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SYNTHESIS AND CHARACTERIZATION OF 3,3'-(ETHANE-1,2-DIYLBIS(SULFANEDIYL))BIS(1-(4-BROMOPH-ENYL)-4-(4-CHLOROPHENYL)AZETIDIN-2-ONE)

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ABSTRACT
This study is concerned with the synthesis and characterization of the3,3'-(ethane-1,2-diylbis(sulfanediyl))bis(1-(4-bromoph-enyl)-4-(4-chlorophenyl)azetidin-2-one) **2b**. This compound was prepared by reacting 2,2'-(ethane-1,2-diylbis(sulfanediyl)) diacetic acid with the appropriate 4-bromo-N-(4-chloro benzylidene) aniline **1b**. The structure of these azetidin-2-one was established on the basis of the spectral data: IR, ^{1}H NMR, ^{13}C NMR and Mass.

KEYWORDS: Imine; Azetidin-2-ones; β-lactam; IR; 1H NMR; 13C NMR; Mass spectroscopy.

1. INTRODUCTION

Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation, within the scientific as well as the public sectors.[1–7] β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole. β-Lactam antibiotics have proved to be chemotherapeutics of incomparable effectiveness, possessing a broad spectrum of biological activities with low host toxicity.[8] First synthesized in 1907 by Staudinger.[9] the four membered cyclic amide derivatives of 3-aminopropionic acids known as β-lactams, did not come to the forefront in organic chemistry until Fleming's landmark discovery of penicillin in 1929.[10] The resulting recognition of the β-lactam moiety as the key pharmacophoric component of the penam antibiotics initiated a flurry of synthetic activity. Today, thousands of compounds containing β-lactam rings are known. Whether isolated from natural sources or synthesized chemically, penicillins and cephalosporins are marked by high efficacy and safe toxicological profiles and are still the most commonly used antibiotics the world over.[11] Further, the discovery bicyclic β-lactams stimulated the search for novel antibiotics. More recent dedicated efforts to find new active molecules and modify the penicillin and cephalosporin structure have resulted in the discovery of simple monocyclic β-lactams such as norcardicins and monobactams.[12,13]

β-Lactam nucleus is the center of the biological activity of a large class of antibiotics characterized by the presence of this Quartet loop and differentiated by side chains, unsaturation's, heteroatoms, and, in many cases, by the presence of five-or six-membered rings.[14] β-lactam antibiotics, including penicillins and the non-penicillin classes, share a basic chemical structure that includes a three-carbon, one-nitrogen cyclic amine structure known as the β-lactam ring. The side chain associated with the β-lactam ring is a variable group attached to the core structure by a peptide bond; the side chain variability contributes to antibacterial activity. The activity of the penicillins and cephalosporins is believed to be due to the β-lactam ring.

After the discovery of penicillins and cephalosporins as classical β-lactam antibiotics and clinically useful active agents, the past few decades have witnessed a remarkable evolution in the field of β-lactam chemistry.[15,16] The need for potentially effective β-lactam antibiotics as well as more effective β-lactamase inhibitors have paid synthetic organic and medicinal chemists to design new functionalized 2- azetidinones. Besides their clinical use as antibacterial agents, these compounds have also been used as synthons in the preparation of various heterocyclic compounds of biological significance.[17.21]

1. The Experimental

In general, the Schiff bases were prepared by heat the mixture of 0.01 mole amine with 0.01 mole aldehyde ,10 mL of methanol 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 TLC. After completion, the solvent evaporated more than recrystallized from a suitable solvent.[22,23] as shown in Table (2-1). Where it is prepared 4-bromo-N-(4-chlorobenzylidene) aniline 1b, it was prepared by the reaction 4-bromoaniline (1.72 g) with 4-chlorobenzaldehyde (1.40 g).

To a suspension of 2,2'-(ethane-1,2-diylbis(sulfanediyl)) diacetic acid (0.4 g, 2 mmole) , 4-bromo-N-(4-chlorobenzylidene) aniline **1b** (1 g, 3.39 mmole) and triethylamine (3 mmole, 1.15 g, 1.59 ml) in 25ml of dry dichloromethane was added drop-wise, under nitrogen atmosphere, a solution of $POCl_3$ (1.5mmole, 0.87g, 0.48ml) in 20ml dry dichloromethane with constant stirring at 0˚C. The reactants were stirred overnight at room temperature. Thereafter, the contents were washed successively with 1N HCL (25mL), 5% $NaHCO_3$ (25mL) and brine salt (25mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude product was column chromatographed over silica gel using 3:7 ethyl acetate\ hexane as eluent and solvent evaporation furnished pure β-lactam **(2b)**[24,25], as shown in Table (2-1).

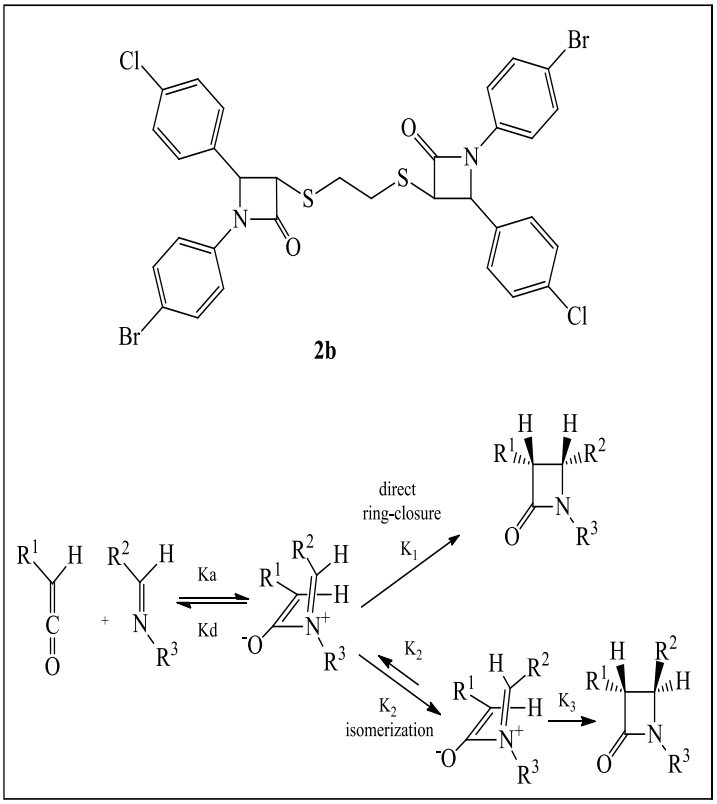
Table: (2-1) Physical data for azetidine-2-(2a) and imine (1a).

Comp.	Yield (%)	M.P. ˚C	Color
1b	85	123 - 125	White Yellowish
2b	76	182-184	White

3. RESULTS AND DISCUSSION

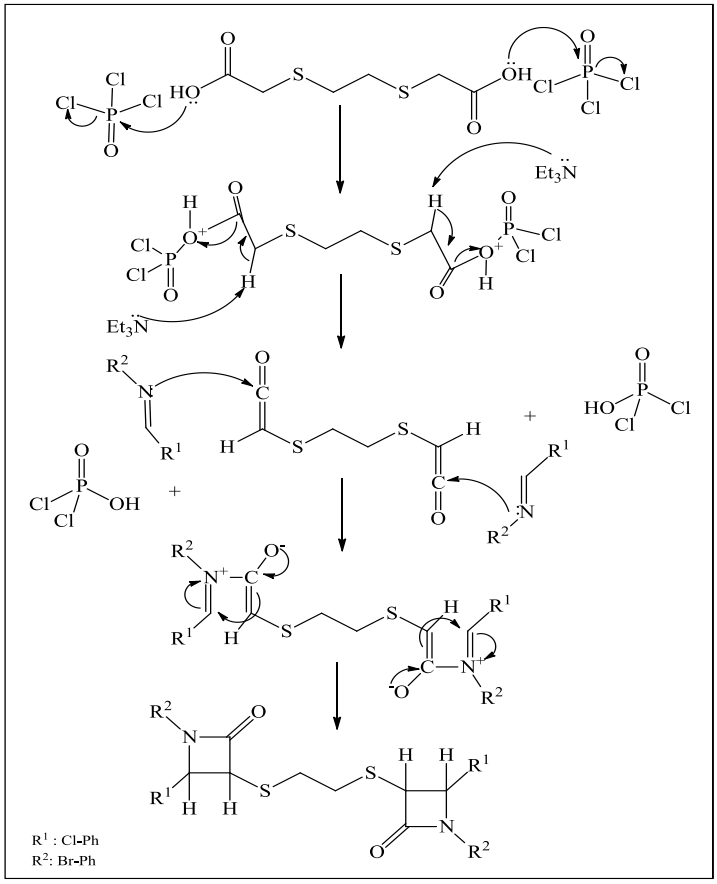
3.1. General

Taking the lead from previous studies.[26,27] we considered to employ ketene-imine cyclization in the presence of triethylamine of the synthesis 3,3'-(ethane-1,2-diylbis(sulfanediyl)) bis(1-(4-bromophenyl)-4-(4-chlorophenyl) azetidin-2-one)**2b**, as shown in (scheme 1).



(scheme 1)

As mentioned in the beginning, the synthesis 3,3'-(ethane-1,2-diylbis(sulfanediyl)) bis(1-(4-bromophenyl)-4-(4-chlorophenyl) aze-tidin-2-one)**2b**, was prepared from 2,2'-(ethane-1,2-diylbis(sulfanediyl)) diacetic acid and appropriate imine **1b** in presence of triethylamine. The active acid chloride reacted with triethylamine to generate the corresponding ketene in situ which further reacted with imine to furnish the corresponding β-lactam in moderate yields, as shown in (Scheme 2).



(scheme 2)

3.2. IR spectra of 1b and 2b

The IR spectra of the imine **1b**, as KBr disc is shown in Figure (3-1). The IR spectra showed an absorption band at 1624.08 cm-1, corresponding to the azomethine of imine compound. The rest of the packages can be summarized in the table (3-1).

The IR spectra of the 3,3'-(ethane-1,2-diylbis (sulfane diyl)) bis(1-(4-bromophenyl)-4-(4-chlorophenyl) azetidin-2-one) **2b**, as KBr disc and, is listed in Table (3-2). The IR spectra of these compound 2b showed an absorption band at (1684 cm-1) for carbonyl amide group as shown in figure (3-1). The IR absorption frequency of carbonyl group depended upon the nature of substituents on phenyl ring by an electron-with drawing group such as bromo group will increased the absorption frequency.[28] The disappearance of imine band and appearance of the carbonyl group band confirmed the correct expected structures of the azetidine-2-one derivative.

w: weak. m: medium. s: strong.

Table (3-1): FT-IR spectra of imine(1b) and azetidine-2-one(2b).

absorption band	1b	2b
Aromatic C-H Str. cm^{-1}	3078 *m* 3053 *w*	3027 *w* 3064 *w* 3133 *m*
Aliphatic C-H Str. cm^{-1}	2859 *s*	2983 *m* 2891 *w* 2675 *m*
C=N Str. cm^{-1}	1624 *s*	
Aromatic C=C Str. cm^{-1}	1589 *m* 1564 *m* 1487 *s*	1591 *s* 1490 *w* 1425 *m*
Aromatic C-H Ben. cm^{-1}	717 *w* 831 *s* 883 *w*	852 *m*
C=O Str. cm^{-1}		1684 *s*

3.3. NMR spectra

3.3.1. The ^{1}H-NMR spectra of 2b

The 1H-NMR spectra data of the 3,3'-(ethane-1,2-diylbis(sulfanediyl))bis(1-(4-brom-ophenyl)-4-(4-chlorophenyl) azetidin-2-one) **2b**. The 1H-NMR spectra of 2b showed three regions, an aliphatic region including tree groups of signals at the region δ 2.81 ppm corresponding SC-H and δ 4.50-5.12 ppm corresponding to methylene, C3-H, and C4-H protons. In the 1H-NMR spectra the range of δ 7.44-8.20 ppm, corresponding to aromatic protons. which are included in Table (3-2) with their spectra, as shown in Figure (3-3).

3.3.2. 13C NMR spectra of 2b

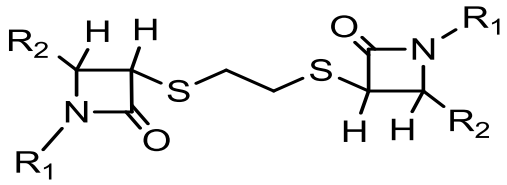
The ^{13}C NMR spectra of the **2b,** of the azetidine-2-one. The resonance as between δ 166 ppm were assigned to the carbonyl [29,30] group. The ^{13}C NMR spectra of the **2b** showed the carbonyl signal at δ164.4 ppm. The chemical shift values of aliphatic carbon atoms within the range δ 30.8-67.3 ppm and values of aromatic carbon atoms within the range δ 122.3-141.6 ppm. which are included in Table (3-2) with their spectra, as shown in Figure (3-4).

Table: (3-2) ^{1}H-NMR and ^{13}C NMR spectra data of azetidine-2-one 2b.

Chemical shift ppm	^{1}H-NMR /CD3OD δ ppm 2b	^{13}C NMR /$CDCl_3$ δ ppm 2b
Aliphatic protons δ ppm	2.814 4.504-4.537 5.124-5.156	30.8, 49.4 67.6, 164.4
Aromatic protons δ ppm	7.441-7.485 8.137-8.207	121.1, 122.3,127.1 131.4,136.7, 138.5,142.5

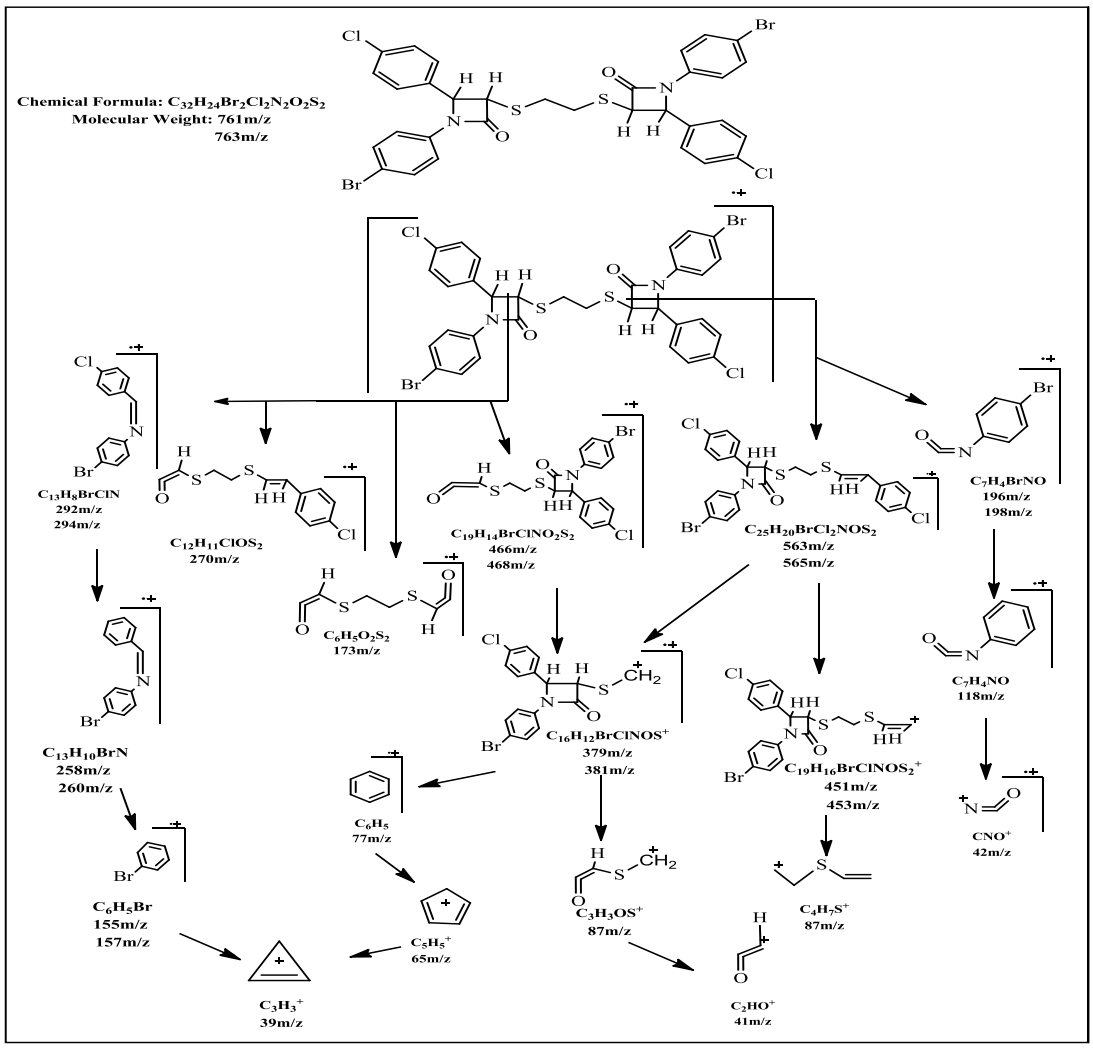
3.3.2 ^{13}C NMR spectra 2b

The mass spectral data of the compound is shown in the Figure (3-5). The mass spectra of compound **2b**, showed the molecular ion peak corresponding to the particular compound M^{+}761 m/z. The fragmentation of **2b** lead to ketene, isocyanate and imine. The fragmentation of **2b** leading to the ketene 270 m/z and 173m/z. corresponding isocyanate 196 m/z and 118 m/z also the fragmentation of this compound **2b** showed the imine peaks 296 m/z. the fragmentation mechanism of compound **2b** is shown below[31.32] in Schemes 2.



R_1: Ph-Br, R_2: Ph-Cl

Mass spectra	m/z
2b	(M^{+})761m/z, (R_2-C=NR_1)292m/z, (R_1-C=O)196m/z, (Ph-N=C=O)118 m/z, (R_2-CH=CH-S-$(CH_2)_2$-S-CH=C=O)270m/z, (R_1-N=C-Ph) 258m/z, (C_6H5^{+})77m/z, (R)155m/z ($^{+}CH_2$-S-CH=C=O)87m/z, ($C_5H_5^{+}$)65m/z



scheme 5

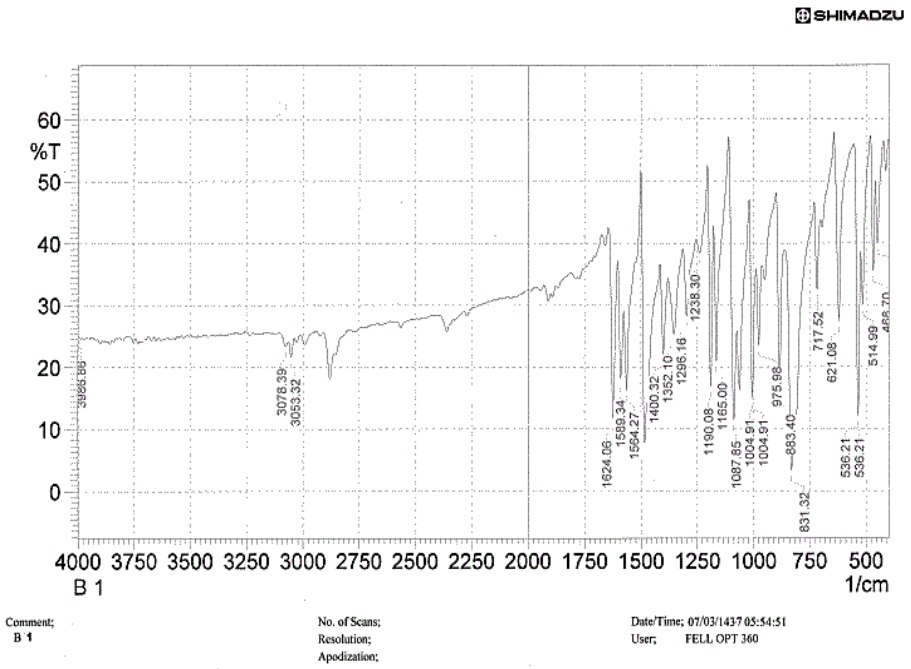


Figure (3-1): FT-IR spectrum of N-(4-bromobenzylidene)-4-chloroaniline1b.

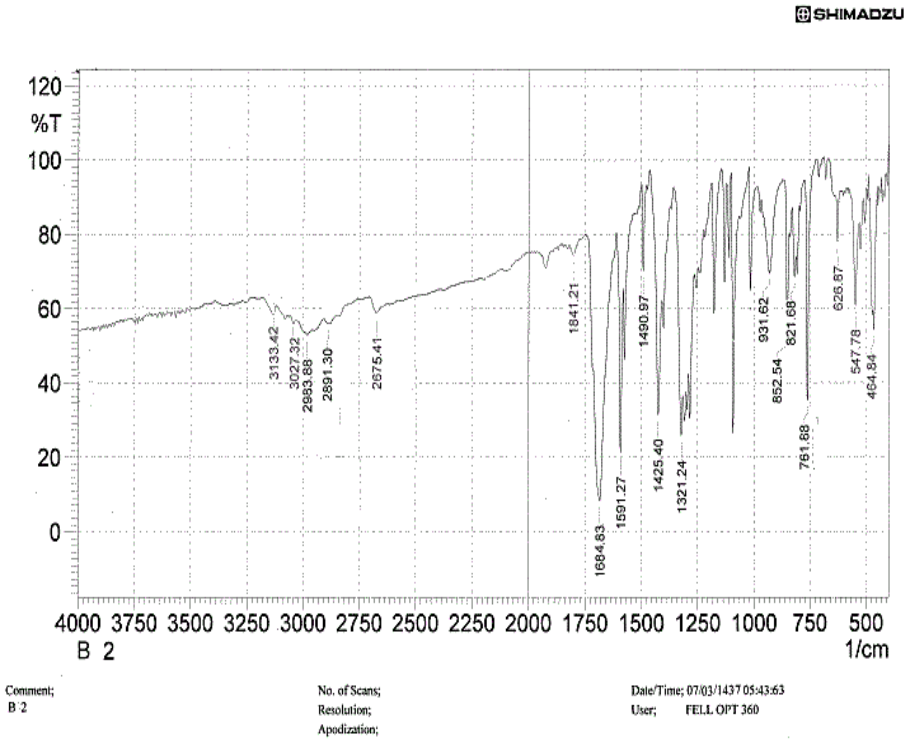


Figure (3-2): FT-IR spectrum of 3,3'-(ethane-1,2-diylbis (sulfanediyl))bis(1-(4-bromophenyl)-4-(4-chlorophenyl) azetidin-2-one)2b.

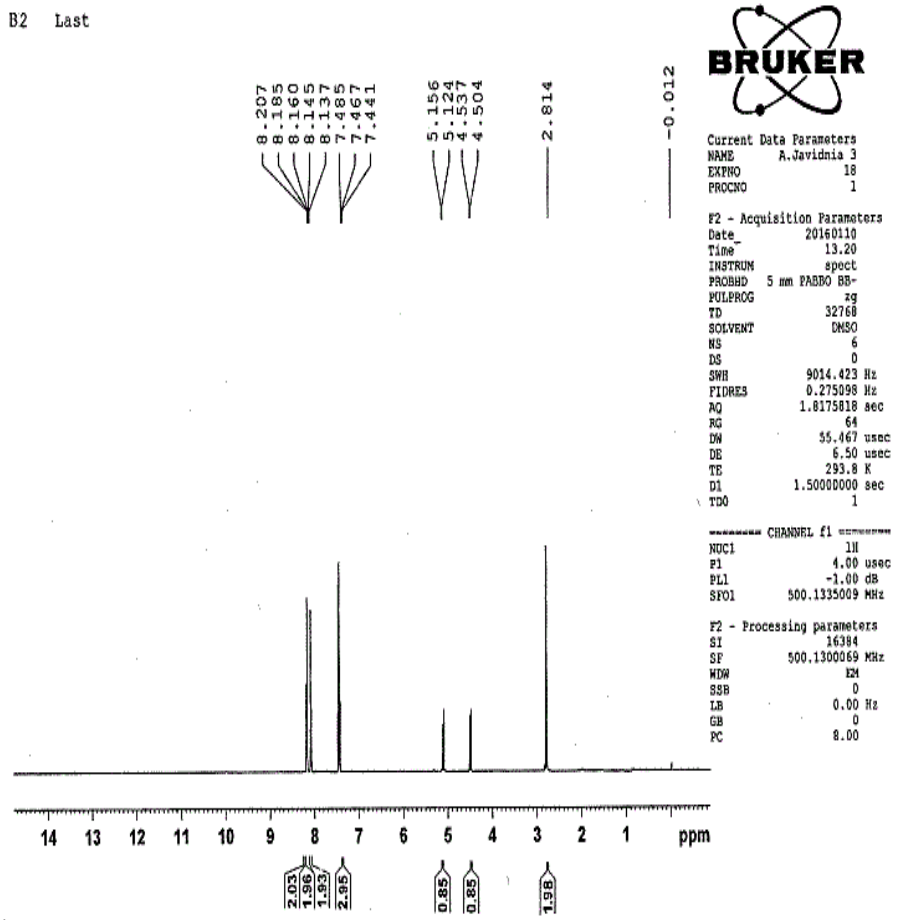


Figure (3-3): ^{1}H-NMR spectrum of 3,3'-(ethane-1,2-diylbis (sulfanediyl))bis(1-(4-bromophenyl)- 4-(4-chlorophenyl) azetidin-2-one)2b.

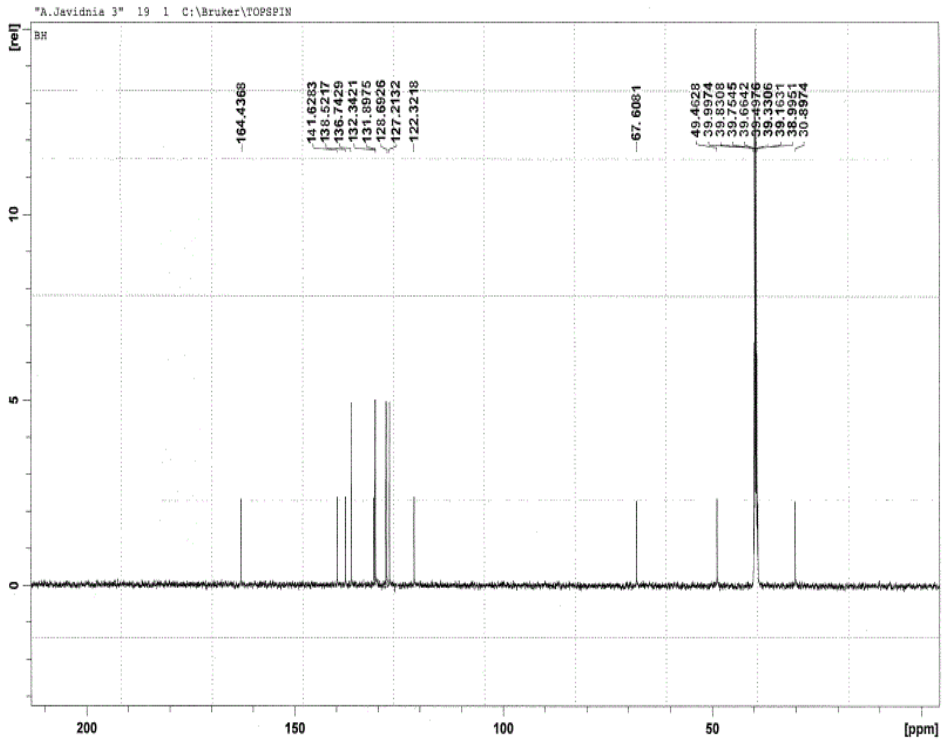


Figure (3-4):^{13}C NMR spectrum of 3,3'-(ethane-1,2-diylbis (sulfanediyl))bis(1-(4-bromophenyl)-4-(4-chlorophenyl) azetidin-2-one)2b.

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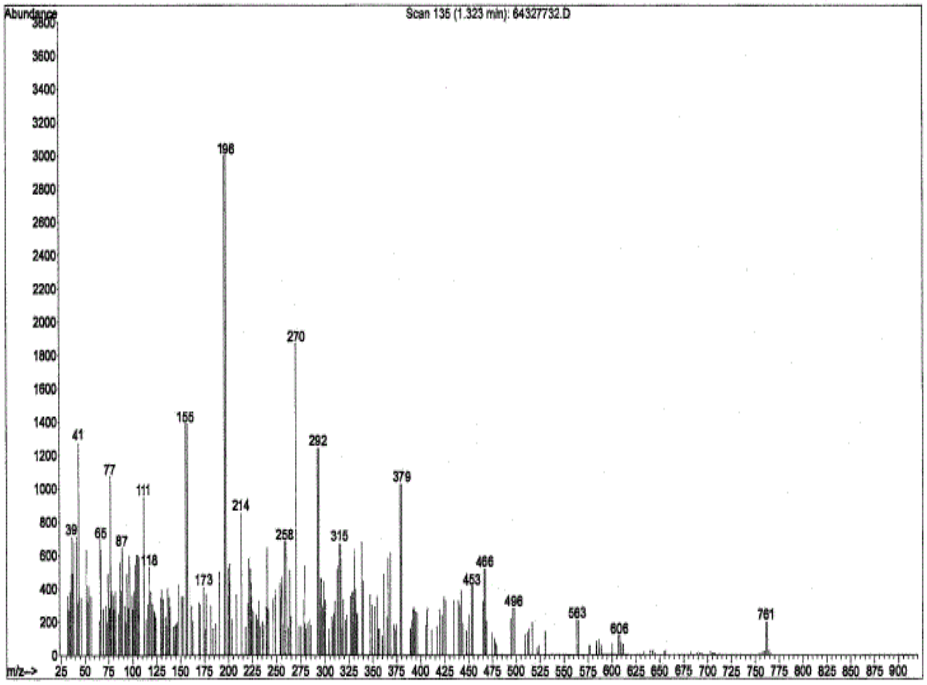

Figure (3-5): Mass spectrum of 3,3'-(ethane-1,2-diylbis (sulfanediyl))bis(1-(4-bromophenyl)-4-(4-chlorophenyl) azetidin-2-one)2b.

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