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Electron Impact Ionization Mass Spectra of 3-Amino 6-Chloro-2-methyl Quinazolin-4-(3H)-one Derivative

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Abstract: Background: Looking at the previous studies on quinazolinones derivatives, only limited information'sare available on their massspectral along with the preparation of novel quinazolin-4-(3H)-one derivatives. Consolidation of Methyl-2-amino-4-Chlorobenzoate with acetic anhydride produced the cyclic compound 2-methyl 7-Chloro-1, 3-benzo-oxazine-4-one (1) which then produced 3-Amino-2-Methyl 7-Chloro quinazolin-4(3H)-ones (2) through the reaction with hydrazine hydrate. These compounds synthesized were indisputably confirmed by means of Infrared, Nuclear Magnetic Resonance (^{1}H and ^{13}C), Gas Chromatography-Mass spectrophotometry and Elemental analysis. Discussion: The molecular ion of m/z 235 fragments to give m/z 220 by loss of –NH group. The ion of m/z 220 was broken to give m/z 206 by losing CH_2 group and fragment to m/z 177 by loss of HCO. This fragmented to m/z 162 by loss of $–CH_3$ group and then m/z 136 by loss of CN group. The loss of O gave m/z 120 which fragment to give m/z 93 by loss of –HCN and finally gave m/z 65 by loss of CO group. Conclusion: The electron impact ionization mass spectra of compound 2 show a weak molecular ion peak and a base peak of m/z 235 resulting from a cleavage fragmentation. Compound 2 give a characteristic fragmentation pattern. From the study of the mass spectra of compound 2, it was found that the molecular ion had fragmented to the m/z 220. The final fragmentation led to ion of m/z 93 and ion of mass m/z 65, respectively.

Keywords: Mass Spectroscopy, 3-amino-7-chloro-2-methyl Quinazolinone, Nucleophile, Quinazolinone, Electron Impact Ionization Mass Spectra

1. Introduction

An opening to Medicinal Chemistry gives us a very accurate look at the world of medicine [1]. Basis of Medicinal chemistry is necessary to consider physiochemical properties, used to establish new pharmacologically active constituents and their components of action and many of them are entered to pharmacological evaluation for determining their biological properties. This arbitrary evaluation process has been incompetent, but it has resulted in recognition of new lead compounds whose structures have been improved to produce clinical agents [2]. A rich tradition of companion design strategies has evolved for creating new compounds within medicinal chemistry research for biological screening [3].

Heterocyclic chemistry is a chemistry involving the heterocyclic compounds, which has atoms of at least two hetero atoms as number of ring. The heterocyclic atoms may be inorganic, though the compound contains carbon atoms in the ring. The word hetero means "distinctfrom carbon and hydrogen"Heterocyclic chemistry comprises at least half of all organic chemistry research globally. In particular, heterocyclic structures form the foundation of many pharmaceutical, agrochemical and veterinary products [4].

Heterocyclic chemistry is an implicit part of the synthetic organic chemistry, covering a broad array of bioactive molecules. Amidst six-memberedheterocycles, quinazoline occupies important area and is commonly found in a wide array of natural products, synthetic pharmaceutical unit, and other functional component [5].

The important role played by heterocycles in drug schemecannot be avoided. Even where the natural substrate or ligand for a biological target does not consist an

heterocycle, drugs bothof natural or man-made agent that act on that target frequently contain heterocyclic class [6].

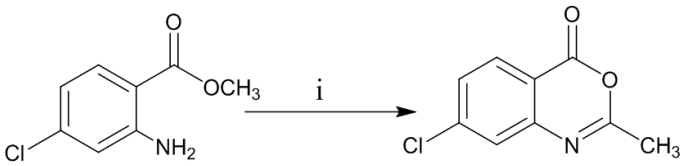
Quinazolinone is one of the most relevant heterocyclic compound, weak base, having different biological activities and still of great scientific concern now a days. They are extensively found in bioorganic and medicinal chemistry with usefulness in drug discovery. Various Literature survey on quinazolinones have displayed that these derivatives acquire a wide variety of biological activities such as antioxidant [7], antifungal [8], antibacterial [9], anticonvulsant [10], anti-inflammatory [11], antihyperlipidemic [12], anticancer [13], antimalarial [14], antispasmodial [15] analgesic [16], antiviral [17], antitubercular [18] and antimicrobial [19] activities.

Looking at the previous studies on quinazolinones derivatives, only limited informationis available ontheir massspectral along with the preparation of novelquinazolin-4-(3H)-one Derivative**.** In this study, a novel3-amino-7-chloro-2-methyl quinazolin-4(3H)-one was synthesized via the reaction between 7-chloro-2-methyl-4H-benzo [d] [1, 3]-oxazin-4-one andhydrazine hydrate anditwasthoughttosynthesize this newquinazolinonederivativeandscreenthe compoundforits electron impact (EI) mass spectral fragmentation.

2. Materials and Methods

2.1. General ExperimentalProcedure

Reagents and solvents were purchased from sigma-Aldrich, Germany. We determined the Melting points on a kofler hot stage apparatus and were uncorrected. IR spectra were recorded on a Buck scientific IR M500 instrument. The ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-*d*6 at 400 MH_z with HAZ VOLATILE V2. M spectrophotometer. We reported the Chemical shifts in ppm relative to tetramethylsilane. Gas chromatography-Massspectra were obtained on a Finingan MAT 44S mass spectrometer operating at 70eV. There were favourable agreement in Elemental analysis for the calculated values Analytical thin layer chromatography (TLC) was used to monitor the reactions.



i = Acetic anhydride, ethanol.

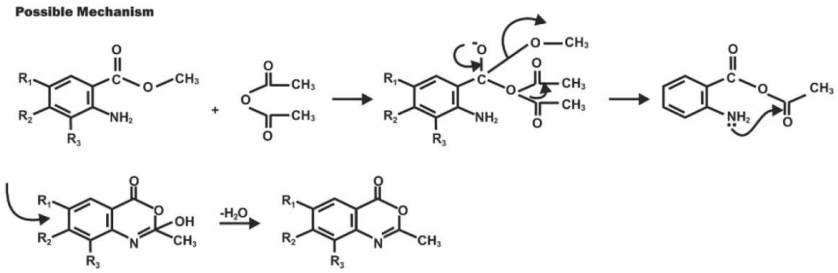
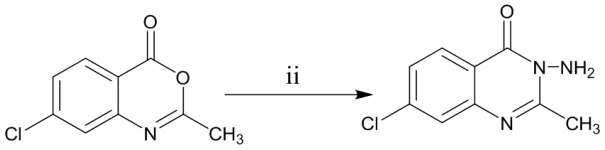


Figure 1. *Possible Mechanism For Synthesis of Compound 1.*



ii = Hydrazine hydrate, ethanol.

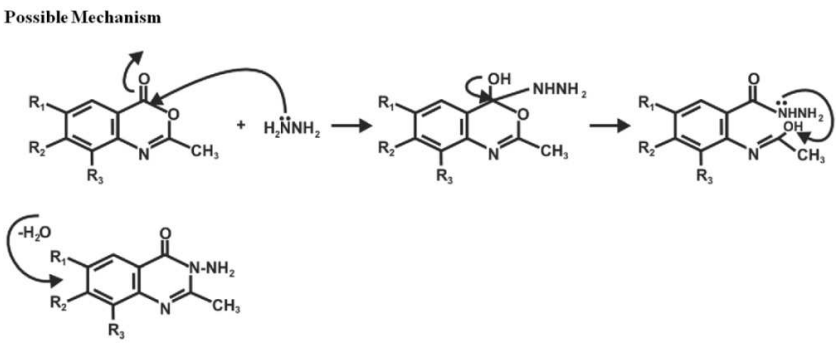


Figure 2. *Possible Mechanism For Synthesis of Compound 2.*

2.2. Synthesis of 7-chloro-2-methyl-4H-benzo [d]-1,3-oxazin-4-one (1)

This involve the condensation of 0.76g (0.005mol) of 4-chloroanthranilate with 1.02g (10 mL, 0.01mol) acetic anhydride in 30 mL ethanol medium. The reaction was heated under reflux with stirring using a magnetic stirrer until the reaction mixture showed no trace of starting material when the TLC was developed (2 hours) (Yield = 2.01 g (96%), mp: 149-151°C).

2.3. Synthesis of 3-amino-7-chloro-2-methyl Quinazolin-4-(3H)-one (2)

Equimolar amounts (1.61g, 0.01mol) of 7-chloro-2-methyl-4H-benzo [*d*] [1,3]-oxazin-4-one, and (0.51g, 0.01mol) hydrazine hydrate were heated under reflux in 30 mL ethanol with stirring using a magnetic stirrer until the reaction mixture showed no trace of starting material when the TLC was developed (3 hours).(Yield = 1.50 g (95%), mp: 138-140°C). At the end of the reaction, the reaction mixture was concentrated in vacuum under reduced pressure using rotary evaporator. The white precipitate formed was then filtered, washed with distilled water (20 mL x 3). The white crystals were dried and recrystallized from dimethylformamide (DMF) to give pure 3-amino-7-chloro-2-methyl quinazolin-4(3H)-one.

2.4. Chemistry

The introduction of 2-Amino substituent is a successful strategy to improve the chemical stability of benzoxazinone. Due to the pharmacological activities of 4(3H)-quinazolinone derivatives, 2,3-disubstituted derivatives of quinazoline-4-one was synthesized via the interaction of the benzoxazinone derivative with nitrogen nucleophile with the aim of obtaining more pricise information about the course of the reaction and some interesting pharmaceutical compounds. The reaction of 4, 5-disubstituted derivatives of methylanthranilate and acetic anhydride yielded the cyclic compound 2-methyl-6, 7-dimethoxyl-benzo-1, 3-oxazin-4-one. The reaction of this compound with hydrazine hydrate yielded the novel 2, 3-disubstituted quinazoline-4-one.

3. Result

The present study reported the synthesis of two derivatives of quinazolinone, 7-chloro-2-methyl-4H-benzo- [*d*]-1,3-oxazine-4-one (1) and 3-amino-7-chloro-2-methylquinazolin-4-(3H)-one (2). The introduction of 2-amino substituent is a successful strategy to improve the chemical stability of benzoxazinone. Due to the pharmacological activities of 4-(3H)-quinazolinone derivatives, 2,3-disubstituted derivative of quinazoline-4-one were synthesized via the interaction of the benzoxazinone derivative with nitrogen nucleophile with the aim of obtaining more precise information about the course of the reaction and some interesting pharmaceutical compounds. The reaction of 4, 5-disubstituted derivatives of methylanthranilate and acetic anhydride yielded the cyclic compound 7-chloro-2-methyl-4H-benzo [*d*]-1,3-oxazin-4-one (Scheme 1). The reaction of this compound with hydrazine hydrate yielded 3-amino-7-chloro-2-methyl-quinazoline-4-(3H)-one (Scheme 2).

Compound 1 has a molecular formula of $C_9H_6ClNO_2$(*m/z* 195.602 [M^+]). Spectrum IR displayed waves for functional group of carbonylmoietyat 1662 cm^{-1}, C-O and C-H stretch vibrations at 1102 cm^{-1} and 2871 cm^{-1} respectively. The ^{1}H NMR spectrum displayed three aromatic protons at δ_H 7.59, 7.16 and 6.40 and a vinyl methyl protons at δ_H2.57. In the ^{13}C NMR spectrum, the ester carbonyl vibrated at δ_C 168.08, while the aromatic carbons resonated in the range δ_C 113.40 – 149.23. The vibration at δ_C 153.13 and δ_C 22.15 were because of the imine oxygenated carbon (C-1) and the methyl carbon respectively (Table 1).

Compound 2, molecular formula $C_9H_8ClN_3O$ (*m/z* 210.033 [M^+]), had NMR data similar to 1, except for an additional signal at δ_H 5.80 in the ^{1}H NMR spectrum which was attributed to the amino protons (2H) (Table 3).

Table 1. *Characterization and Physical data of Synthesized Compounds.*

Compound No	Solvent	Formula M. wt	Analysis% Calc/FoundCH	
1	Ethanol	$C_{11}H_{11}N0_4$ (221.209)	62.20 62.10	5.18 4.98
2	Ethanol	$C_{11}H_{13}N_30_3$ (235.239)	56.11 56.40	5.53 5.41

Table 2. *^{13}C-NMR of Synthesized Compounds.*

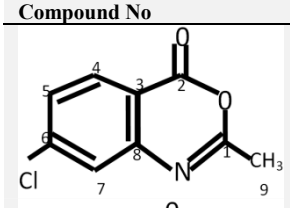
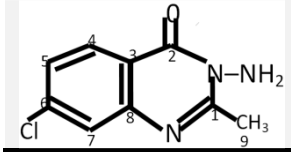
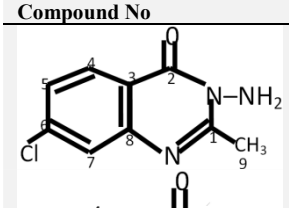
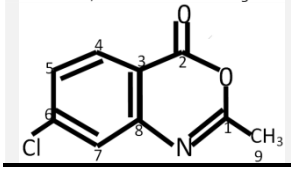
Compound No	δ (ppm) Carbon atom number
	153.13(C-1), 168.08(C-2),120.80(C-3) 128.18 (C-4), 1132.10 (C-5), 113.40 (C-6) 1122.13 (C-7), 1149.23 (C-8),22.15 (C-9)
	154.57 (C-1), 160.28 (C-2), 120.24(C-3), 128.07(C-4), 133.60 (C-5), 113.67 (C-6), 122.12 (C-7), 148.07 (C-8), 22.58 (C- 9).

Table 3. *^{1}H-NMR of Synthesized Compounds.*

Compound No	δ (ppm)
	7.59 (s, 1H), 7.16 (s, 1H), 6.40 (s, 1H), 2.57 (s, 3H)
	7.58 (s, 1H),7.41 (s, 1H), 7.10 (s, 1H), 5.80 (s, 2H), 2.58 (s, 3H)

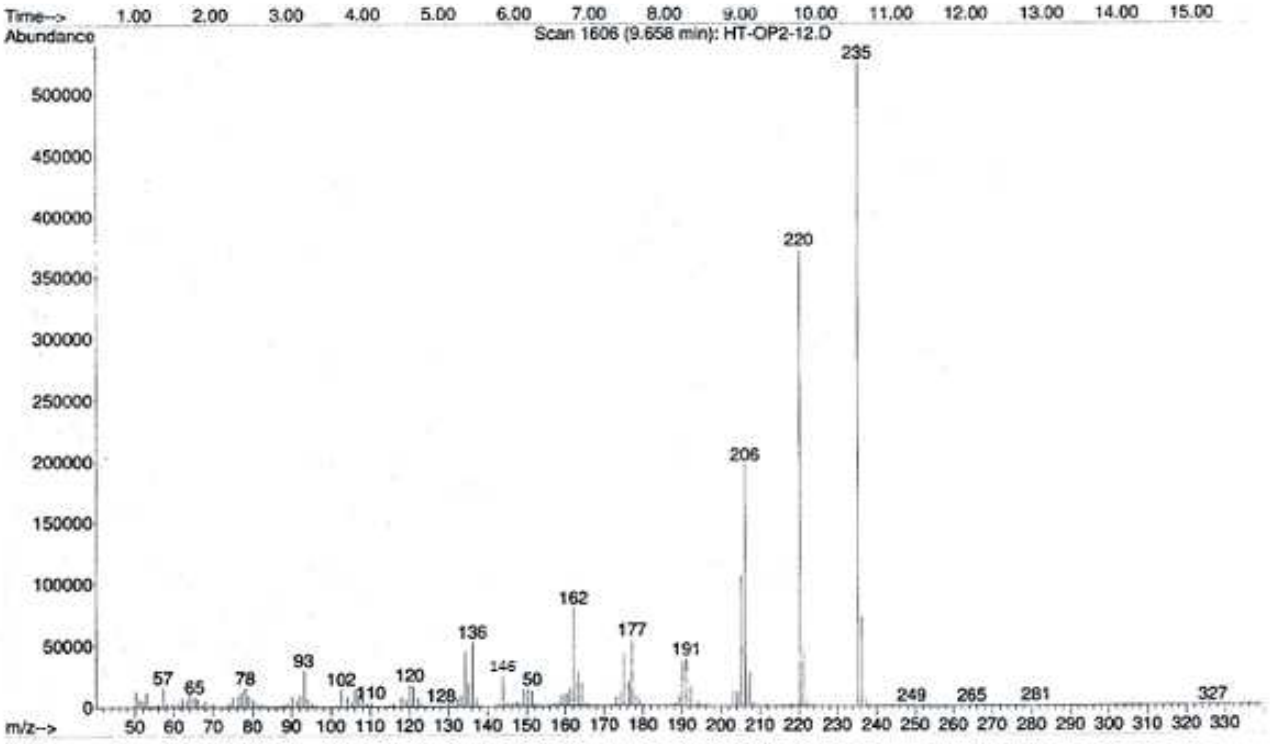


Figure 3. *Mass Spectra of Compound 2.*

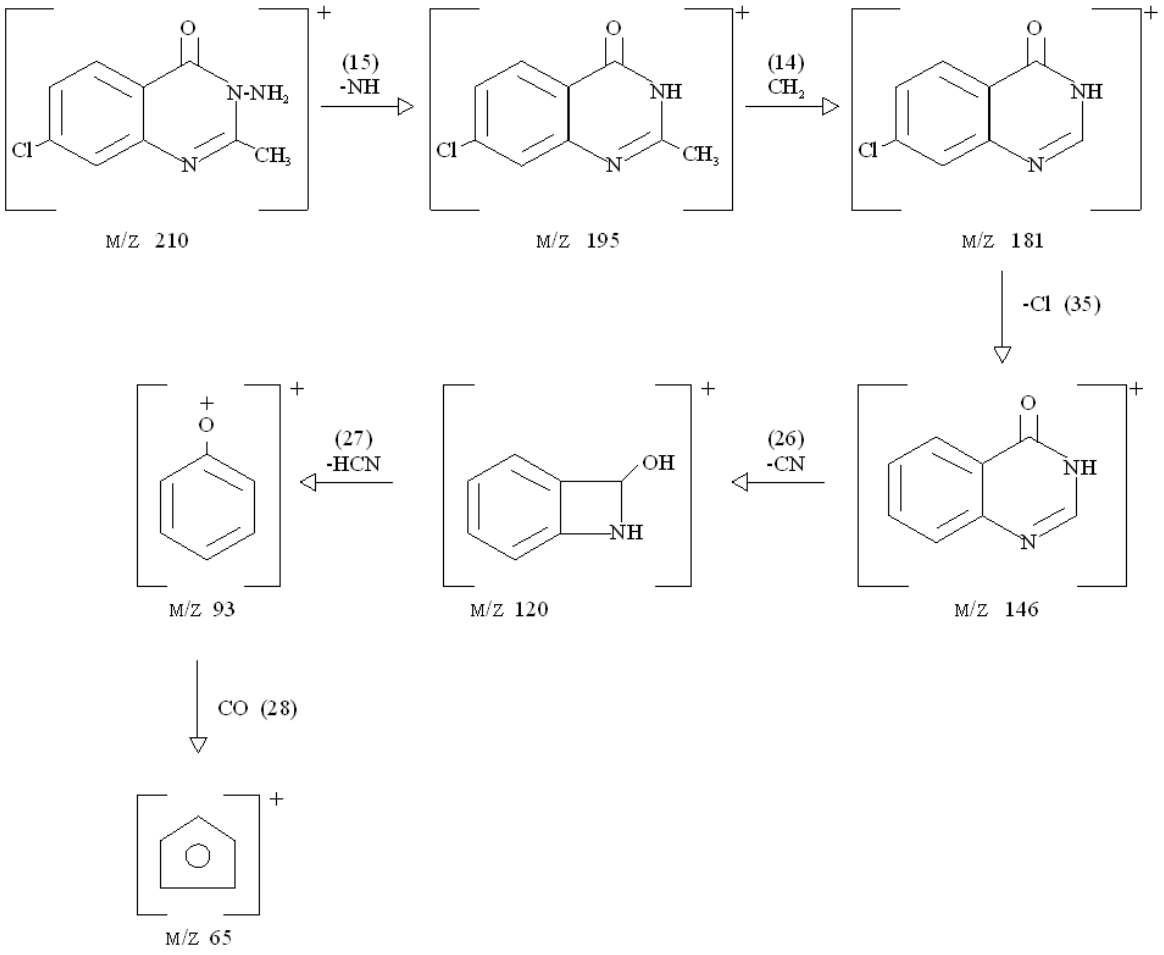


Figure 4. *Main Fragmentation Pathway of Compound 2.*

Table 4. *E1 Mass Spectra (70ev) of Compound 2 m/z (relative intensity %).*

Compound	M_+	M_-	m/z	Other ions
2	$[C_9H_8ClN_3O]^+$ 210(100)	NH	$[C_9H_7ClN_2O]^+$195 ()	
		CH_2	$[C_8H_5ClN_2O]^+$181()	
		Cl	$[C_8H_5N_2O]^+$146 ()	
		CN	$[C_7H_5NO]^+$120 ()	
		HCN	$[C_6H_4O]^+$93 ()	
		CO	$[C_5H_4]^+$65 ()	

3.1. Characterization of 2-methyl-4,5-disubstituted 1,3-benzooxazine-4-one (1)

^{1}H NMR (400MHz, DMSO) δ 7.16 (s, 1H), 6.40 (s, 1H), 3.78 (s, 6H), 3.68 (s, 3H), ^{13}(NMR (400MHz, DMSO) δ 168.28, 155.80, 149.23, 140.28, 113.37, 100.56, 100.05, 56.94, 56.94, 56.13, 51.93, 16.95: IR (KBr, cm^{-1}) 3381, 3203, 3135, (NHz), 3018 (CH aromatic), 2951, 2871, 2718 (CH aliphatic), 1662 (C=0). Anal. Cal 1159 (c-0) for $C_{11}H_{11}N0_4$; C 62.20; H 5.18. Found: C 62.10, H 4.98.

3.2. Characterization of 3-amino-2-methyl-quinazoline-4-one (2)

^{1}H NMR (400 MHz, DMSO) δ 7.41 (s, 1H), 7.10 (s, 1H), 5.80 (s, 2H), 3.90 (s, 6H), 2.58 (s, 3H), ^{13}C NMR (400MHz, DMSO) δ 160.28, 155.29, 154.57, 149.07, 143.77, 113.65, 108.24, 105.64, 56.80, 56.63, 22.58, IR (KBr, cm^{-1}) 3301 (NH_2), 1622 (C=0), Anal. Cal. for $C_{11}H_{13}N_3O_3$; C 56.11, H 5.53; Found, C 56.40, H 5.41.

4. Discussion

The present study reported the synthesis of two derivatives of quinazolinone, 7-chloro-2-methyl-4H-benzo- [*d*]-1,3-oxazine-4-one (1) and 3-amino-7-chloro-2-methylquinazolin-4-(3H)-one (2). The introduction of 2-amino substituent is a successful strategy to improve the chemical stability of benzoxazinone. Due to the pharmacological activities of 4-(3H)-quinazolinone derivatives, 2,3-disubstituted derivative of quinazoline-4-one were synthesized via the interaction of the benzoxazinone derivative with nitrogen nucleophile with the aim of obtaining more precise information about the course of the reaction and some interesting pharmaceutical compounds. The reaction of 4, 5-disubstituted derivatives of methylanthranilate and acetic anhydride yielded the cyclic compound 7-chloro-2-methyl-4H-benzo [*d*]-1,3-oxazin-4-one (Scheme 1). The reaction of this compound with hydrazine hydrate yielded 3-amino-7-chloro-2-methyl-quinazoline-4-(3H)-one (Scheme 2).

Structural elucidations of compounds synthesized were characterized by correct elemental analysis and careful inspections of spectral data. Looking at the ^{1}H NMR spectra of the compounds synthesized, compound 1 gave a singlet indication at: δ 3.78 due to methoxy group and singlet at δ 3.68 which was due to methyl group. Singlets came out at δ7.16 and 6.40 due to aromatic protons. The, ^{1}H NMR spectrum of compound 2 manifested a trait signal at δ 2.56 (singlet) comparable to methyl group and duplet at: δ 3.90 for methoxy group. Two singlets appeared at δ7.41 and 7.10 traceable to aromatic protons. Another signal aroused at 5.80 which was due to the protons of the amino group. For the IR spectra, compound 1 was attributedto absence of υ NH_2 and presence of υ C-O stretch in 1101cm^{-1} region of the compound. Compound 2 was peculiar to absence of υ C-0 and presence of υNH_2 in 3301cm^{-1} region of the compound.

The ^{13}C NMR spectrum of compound 1, disclosed alarm at δ16.95, 51.93 and 56.13 distinct to methyl and the two methoxy groups respectively, while the aromatic carbon atoms aroused between δ values 100.05-168.28 with the carbonyl carbon atom coming out as the highest δ value of 168.28. Similarly, compound 2 demonstrated signals at δ22.58, 56.63 and 56.80 because of methyl and the two methoxy groups respectively, while the aromatic carbon atoms came out between δ values 105.64-160.28, with the carbonyl carbon atom appearing as the highest δ value of 160.28.

The ^{13}C nuclear magnetic resonance revealed low δ values for the aliphatic carbons. This is because the alkyl group is electron donating and hence produces a shielding effect which makes the carbon atom to resonate at low δ values. The aromatic and the carbonyl carbon atoms appeared at high δ values. This is because the aromatic ring is electron withdrawing and the aromatic carbons are highly deshielded and resonate at high frequency. The electronegative effect of the oxygen atom on the carbonyl group makes the carbonyl carbon to appear at higher δ value.

The molecular formula of compound 1 was $C_9H_6ClNO_2$(*m/z* 195.602 [M^+]). The IR spectrum presentalert for carbonyl functional group at 1662 cm^{-1}, C-O and C-H stretch resonance at 1102 cm^{-1} and 2871 cm^{-1} respectively. The ^{1}H NMR spectrum gave three aromatic protons at δ_H 7.59, 7.16 and 6.40 and a vinyl methyl protons at δ_H2.57. In the ^{13}C NMR spectrum, the ester carbonyl resonated at δ_C 168.08, while the aromatic carbons resonated in the range δ_C 113.40 – 149.23. The vibrations at δ_C 153.13 and δ_C 22.15 were due to the imine oxygenated carbon (C-1) and the methyl carbon respectively (Table 1).

Compound 2, molecular formula $C_9H_8ClN_3O$ (*m/z* 210.633 [M^+]), had NMR data similar to 1, except for an additional signal at δ_H 5.80 in the ^{1}H NMR spectrum which was attributed to the amino protons (2H) (Table 2).

Table 4 lists the m/z (relative abundance, %) values of principal fragments of the studied compound, while figure 1 illustrates the mass spectrum of the compound. The mass spectrum of the compound shows a molecular ion of m/z 210 corresponding to the molecular mass of the compound. The molecular ion of m/z 210 fragment to give m/z 195 by loss of

–NH group. The ion of m/z 195 was broken to give m/z 181 by losing CH_2 group and fragment to m/z 146 by loss of Cl. This fragmented to m/z 120 by loss of –HCN group which fragment to give m/z 93 by loss of –HCN and finally gave m/z 65 by loss of CO group.

5. Conclusion

The present work shows that the mass spectra of compound 2 has relatively small molecular ion and peaks typical of a cleavage and rearrangement processes type fragmentation. Compound 2 give a characteristic fragmentation pattern with a very stable fragment of benzopyrazolone (m/z210). The molecular ion of m/z 210 finally gave m/z 65 after lossing -CO, –NH group, -CH_2 -Cl, –HCN and –HCN groups. From the study of the mass spectra of Compound 2, it shows that the Compound give a characteristic cleavage fragmentation pattern.

Conflict of Interest

The authors declare that they have no competing interests.

Author Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them..

Ethics Approval and Consent to Participate

Ethic approval, consent to participate and the procedure used was approved by the Ethic approval committee of Ondo State University of Science and Technology, Okitipupa, Ondo State, Nigeria.

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