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Design, Synthesis and Investigation of Mefenamic Acid Containing Thiazolidine-4-one

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ABSTRACT

Mefenamic acid and chloroacetyl chloride were mixed together to make 2-(2-chloro-N-(2,3-dimethylphenyl) acetamido) benzoic acid. The last compound prepared reacted with hydrazine hydrate to get 2-(N-(2,3-dimethylphenyl)-2-hydrazineylacetamido) benzoic acid, Condensed substituted benzaldehydes were utilized to make Schiff bases; Through cyclization reactions with thioglycolic acid, these compounds were transformed into 2,3-disubstituted thiazolidine-4-one; and finally, all structures were described using FT-IR, 1H-NMR, and mass spectrometry.

Keywords- Thiazolidine-4-one, Mefenamic Acid.

I. INTRODUCTION

2-[N-(2,3-dimethylphenyl)amino]benzoic acid (mefenamic acid) or ponstan, is a kind of nonsteroidal anti-inflammatory medication (NSAID) that demonstrates properties that are anti-inflammatory, analgesic, and antipyretic. [1,2]. It has a wide range of applications as a therapeutic agent, and in 2012 alone, more than 100 million treatments with NSAIDs were carried out all over the world.[3] The maximum safe dose of this medication is between 500 and 250 milligrams spread out over a period of seven days. Mefenamic acid works by inhibiting COX (cyclooxygenase enzymes), which are essential for the generation of prostaglandins. This is how it achieves its therapeutic effects [4,5]. Structure of the aromatic amino acid mefnamic acid (Figure 1). This may also have physiologic effects.[6].

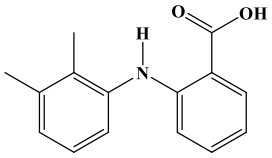

Figure1: Mefenamic acid structure

This chemical has a limited biological half-life of two hours and has very poor solubility in gastrointestinal irritants and biological fluids.[7] People still use it to treat pain, gout, and headaches. Doctors don't really know what causes pain. The World Health Organization says that 90% of all diseases cause pain. [8-9]. Mefenamic acid (MA) has been identified as an antirheumatic agent. Moreover, new research have reported on the therapeutic potential of this medicine for cancer cell lines and Alzheimer's disease.[10, 11].

II. EXPERIMENTAL PART

2.1. Material & Methods

Every one of the compounds that were employed was of the purest possible kind. This entire paper's worth of beginning materials came from Sigma-Aldrich, where they were all purchased. The following are some of the equipment that were utilized for the characterisation of the compounds that were prepared: Melting points were calculated using an instrument called the Gallenkamp MFB-600-Melting point Stuart, and FT-IR spectra were obtained using a spectrometer called a Bruker. 1H-NMR was captured using a Bruker AC 400 NMR spectrometer,

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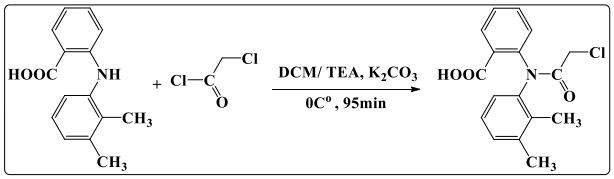
which had a recording frequency of 400 MHz for 1H-NMR and a recording frequency of 100 MHz for 13C-NMR. All chemical changes, denoted by the symbol, are given in terms of parts per million (ppm), with tetramethylsilane (TMS) serving as the standard (=0.0 ppm). In order to conduct the analysis of mass spectra, the equipment known as the Agilent Technology MS 5973 was utilized.

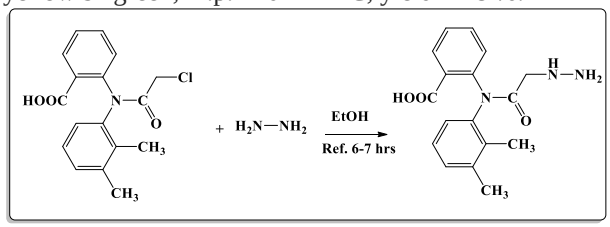
2.1.2. Procedure for Synthesis of 2-(2-chloro-N-(2,3-dimethylphenyl) acetamido) benzoic acid compound (A)

1 g (0.00414 mol) of Mefenamic Acid in 4 mL of DCM was dissolved in a 100 mL two-neck round bottom flask and added to 0.4 mL of TEA. The mixture was stirred for ten minutes in an ice bath, and then added, 0.467 mL) (0.00414mol) from Chloroacetyl chloride through a drop-by-drop distillation funnel. For forty minutes, the mixture was stirring in r.t. Leaching a precipitate with a Buechner funnel, and the result was recrystallized from ethanol. Color yellow, m.p. 170-172 oC, yield = 82 %.



2.1.3. Procedure for Synthesis 2-(N-(2,3-dimethylphenyl)-2-hydrazineylacetamido) benzoic acid compound (B)

1 g (0.00414 mol) of compound A prepared in 5 mL of ethanol absolute was dissolved in a 50 mL two-neck round bottom flask and added to 3 mL of hydrazine hydrate. The mixture was refluxed for 7 hours. The reaction mixture was left to cool, then stirred for an hour. Using a Buechner funnel, a precipitate was leached, and the result was recrystallized from ethanol. Color: yellowish green, m.p. 140–142 °C, yield = 78 %.



2.1.4. Procedure for Synthesis Schiff bases compound (C1-C9)

In a 100 mL two-neck round bottom flask, (0.021mol) mole of benzaldehyde or one of its derivatives and absolute ethanol plus(4drops) of glacial acetic acid were added. The mixture was agitated for ten minutes before (0.021mol of compound B dissolved in 20 ml of absolute ethanol) was added through a distillation funnel drop-by-drop. For 3 hours, the mixture was refluxed. After allowing the reaction mixture to settle, it was agitated for one hour. A precipitate was leached using a Buechner funnel, and the result was recrystallized from ethanol. Table (1) lists the physical constants of the prepared Schiff's bases.

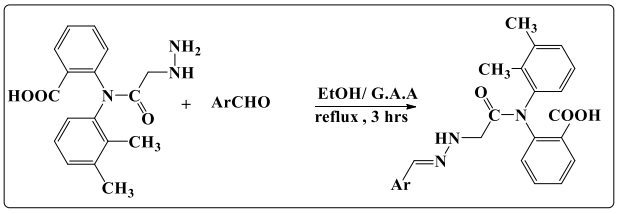
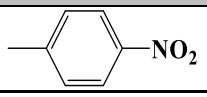
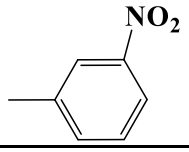
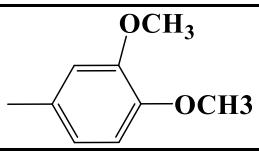
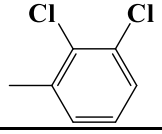


Table (1): The Molecular formula, physical constants of Schiff's base compounds (C_1-C9).

Comp. Symb.	Ar	Molecular Formula	Mol. Wt. gm/mole	Yields%	M.P	Color
C1		C24H21N3O5	431.45	83	188-190	Yellow
C2		C24H21N3O5	431.45	83	195-197	Yellowish green
C3		C26H26N2O5	446.50	75	189-191	Yellow
C4		C24H20Cl2N2O3	455.34	70	199-201	Yellow

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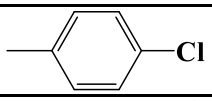
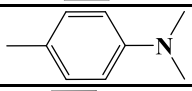
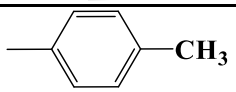
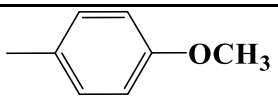
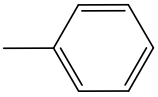
C5		**C24H21ClN2O3**	**420.89**	**77**	**226-228**	**Yellow**
C6		**C26H27N3O3**	**429.52**	**96**	**234-236**	**Yellowish green**
C7		**C25H24N2O3**	**400.48**	**78**	**222-224**	**Yellow**
C8		**C25H24N2O4**	**416.48**	**80**	**208-210**	**Yellow**
C9		**C24H22N2O3**	**386.45**	**77**	**205-207**	**Yellow**

2.1.3. Method for the preparation of 1,3-Thiazolidine-4-one Derivatives (D_1-D_9)

In a two-neck, round-bottom flask containing a condenser, 0.002 mol of Schiff base was dissolved in 15 ml of dioxane and stirred for ten minutes. placed in a water immersion at 68 degrees Celsius. Then dissolve 0.02 mol of thioglycolic acid in 20 ml of dioxane. Then, the mixture was introduced through the distillation receptacle drop by drop, and as soon as the reaction components were thoroughly combined, the turbidity of the mixture was observed. The mixture was subjected to about six hours of refluxing. After the conclusion of the escalation period, a portion of the solvent was exhausted, and a precipitate was observed to form. Using a Buechner funnel, the precipitate was filtered, rinsed with distilled water, allowed to dry, and then re-washed with chloroform. 1,3-Thiazolidine-4-one physical characteristics the following derivatives are listed in Table 2:

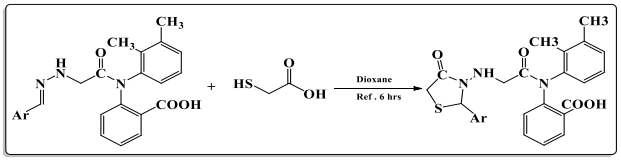


Table (2): The Molecular formula melting point of compounds (D_1-D9)

Comp. Symb.	Molecular Formula	Mol. Wt. gm/mole	Yields%	M.P	Color
D1	**C26H23N3O6S**	**505.55**	**81**	**225-227**	**Orange**
D2	**C26H23N3O6S**	**505.55**	**94**	**256-258**	**Yellow**
D3	**C28H28N2O6S**	**520.60**	**83**	**279-281**	**Yellow**
D4	**C26H22Cl2N2O4S**	**529.43**	**87**	**233-235**	**Yellow**
D5	**C26H23ClN2O4S**	**494.99**	**89**	**279-281**	**Yellow**
D6	**C28H29N3O4S**	**503.62**	**60**	**233-235**	**Orange**
D7	**C27H26N2O4S**	**474.58**	**77**	**221-223**	**Oil Yellow**
D8	**C27H26N2O5S**	**490.57**	**80**	**279-281**	**Yellow**
D9	**C26H24N2O4S**	**460.55**	**72**	**233-235**	**Yellow**

III. RESULTS & DISCUSSION

3.1. Preparation and identification of 2-(2-chloro-N-(2,3-dimethylphenyl)acetamido)benzoic acid (A)

Compound A was synthesized by reaction of Mefenamic Acid and Chloroacetyl chloride , Compound A FT IR spectram indicated a wide band in the range 2526-3341 cm-1 due to the OH group assigned to the carboxylic group, as well as substantial absorption in the region 3070 cm-1 attributed to the Aromatic (C-H). The (C=O) group has an absorption band with a wavelength of 1712 cm-1.[12]

Further identification for compound A was performed using 1H-NMR, spectram of the compound was comprised of a single signal in [δ=1.92 ppm,(s,3H),CH3] ppm which ascribed to the methyl group aliphatic, and a single signal in [δ=6.68 ppm,(s,2H),CH2] ppm which ascribed to the methylene group, several different signals within the range [δ=7.04–7.88 ppm,(m,7H), Ar-H] ppm which ascribed to the aromatic rings, and a single signal in [δ=7.90 ,(s,1H),OH] ppm, which ascribed to the carboxylic acid proton. The 1H-NMR spectra for compound A are shown in Fig. 2.[13]

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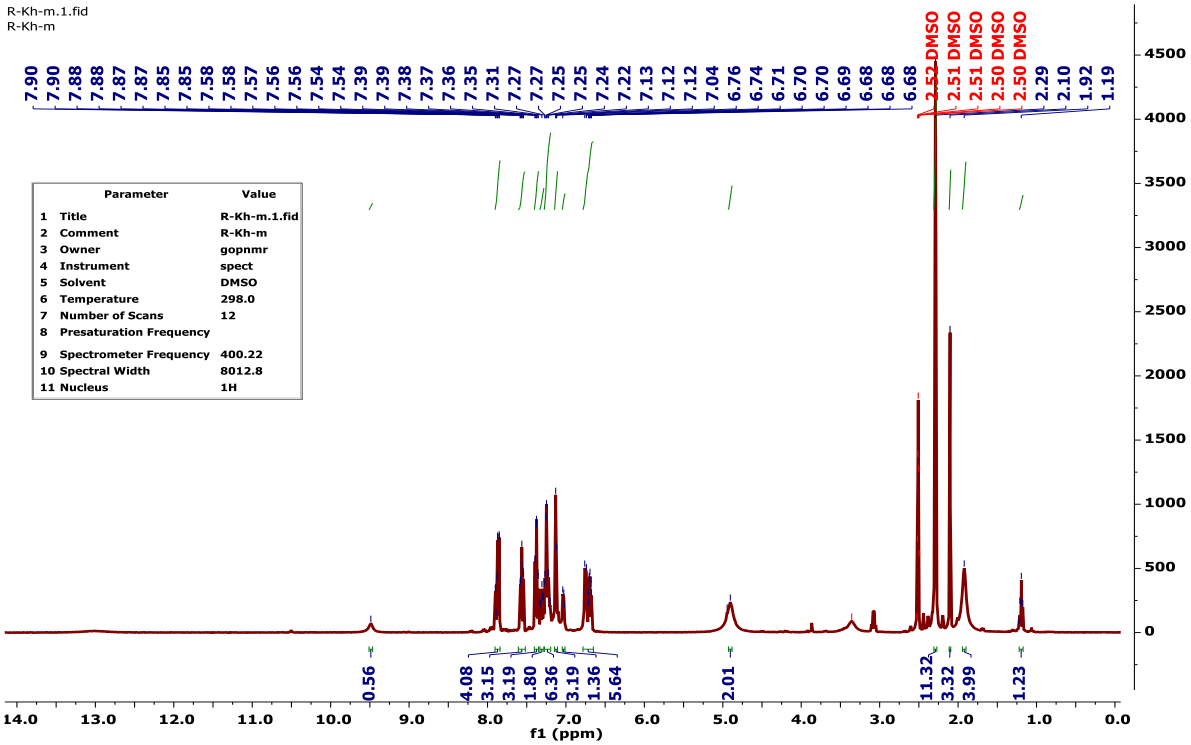

Figure 2: ^{1}H NMR spectrum of compound A

Further identification for compound A was performed using 13C-NMR, spectram of compound was comprised of a signal in [δ=14.14 ppm] which ascribed to the aliphatic methyl carbon , and a signal in [δ=20.39 ppm] ppm which ascribed to the methylene group, a several different signals within the range [δ=111.87-144.21 ppm] which ascribed to the aromatic rings, and a signal in [δ=166.56 ppm] which ascribed to the carbonyl amide, and a signal in [δ=170.70 ppm] carboxylic acid . The 13C-NMR spectram for compound A is shown in the fig(3)[13].

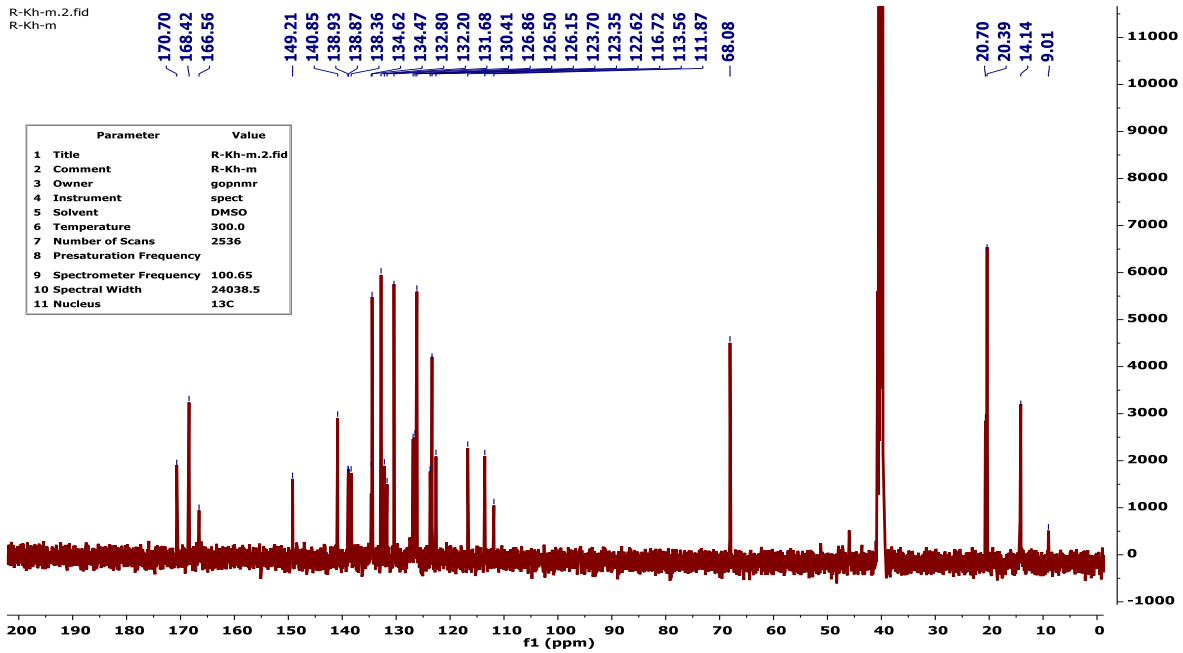

Figure 3: ^{13}C NMR spectrum of compound A

Mass spectrometry was used to calculate the molecular mass of the compound by identifying the molecular ion and base Peak. The fragmentation pattern of the compound (A) is depicted in Fig. (4). [14].

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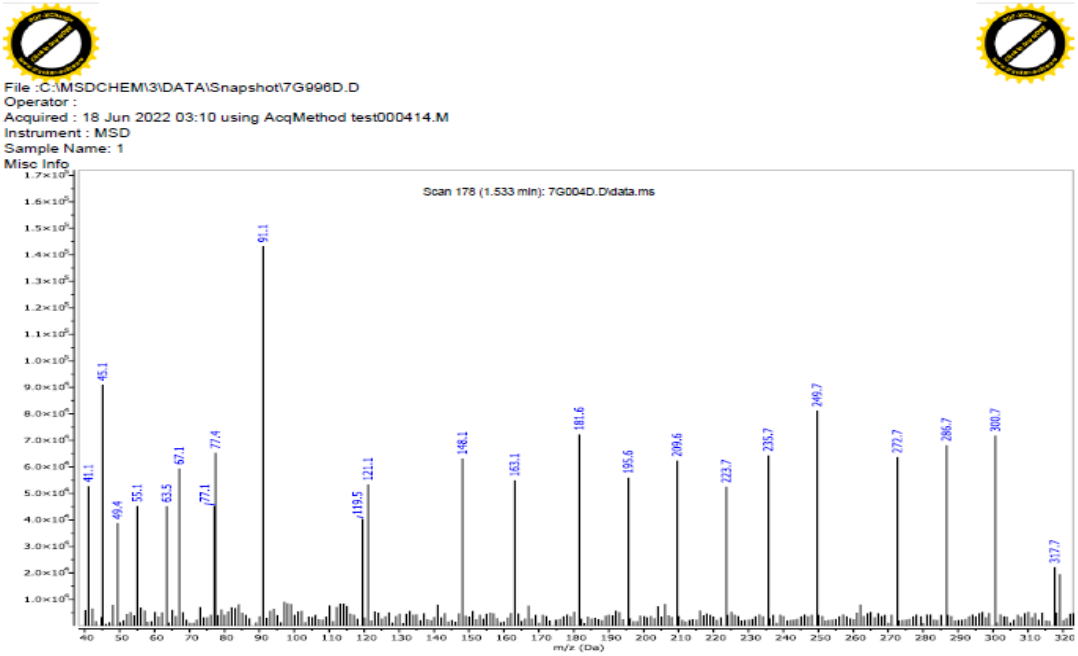
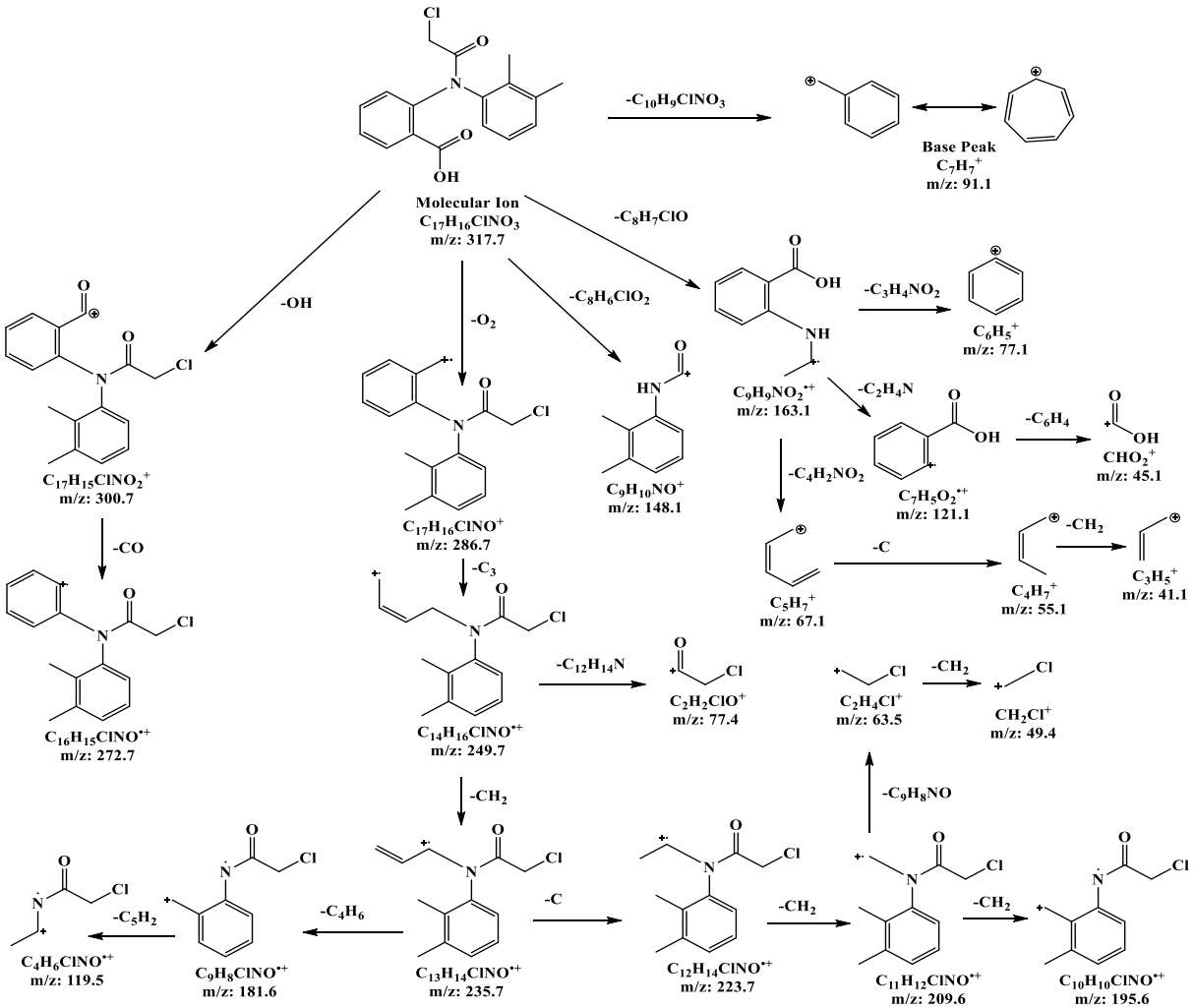


Figure 4: Mass spectrum of compound A



Scheme 1: fragmentation pattern of compound A

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3.2. Synthesis and characterization of 2-(N-(2,3-dimethylphenyl)-2-hydrazineylacetamido) benzoic acid compound (B)

Compound B was synthesized by reaction of compound A prepared and hydrazine hydrate , Compound B FT IR spectram indicated a Double band in the range (3371, 3336 cm-1) attributed to the NH2 group assigned to the amin group, as well as substantial absorption in the region 3066 cm-1 attributable to the Aromatic (C-H). The (C=O) group has an absorption band with a wavelength of 1633 cm-1.[12]

Further identification for compound B was performed using 1H-NMR, spectram of the compound was comprised of a single signal in [δ=2.11 ppm,(s,3H),CH3] ppm which ascribed to the methyl group aliphatic, and a single signal in [δ=3.25 ppm,(s,2H),CH2] ppm which ascribed to the methylene group, and a single signal in [δ=3.44 ppm,(s,1H),NH] ppm which ascribed to the amine secondary group, and a single signal in [δ=4.59 ppm,(s,2H),NH2] ppm which ascribed to the amine primary group, several different signals within the range [δ=6.69-9.48 ppm,(m,7H), Ar-H] ppm which ascribed to the aromatic rings, and a single signal in [δ=9.82 ppm,(s,1H),OH] ppm, which ascribed to the carboxylic acid proton. The 1H-NMR spectra for compound B are shown in Fig.5. [13]

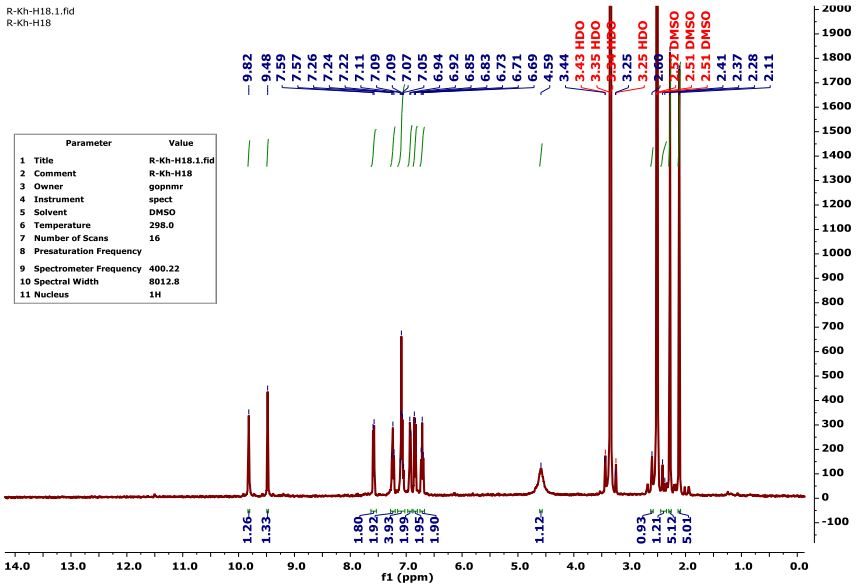

Figure 5: ^{1}H NMR spectrum of compound B

Mass spectrometry was used to calculate the molecular mass of the compound by identifying the molecular ion and base Peak. The fragmentation pattern of the compound (B) is depicted in Fig. (6). [14].

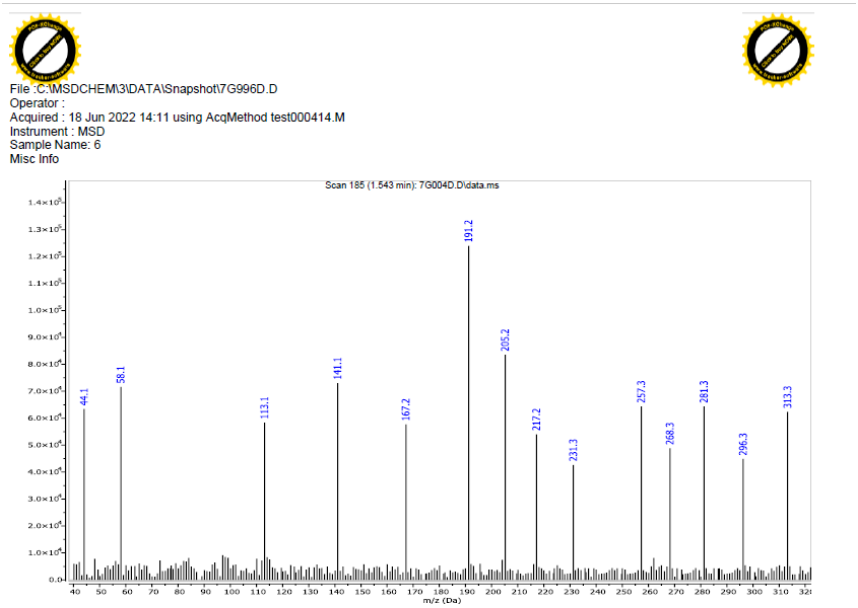

Figure 6: Mass spectrum of compound B

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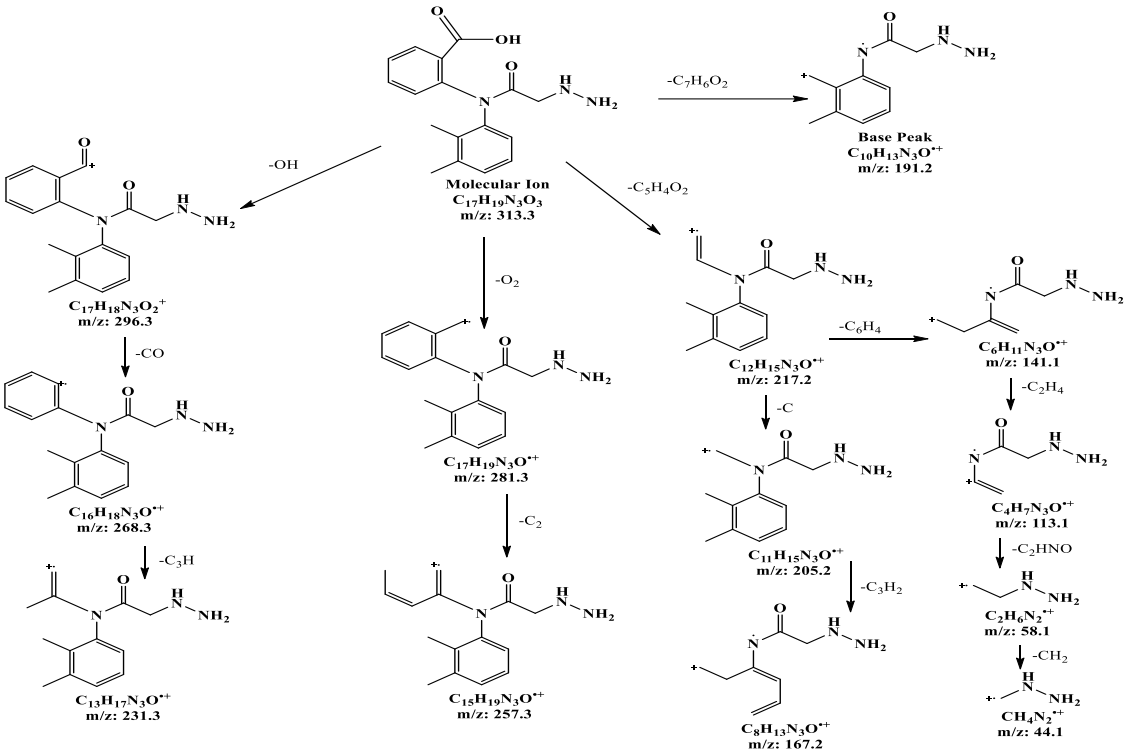

Scheme 2: fragmentation pattern of compound B

3.3. Synthesis and characterization of Schiff's basescompounds(C1-C9)

Compound B was produced by reacting benzaldehyde or one of its derivatives with Schiff's bases. The FT IR spectra of compounds (C1-C9) exhibited an absorption band within the range (3088-3026 cm-1) attributed to the aromatic (C-H). The (C=N) absorption band is located in the range ((1653-1627 cm-1). azomethine group (C=N) absorption in the region 1622-1636cm-1 [12]. Table (4) shows the findings, in addition to the presence of stretching absorption in the other groups.

Table (3): IR characteristic absorption of compounds C_1-C9 cm^{-1}

Comp	NH	νC-H		νC=N	ν C==C		Others
		Arom	Aliph.				
C1	3344	3068	2983	1653	1597	1437	NO2 asym 1570 Sym 1381
C2	3404	3068	2922	1631	1583	1494	NO2 asym 1518 Sym 1450
C3	3311	3072	2966	1653	1575	1444	C-O 1016
C4	3344	3088	2916	1653	1568	1487	C-Cl 746
C5	3404	3028	2945	1629	1583	1467	C-Cl 744
C6	3304	3030	2912	1627	1581	1450	C-N 1046
C7	3311	3069	2916	1651	1575	1448	C-H alp.2916
C8	3311	3063	2972	1651	1575	1450	C-O 1024
C9	3352	3026	2941	1629	1504	1446	……

Further identification of compounds (C1-C9) was performed using 1H-NMR. Compound spectra consisted of a single signal within the range [1.92-3.83 (s)] ppm attributed to the aliphatic proton of the methyl and methylene groups, and several different signals within the range [6.68 - 8.73 (m)] attributed to the protons aromatic rings and secondary amine group. and a single signal in the range [7.92- 9.30 (s, 1H)] ppm attributed to the C=N proton, and a single signal in the range [8.73-11.95 (s,1H),OH] ppm attributed to the carboxylic acid proton. Table 4 displays the 1H-NMR data and spectra for compounds (C1-C9). [13].

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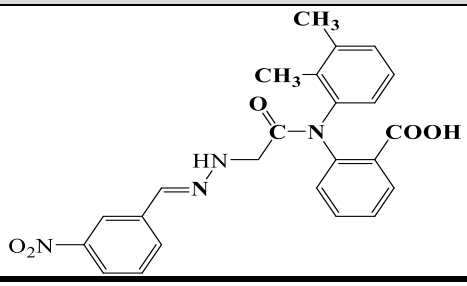
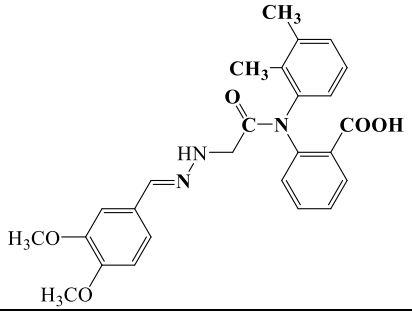
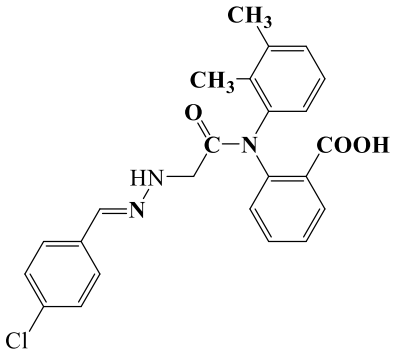
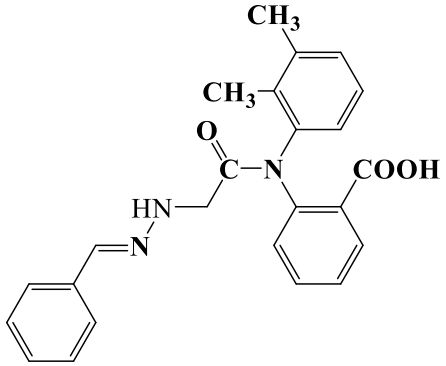
Table (4): ^{1}H-NMR spectra for compounds C2-C9

Comp. Symb.	Structure	Chemical Shift(ppm)	No. of Protons	Type of single	Group
C2		2.10- 2.29	8	s	CH3-CH_2-alip.
		6.68- 8.73	12	m	C**H**-Ar.
		8.93	1	s	C=N
		11.50	1	s	-O**H** Carbox.
C3		2.10-3.83	14	s	CH3-CH_2-alip.
		6.68-7.90	11	m	C**H**-Ar.
		8.64	1	s	C=N
		9.49	1	s	-O**H** Carbox.
C5		1.92-2.26	8	s	CH3-CH_2-alip.
		6.58-7.90	12	m	C**H**-Ar.
		7.92	1	s	C=N
		8.73	1	s	-O**H** Carbox.
C9		2.13-2.51	8	s	CH3-CH_2-alip.
		6.79-8.47	13	m	C**H**-Ar.
		9.30	1	s	C=N
		11.95	1	s	-O**H** Carbox.

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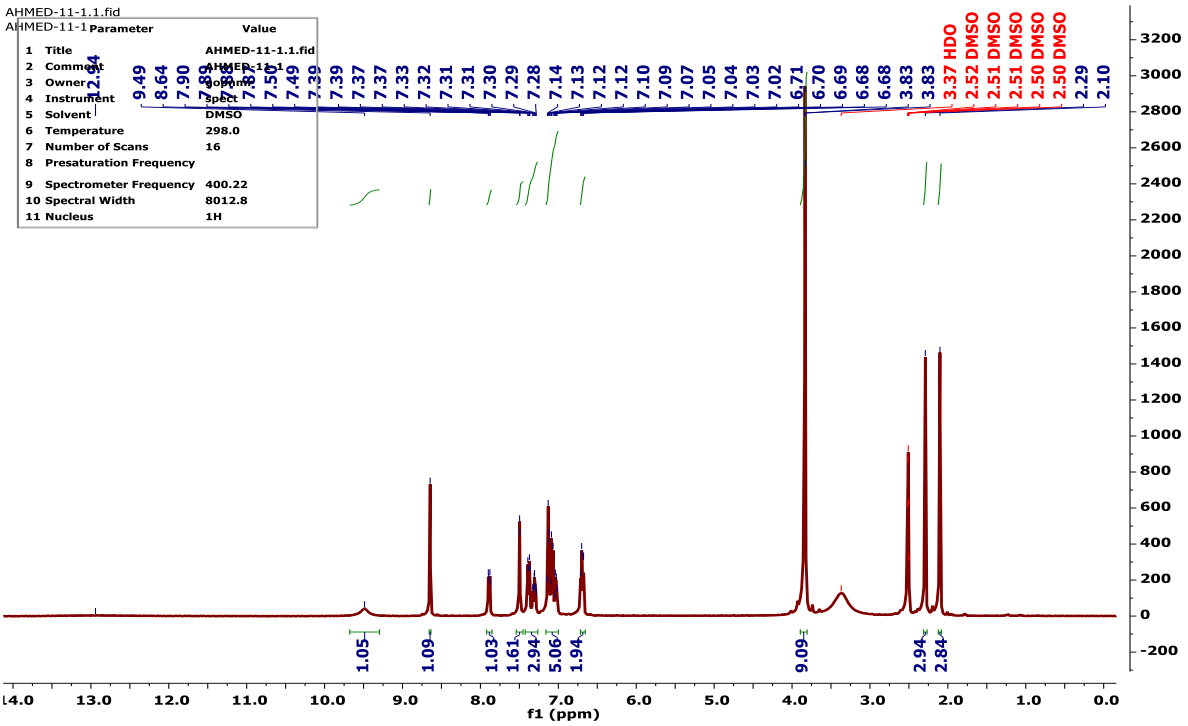

Figure 7: ^{1}H NMR spectrum of compound C3

Further identification for compounds (C1-C9) was performed using 13C-NMR, spectra of compounds were comprised of a signal within the range [δ=14.00 - 14.14 ppm] which ascribed to the aliphatic methyl carbon , and a signal within the range [δ=20.70-20.83 ppm] ppm which ascribed to the methylene group, and a signal within the range [δ=138.86- 140.91 ppm] ppm which ascribed to the C=N ,a several different signals within the range [δ=109.61-152.08 ppm] which ascribed to the aromatic rings, and a signal within the range [δ=148.36-161.22 ppm] which ascribed to the carbonyl amide, and a signal within the range [δ=166.09-172.64 ppm] carboxylic acid . The 13C-NMR data and spectra for compounds (C1-C9) are shown in table 5 [13].

Table (5): ^{13}C-NMR spectra for compounds C2-C9

Comp. Symb.	C-CH3	C-CH2	C=N	Ar-C	C=O amide	C=O carboxylic
C2	14.13	20.70	140.71	112.73- 149.02	160.94	170.94
C3	14.14	20.70	138.86	109.61-152.08	161.22	170.70
C5	14.14	20.83	140.91	113.23- 147.40	161.07	172.64
C9	14.00	20.75	139.53	114.57-147.15	148.38	166.09

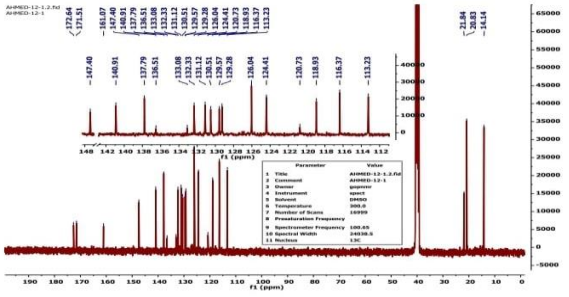

Figure 8: ^{13}C NMR spectrum of compound C5

Table (6) displays the m / z values of the M + molecular ion as well as some of the produced compounds' base peak.

Table (6): The m / z values of the M + molecular ion and some of compounds C1-C5

Compounds Symb.	m/z	
	Molecular Ion	Base Peak

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C1	**C24H22N4O5 446.4**	**C7H7+ 91.1**
C2	**C24H20N4O5 +• 444.1**	**C7H6+• 90.1**
C3	**C26H25N3O5+• 459.1**	**C7H6+• 90.1**
C4	**C24H21Cl2N3O3 470.3**	**C7H7+ 91.1**
C5	**C24H20ClN3O3+• 433.1**	**C7H6+• 90.1**

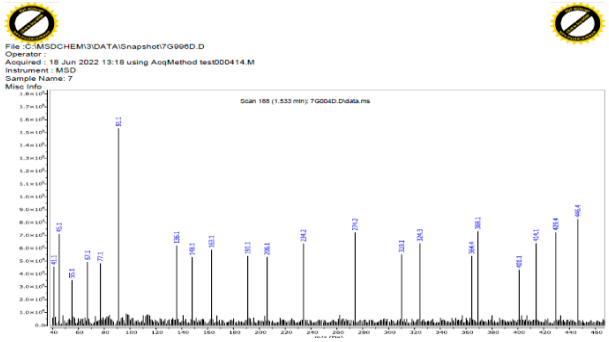
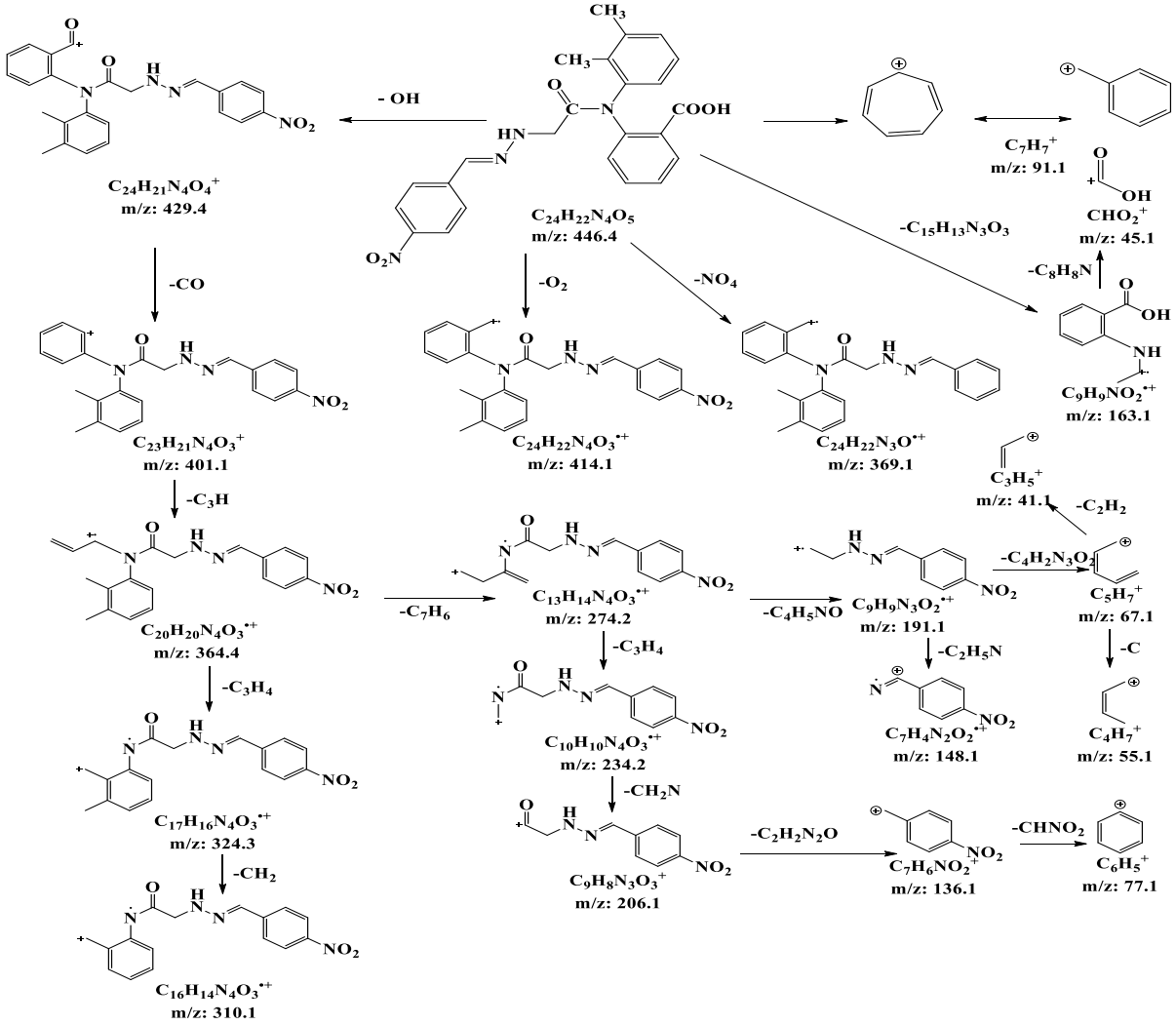


Figure 9: Mass spectrum of compound C1



Scheme 3: fragmentation pattern of compound C1

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3.2.Preparation and identification of 1,3- Thiazolidine-4-one Derivatives(D_1-D9)

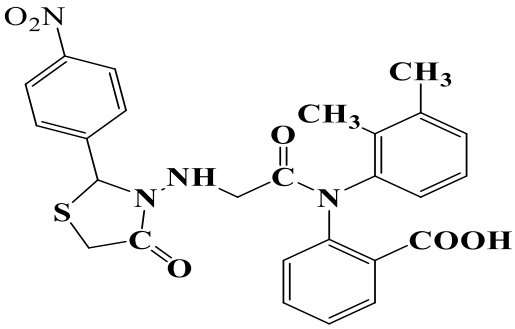
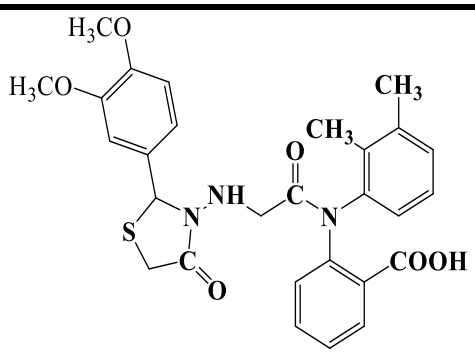
Thiazolidine-4-one Derivatives were produced utilizing Dioxane as a solvent in reactions of Schiff base and thioglycolic acid. FT IR spectra for compounds (D1-D9) revealed the lack of the (vC=N) absorption band for the azomethine group. Compound FT-IR spectra indicated an absorption band in the range 3058-3130cm-1 owing to the aromatic (C-H) group, as well as a significant absorption band in the range 1655-1685cm-1 attributable to the (C=O) carboxylic acid and lactam group [12]. Table 7 includes data on the stretching absorption of the other groups in addition to the appearance of stretching absorption.

Table (7): IR characteristic absorption of compoundsD_1-D_9 cm^{-1}

Comp	NH	νC-H		νC=O lactame	ν C=C		C-S	Others
		Arom	Aliph.					
D1	3344	3007	2985	1728	1597	1437	686	NO2 asym 1521 Sym 1437
D2	3444	3051	2939	1726	1597	1473	782	NO2 asym 1579 Sym 1448
D3	3360	3070	2986	1734	1575	1423	657	C-O 1020
D4	3311	3088	2974	1732	1579	1450	665	C-Cl 752
D5	3346	3007	2974	1728	1573	1446	663	C-Cl 752
D6	3313	3032	2910	1629	1597	1446	650	C-N 1176
D7	3311	3007	2972	1726	1575	1446	661	C-H alp.2973
D8	3311	3009	2974	1730	1590	1446	663	C-O 1026
D9	3352	3028	2937	1712	1577	1448	642	……

Further identification for compounds (D1-D8) was performed using 1H-NMR, spectra of compounds were comprised of a single signal within the range [2.10-5.26 (s)] ppm which ascribed to the methyl and methylene group aliphatic proton, and a several different signals within the range [δ 6.68 – 8.64 (m)] attributed to the protons aromatic rings and secondary amine group. and a single signal in [6.67 (s, 1H)] ppm which ascribed to the C-H Thiazolidine proton, and a single signal in [δ=9.50-9.51 ppm,(s,1H),OH] ppm, which ascribed to the carboxylic acid proton. The 1H-NMR data and spectra for compounds (D1-D8) are shown in table 8 [13].

Table (8): ^{1}H-NMR spectra for compounds D2-D8

Comp. Symb.	Structure	Chemical Shift(ppm)	No. of Protons	Type of single	Group
D1		2.10- 3.76	10	s	CH3-CH_2-alip.
		3.76	1	s	CH-Thiazolidine
		6.67	1	s	N-H
		6.68-7.90	11	m	C<u>H</u>-Ar.
		9.50	1	s	-O<u>H</u> Carbox.
D3		2.10-5.26	16	s	CH3-CH_2-alip.
		5.28	1	s	C-H Thiazolidine
		6.67	1	s	N<u>H</u>
		6.68-8.64	10	m	C<u>H</u>-Ar.
		9.50	1	s	-O<u>H</u> Carbox.

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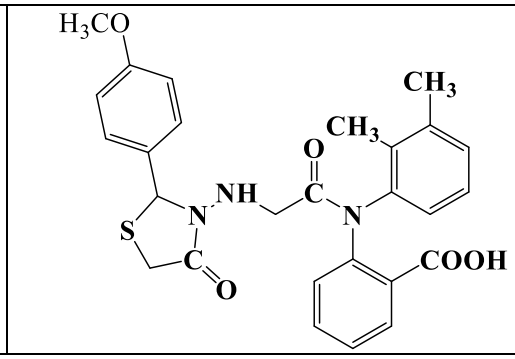
D8		2.10-3.78	10	s	CH3-CH$_2$-alip.
		3.85	1	s	C-H Thiazolidine
		6.67	1	s	NH
		6.68-8.64	11	m	CH-Ar.
		9.51	1	s	-OH Carbox.

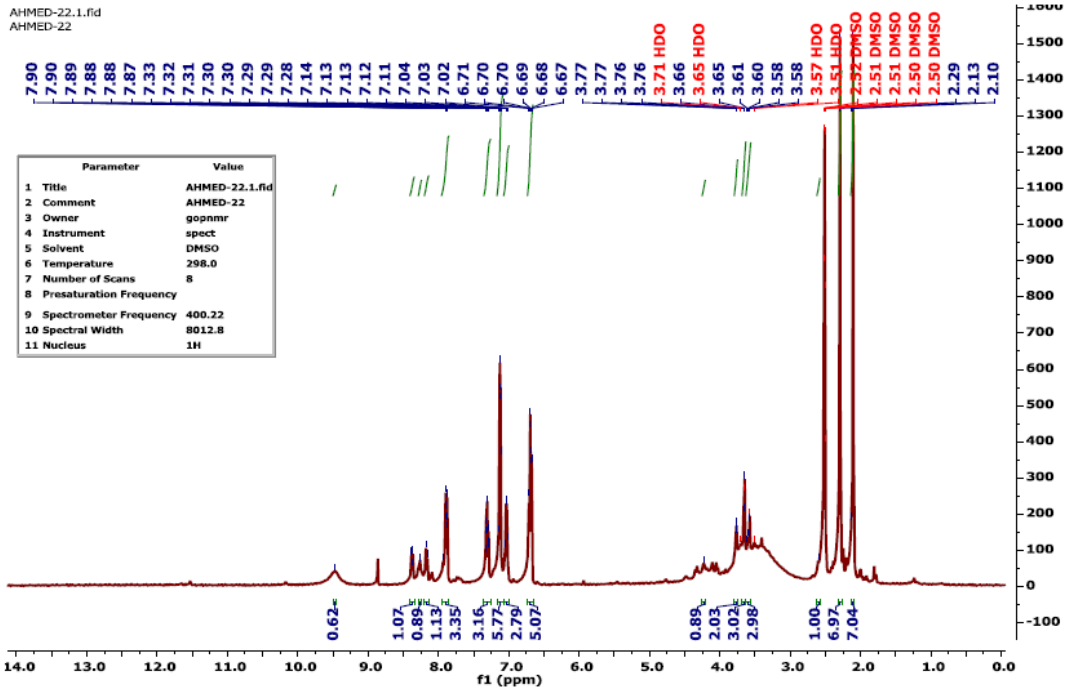


Figure 10: ^{1}H NMR spectrum of compound D1

Further identification for compounds (D1-D8) was performed using 13C-NMR, spectra of compounds were comprised of a signal within the range [δ=14.12 - 14.14 ppm] which ascribed to the aliphatic methyl carbon , and a signal within the range [δ=20.69-20.71 ppm] ppm which ascribed to the methylene group, and a signal within the range [δ=55.85-66.83 ppm] ppm which ascribed to the C-Thiazolidine ,a several different signals within the range [δ=109.59-149.20 ppm] which ascribed to the aromatic rings, and a signal within the range [δ=149.22- 161.22 ppm] which ascribed to the carbonyl amide, and a signal within the range [δ=170.69-171.29 ppm] carboxylic acid . The 13C-NMR data and spectra for compounds (D1-D8) are shown in table 9 [12].

Table (9): ^{13}C-NMR spectra for compounds D1-D8

Comp. Symb.	C-CH3	C-CH2	C Thiazolidine	Ar-C	C=O amide	C=O carboxylic
D1	**14.14**	**20.71**	**66.83**	**111.76- 138.83**	**149.22**	**170.69**
D3	**14.12**	**20.69**	**63.28**	**109.59-138.86**	**161.22**	**171.29**
D8	**14.14**	**20.70**	**55.85**	**111.85-149.20**	**160.96**	**170.72**

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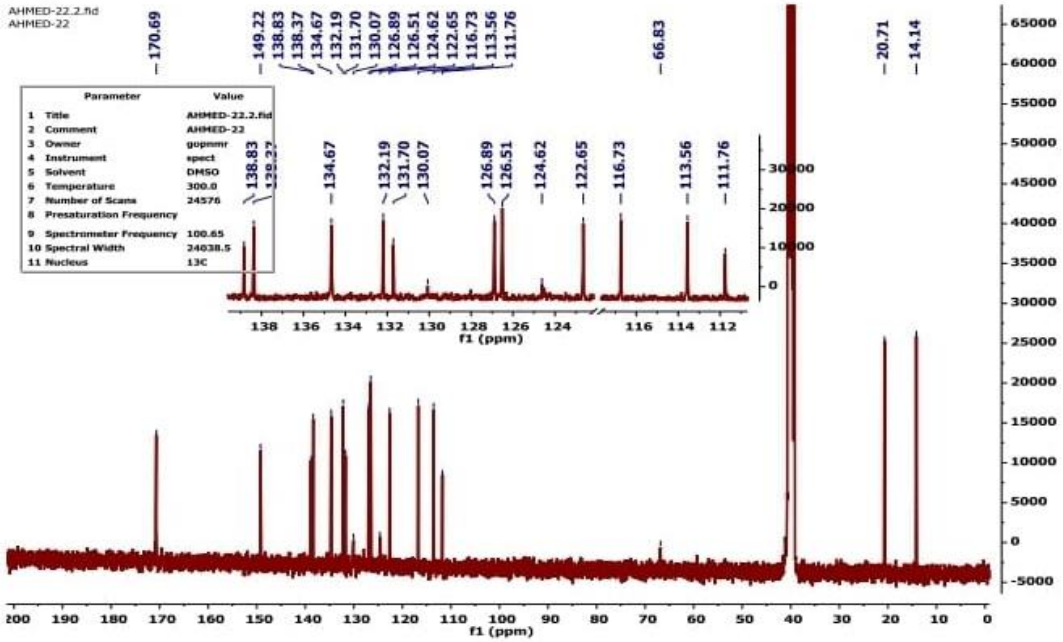

Figure 11: ^{13}C NMR spectrum of compound D1

Table (10) shows the m / z values of the M + molecular ion and some of the generated fragments of the prepared compounds

Table (10): The m / z values of the M + molecular ion and some of compounds D1-D9

Compounds Symb.	m/z	
	Molecular Ion	Base Peak
D2	C26H22N4O6S+• 519.1	C7H6+• 90.1
D3	C28H27N3O6S+• 533.1	C7H6+• 90.1
D4	C26H21Cl2N3O4S+• 541.1	C7H7+ 92.1
D5	C26H22ClN3O4S+• 507.1	C7H6+• 90.1
D6	C28H28N4O4S+• 516.1	C7H6+• 90.1

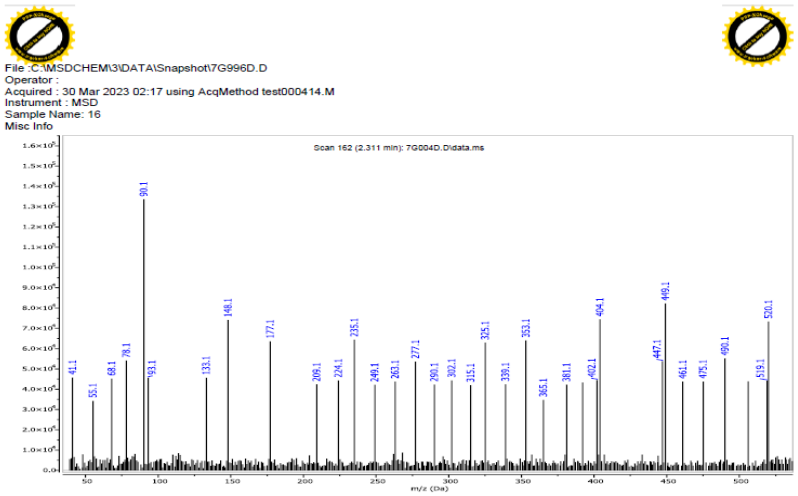

Figure 12: Mass spectrum of compound D2

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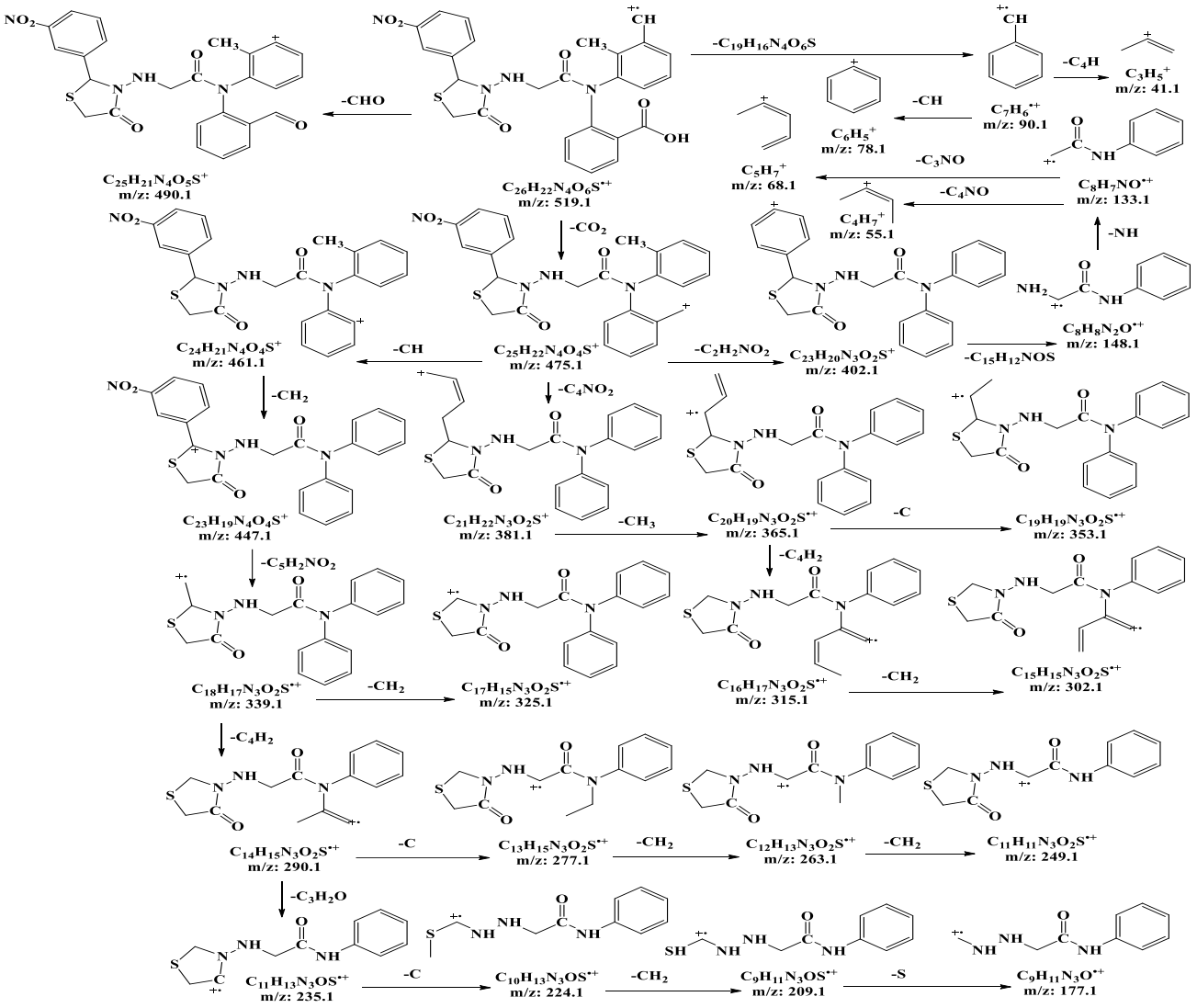

Scheme 4: fragmentation pattern of compound D2

The comprehensive analysis of spectroscopic data (including FT-IR, 1H-NMR, and Mass) provided valuable insights on the structural assignments of these compounds.

IV. CONCLUSIONS

Finally, we developed and synthesized eight new chemical derivatives of mefenamic acid. This innovative class of chemicals will be beneficial in the creation of future medicines.

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