. 1H-NMR(500 MHz, DMSO-d6) δ=3.71(C7-H),4.36 (d, C3-H), 4.24 (s,C4-H) , 7.15- 7.30- 7.43-7.71 – 7.90 (m,Ar-H); 10.39 (N-H) . 13C-NMR (75MHz, DMSO-d6) δ = 8, 28, 42, 45, 54-53, 102, 121- 151, 160. Mass Spectra 403m/z (0.9%), 327 m/z(2%) ,236m/z (4%) , 205 m/z (6%) , 167m/z(8%) , 133m/z(28%) , 114m/z (4%) , 76m/z (48%), 72m/z(18%), 57m/z(22%).

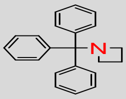
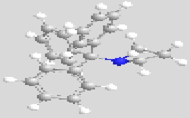
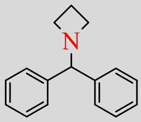
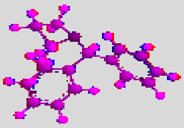
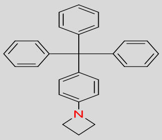
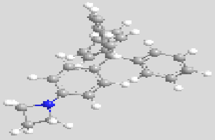
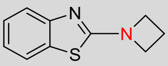
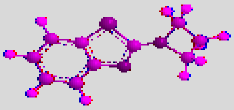
2. Results and Discussion

Azetidine was prepared by reacting alkyl halide 1,3-dibromopropane with the primary amine and using a sodium carbonate catalyst in a suitable solvent (ethanol).As shown in these structure table.

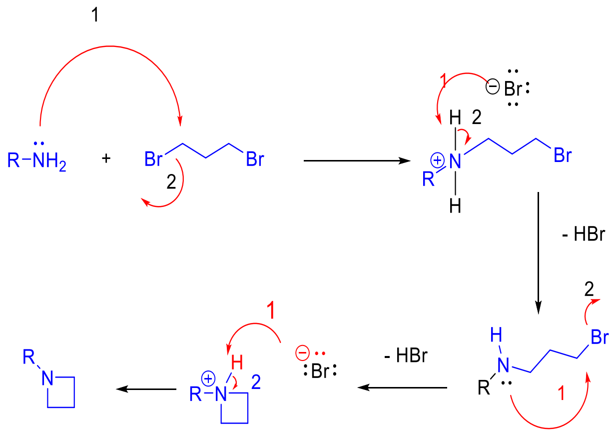


Scheme 1:Genaral reaction for the synthesis of azetidines.

Table (1): The chemical structure of prepared azetidines 1(a-d)

COMP.	Molecular formula M.Wt(g/mol	Structure formula	Structure three dimention	Name of proudect
1a	C22H21N M.W=299			1-tritylazetidine
1b	C16H17N M.W=223			1-benzhydrylazetidine
1c	C28H25N M.W=375			1-(4-tritylphenyl)azetidine
1d	C10H10N2S M.W=190			2-(azetidin-1-yl)benzo[d]thiazole

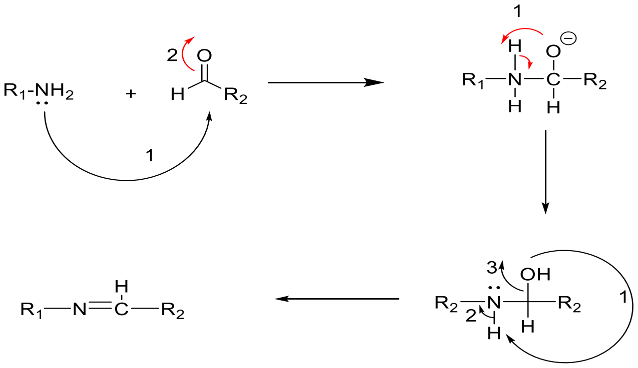
Azetidine derivatives are synthesised by the reaction of amine and 1,3- dipromopropanein the presence of ethanol .The suggestion mechanism for the reaction can be shown in scheme.



Scheme2. Mechanism of formation of Azetidine

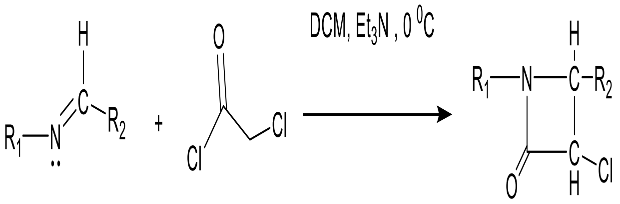
Schiff bases

Schiff bases are formed by condensation of primary amine , and an aldehyde or ketone. Schiff bases are important intermediates for the synthesis of various an bioactive compound[10] .Furthermore , Schiff bases show variety of biological activities including antibacterial ,anti-cancer ,antifungal ,and herbicidalactivities[11] . The suggestion mechanism for the reaction Schiff bases can be shown in scheme(3)



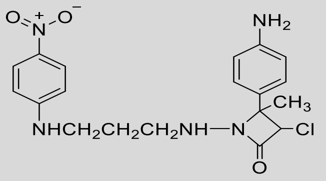
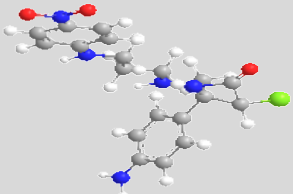
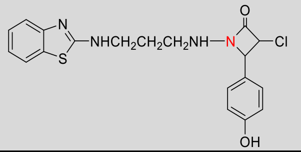
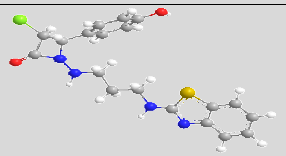
Scheme3. Mechanism of formation of Schiff base

Azetidine-2-onesh have been prepared by reaction of the appropriate Schiff bases with triethylamine in a suitable solvent (DMC or THF).

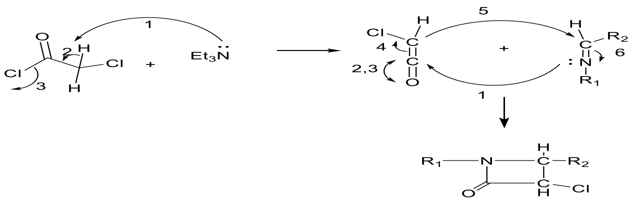


Scheme 4:Genaral reaction for the synthesis of azetidine-2-ones.

Table (2): The chemical structure of prepared **β** –Lactam 2(a-b)

Symbol	Molecular Formula M.Wt(g/mol)	Structural Formula	Three dimension Structural
2a	C19H22ClN5O3 403		
2b	C19H19ClN4O2S 402		

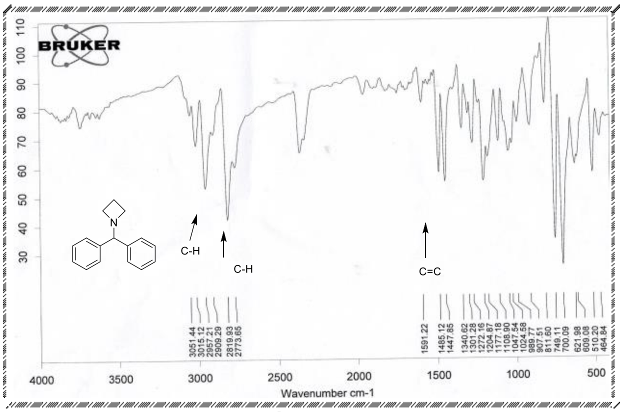
Both the ketene and the imine are molecules that can act as either nucleophiles or electrophiles. In the first step, the imine adds to the ketene as a nucleophile. The subsequent cycloaddition delivers the β-lactam .



Scheme5. Mechanism of formation of Azetidine-2-one

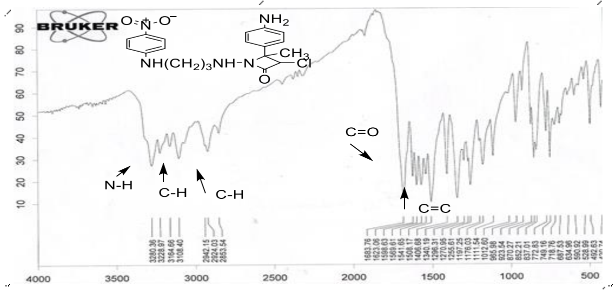
Analysis of infrared spectra

The IR spectra of Azetidine in KBr disk show six band groups correspond to the stretching vibration of the, aromatic C-H, aliphatic, aromatic C=C, the C-N and bending vibration of 3228, 3108 , 2942, 1683 and (1598)bonds, occur within the ranges cm-1 respectively.



Fig(3) IR spectrum of 1-benzhydrylazetidine (1b)

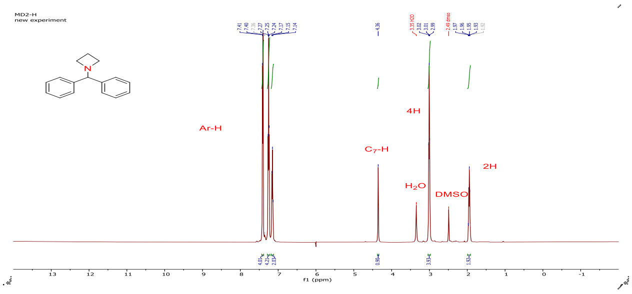
The IR spectra of Azetidine-2-ones (2a) in KBr disk show six band groups correspond to the stretching vibration of the N-H, aromatic C-H, aliphatic, carboxyl amide aromatic C=C, the C-N and bending vibration of bonds, occur within the ranges 3228, 3108 , 2942, 1683 and 1598 cm-1 respectively



Fig(4): IR spectrum of 4-(4-aminophenyl)-3-chloro-4-methyl-1-((3-((4-nitrophenyl)amino)propyl)amino)azetidin-2-one(2a).

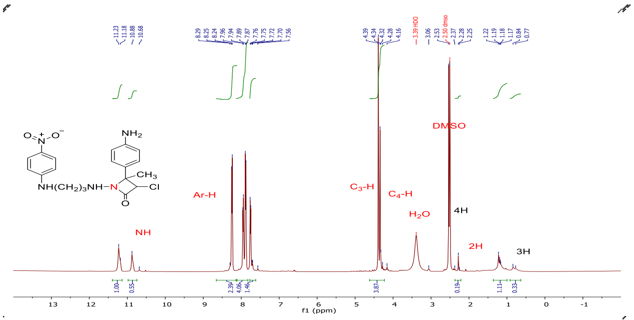
1H-NMR spectral analysis

The 1H-NMR spectrum of 1b , shows signal at chemical shift 2.49ppmfor DMSO solvent. Also it showed signal at chemical shift 3.39 ppmfor HDO,and showed proton carbon(s,C7-H)at 4.36ppm, also it showed signal at chemical shift1.95ppm (m,2H, J= 5 Hz) , and signal at chemical shift 3.1ppm (t,4H,J=5Hz), of azetidine ring , also the spectrum showed signal at chemical shift (m,7.15-7.25-7.41ppm, J = 10Hz) for protons of aromatic .



Fig(5):1H-NMR spectrum(500MHz) of 1-benzhydralazetidine(1b)in H20+DMSO at 298k.

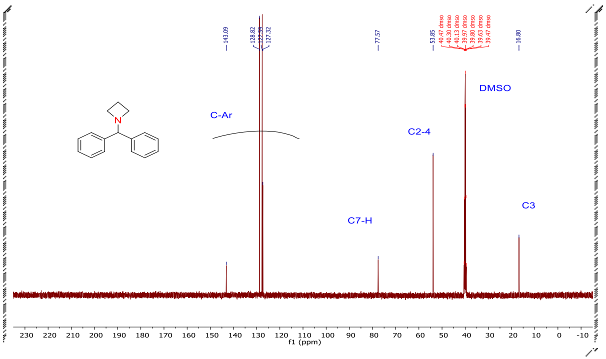
The1H-NMR spectrum of 2a , shows signal at chemical shift (2.50 ppm)for DMSO solvent . Also it showed signal at chemical shift (3.39 ppm) for HDO.1H-NMR of shows proton carbon (d, C3-H)at(4.39ppm) , and showed proton carbon 4.16(s, C4-H). Also it showed signal at chemical shift 2.25(t,4H),And it showed signal at chemical shift 0.78(d, 3H). And it showed signal at chemical shift 1.18(m, 2H) of B-lactam ring . Also the spectrum showed a multi signal at 7.70-8.25 ppm for twelve protons of aromatic protons and finally showed singlet signal at chemical shift (11.23 11.18) for one proton of isatin amide .



Fig(6):1H-NMRspectrum (500MHz) of 4-(4-aminophenyl)-3-chloro-4-methyl-1-((3-((4-nitrophenyl)amino)propyl)amino)azetidin-2-one(2a)in DMSO-d6 at 298K.

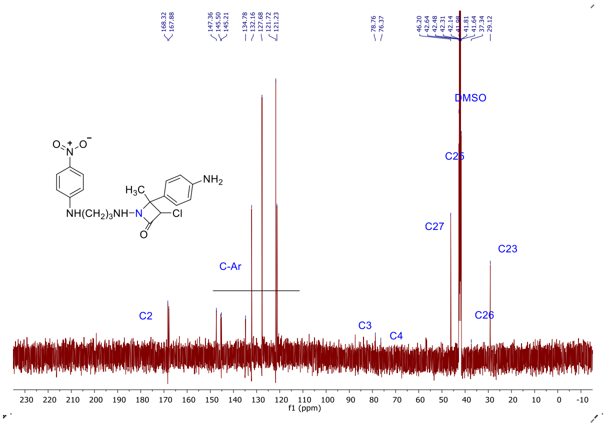
Analysis of 13C-NMR spectra

13C-NMR of (1b) azetidine ring signal at δ 53.85ppm for carbon methylene group.One singlet signal at δ16.80ppm for carbon methylene group No 16(C16) and another singlet signal at δ 77.57 ppm for carbonNo.7(C7) in azetidine .The 13C-NMR DEPT spectrum of (1b) also showed signals at δ 127.32-143.09ppm for carbon aromatic atoms .



Fig(7):^{13}C-NMR spectrum (500MHz) of 1-benzhydrylazetidine (1b)in DMSO-d6 at 298 K

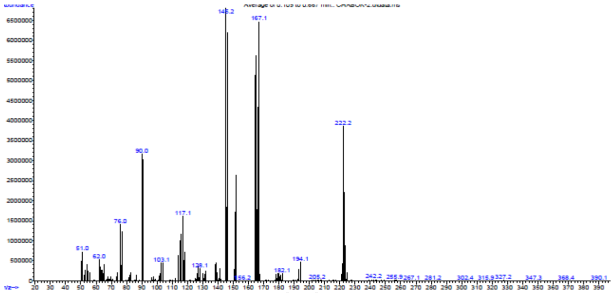
13C-NMR of (2a) azetidine-2-one ring signal at δ 78.76 ppm for carbon (C-H) No. 3 (C3). Also show singlet signal at δ 76.37 ppm for carbon (C-H) No. 4 (C4).one singlet signal at δ42.64 ppm for carbon methylene group No. 25(C25), also show singlet signal at δ46.20 ppm for carbon methylene group No. 27(C27) , also show singlet signal at δ37.34 ppm for carbon methylene group No. 26(C26). and show singlet signal at δ 29.12 ppm for the carbon methane in azetidin-2-one.The 13C-NMR spectrum of also showed signals at δ 121. 23-147.36 ppm for carbon aromatic atoms. Finally a singlet signal appered at δ (168.32 ppm) for the carbon No. 2(C2) of B-lactam .



Fig(8):^{13}C-NMR spectrum (500MHz) of4-(4-aminophenyl)-3-chloro-4-methyl-1-((3-((4-nitrophenyl)amino)propyl)amino)azetidin-2-one(2a) in DMSO-d6 at 298 K.

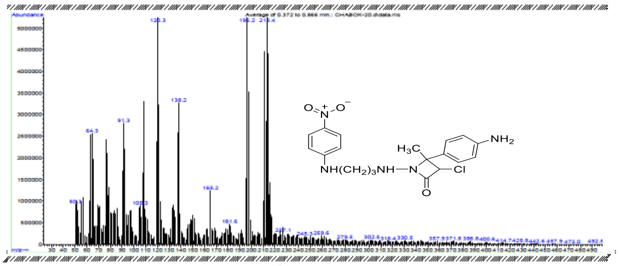
Analysis of mass spectra

The Mass spectral date of 1b (azetidine) showed the molecular ion peak corresponding to the particular compound at 223 m/z (46%) , 195 m/z(10%) , 119 m/z(14%) , 78 m/z (25%). Which attributed to the fragments of $C_{16}H_{17}N$, $C_{14}H_{13}N$,C8H9N , C_6H_6 .



Fig(9): mass spectrum of of1-benzhydrylazetidine (1b)

The Mass spectral date Show of 2a (azetidine-2-one). showed the molecular ion peak corresponding to the particular compound at 403m/z (0.9%), 327 m/z(2%) ,236m/z (4%) , 205 m/z (6%) , 167m/z(8%) , 133m/z(28%) , 114m/z (4%) , 76m/z (48%), 72m/z(18%), 57m/z(22%). Which attributed to the fragments of $C_{19}H_{22}ClN_5O_3$, $C_{17}H_{21}N_5O_2$,$C_{10}H_{12}N_4O_3$, $C_{11}H_{17}N_4$, C_2HClO , $C_9H_{10}ClN$, $C_4H_8N_3O$, C_3H_7N, $C_8H_9N_2$, $C_3H_8N_2$



Fig(10):mass spectrum of 4-(4-aminophenyl)-3-chloro-4-methyl-1-((3-((4-nitrophenyl)amino)propyl)amino)azetidin-2-one(2a

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