

Electron Impact Ionization Mass Spectra of 3-Amino 5,6-dimethoxyl-2-methyl quinazolin-4-(3H)-one Derivative

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Abstract. The synthesis of novel heterocyclic derivatives has attracted considerable attention. The explosive growth of heterocyclic chemistry is emphasized by the large number of research publications, monographs, and reviews. The heterocyclic organic compounds are extensively disseminated in natural and synthetic medicinal chemistry and are vital for human life. Looking at the previous studies on quinazolinones derivatives, only limited information is available on their mass spectral along with the preparation of novel quinazolin-4-(3H)-one derivatives. Objective of this study, was to synthesize a novel 2-Methyl-6, 7-dimethoxy-quinazolin-4-one was synthesized via the reaction between 2-Methyl-6, 7-dimethoxy-benzo-1,3-oxazin-4-one and hydrazine hydrate and study their electron impact (EI) mass spectral fragmentation. The condensation of 2-amino-methyl-4, 5-dimethoxybenzoate with acetic anhydride yielded the cyclic compound 2-methyl-4, 5-disubstituted-1, 3-benzo-oxazine-4-one which further produce a novel 2,3-disubstituted quinazolin-4 ones via the reaction with hydrazine hydrate. The compounds synthesized were unequivocally confirmed by means of Infrared, Nuclear Magnetic Resonance (¹H and ¹³C), Gas Chromatography Mass Spectrophotometer and Elemental analysis. The molecular ion of m/z 235 fragment 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 CH₂ group and fragment to m/z 177 by loss of HCO. This fragmented to m/z 162 by loss of –CH₃ 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. 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.

Key words: Mass spectroscopy, Synthesis, Quinazoline-4-one, 2-methyl 6, 7-disubstituted 1, 3-benzo-oxazine-4-one, Nucleophile, Electron Impact Ionization Mass Spectra.

Introduction

Heterocyclic compounds are cyclic compounds with the ring containing carbon and other elements, the commonest being oxygen, nitrogen and sulphur (Finar, 2007: 826). Some of the medicinally important heterocyclic compounds are the quinazolines. Quinazoline is a compound made up of two fused six-membered simple aromatic rings, benzene ring and a pyrimidine ring. Quinazoline, earlier known as benzo-1,3-diazine was first prepared in the laboratory by Gabriel in 1903, although one of its derivatives was known much earlier (Anti-inflammatory agents, 2008).

Of the many derivatives of quinazoline system known so far, keto-quinazolines also called quinazolinones, are the most important compounds. Depending upon the position of the keto or oxo group, these compounds may be classified into two. The two structural isomers are 2-quinazolinone and 4-quinazolinone, with the 4-isomer being the most common (Quinazolinone encyclopedia, 2010).

Quinazolinone form a large group among the pharmacologically active chemical moieties and are generally of little toxicity without serious side effects to the human body. Quinazolinones are versatile nitrogen heterocyclic compounds, displaying a broad spectrum of biologically and pharmacological activities in animal as well as in human systems. The chemistry and pharmacology of quinazolinones have been of great interest to medicinal chemist (Shradha and Scrivastava, 1994: 143). Quinazolin-4-one and its derivatives possess a diverse range of biological activities including analgesic (Scrivatva et al., 1993), anticancer (Scrivatva et al., 1993: 596-600) and antidiabetic activity (Hour, 2000: 4479-4487; Hamel et al., 1996: 53-59; Mayer et al., 1997: 8445; Jiang et al., 1990: 1721).

Heterocyclic compounds have a wide range of application: they are predominant among the type of compounds used as pharmaceuticals, as agrochemicals and as veterinary products. They also find applications as sentizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dyestuff (Kozikowski, 1984: 112-121).

Quinazolinone peptides were reported for their anti-inflammatory, antioxidant, anthelmintic, antibacterial and antifungal activities (Desai A. and Desai K, 2005: 98-108; Laddha and Bhatnagar, 2009: 6796–6802).

Quinazolin-4(3H)-ones with 2,3-substitution are reported to possess significant analgesic, anti-inflammatory (Abdel-Rahman et al., 2003: 372-377; Chambhare et al., 2003: 89-100) and anticonvulsant activities (Santagati et al., 1995: 689-695).

Looking at the previous studies on quinazolinones derivatives, only limited information is available on their mass spectral along with the preparation of novel quinazolin-4(3H)-one Derivative. In this study, a novel 2-Methyl-6, 7-dimethoxy-quinazolin-4-one was synthesized via the reaction between 2-Methyl-6, 7-dimethoxy-benzo-1,3-oxazin-4-one and hydrazine hydrate and study their electron impact (EI) mass spectral fragmentation.

Materials and Methods

General Experimental Procedure

Reagents and solvents were purchased from sigma-Aldrich chemical supplier in Germany. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Buck scientific IR M500 instrument. The ¹H and ¹³C NMR spectra were recorded in DMSO-d₆ at 400MHz with HAZ VOLATILE V2.M. Chemical shifts are reported in ppm relative to tetramethylsilane period. Gas chromatography mass (GC/MS) spectra were obtained on a Finigan MAT 44S mass spectrometer operating at electron impact energy of 70eV. Elemental analysis data agreed with the calculated values. Analytical thin layer Chromatography (TLC) was used to monitor the reactions.

Experimental

Reagents and solvents were purchased from sigma-Aldrich chemical supplier in Germany. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Buck scientific IR M500 instrument. The ¹H and ¹³C NMR spectra were recorded in DMSO at 400MHz with HAZ VOLATILE V2.M. Chemical shifts are reported in ppm relative to tetramethylsilane. Gas chromatography

Mass spectra were obtained on a HAZ VOLATILE V2.M (400MHz) and chemical shifts are reported in ppm relative to tetramethylsilane as reference standard. Elemental analysis agreed favourably with the calculated values. Analytical thin layer Chromatography (TLC) was used to monitor the reactions (Fig.1, Fig.2).

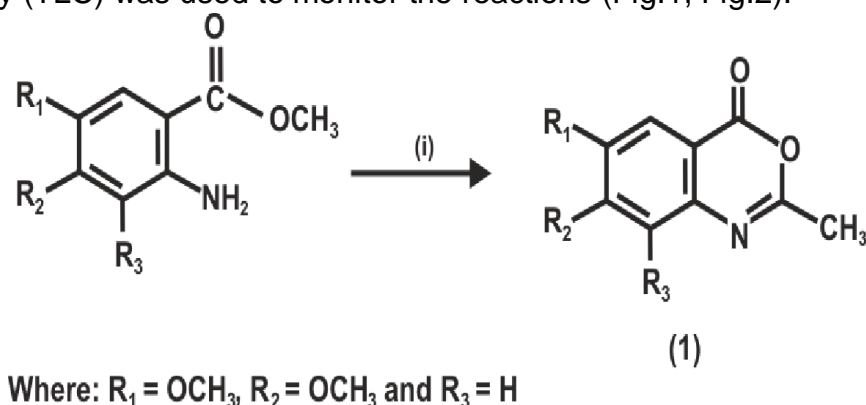


Fig. 1. Possible mechanism for synthesis of compound 2

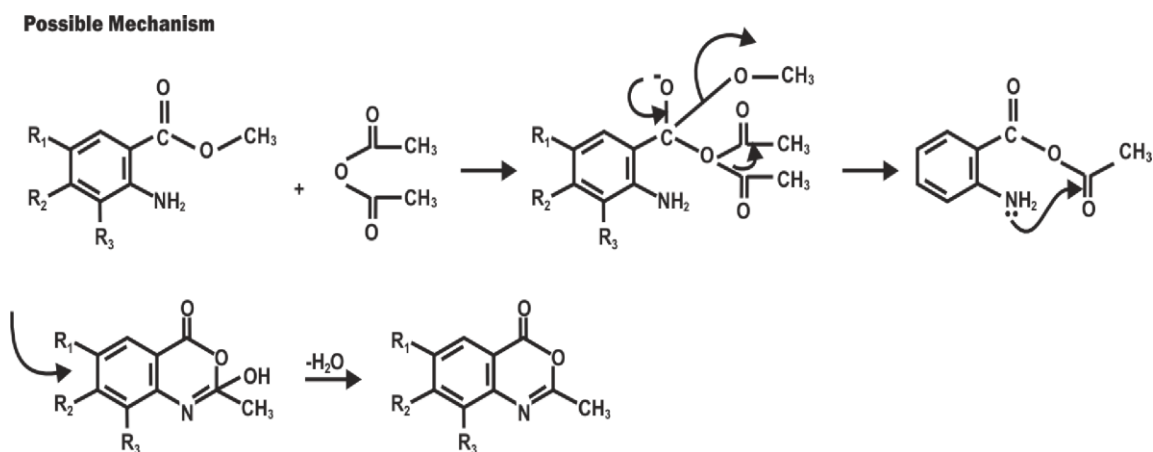


Fig. 2. Possible mechanism for synthesis of compound 2

Results

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 quinazolinone was 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 methylantranilate 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 quinazolinone-4-one (Tables 1, 2).

Table 1. Characterization and Physical data of Synthesized Compounds

Compound No	Solvent	Formula M. wt	Analysis% Calc/Found	
			C	H
1	Ethanol	$\text{C}_{11}\text{H}_{11}\text{NO}_4$ (221.209)	62.20	5.18
			62.10	4.98

2	Ethanol	$C_{11}H_{13}N_3O_3$ (235.239)	56.11 56.40	5.53 5.41
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Table 2: ^{13}C -NMR of Synthesized Compounds

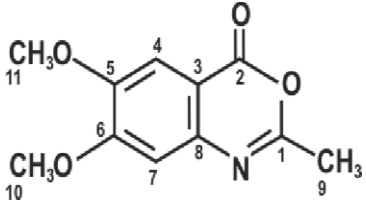
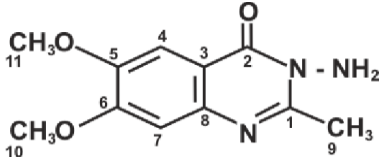
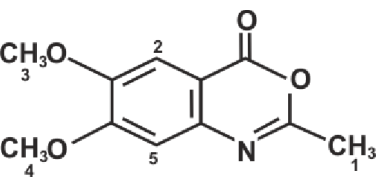
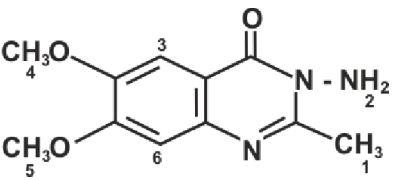
Compound No	δ (ppm) Carbon atom number
	168.28(C-2), 155.80(C-6), 149.23(C-8) 140.28 (C-1), 113.37 (C-5), 100.56 (C-4) 100.05 (C-3), 100.01 (C-7), 16.95 (C-9) 56.13 (C-10), 51.93 (C-11)
	160.28 (C-2), 155.29 (C-6), 154.57 (C-1) 149.07 (C-8), 143.77 (C-5), 113.65 (C-1) 108.24 (C-3), 105.64 (C-7), 56.80 (C-10) 56.63 (C-11), 22.58 (C-9)

Table 3: ^{13}C -NMR of Synthesized Compounds

Compound No	δ (ppm)
	7.16 (s, 1H), 6.40 (s, 1H), 3.78 (s, 6H), 3.68 (s, 3H)
	7.41 (s, H), 7.10 (s, 1H), 5.80 (s, 2H), 3.90 (s, 6H), 2.58 (s, 3H)

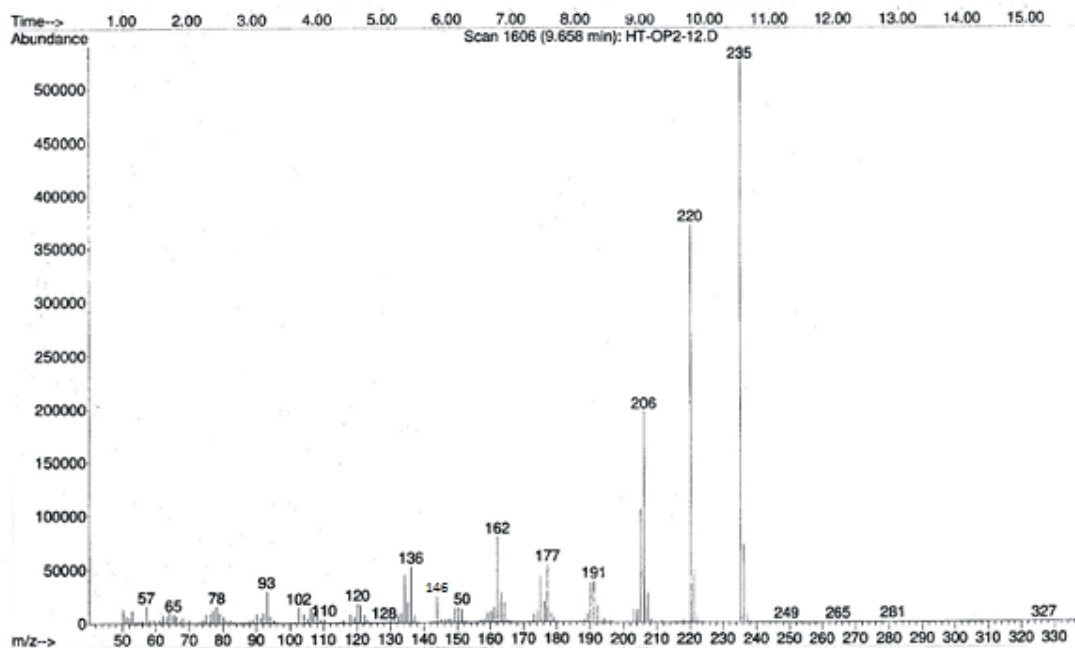


Fig. 3. 70Ev Mass Spectrum of compounds 2

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

Compound	M+	M-	m/z	Other Ions
2	$[C_{11}H_{13}N_3O_3]^+$ 235 (100)	NH	$[C_{11}H_{12}N_2O_3]^+$ 220 (70)	191 (8), 136 (10), 102 (3), 93 (5), 78 (3), 57 (3)
		CH ₂	$[C_{10}H_{10}N_2O_3]^+$ 206 (37)	
		HCO	$[C_9H_9N_2O_2]^+$ 177 (10)	
		CH ₃	$[C_8H_6N_2O_2]^+$ 162 (15)	
		OH	$[C_8H_6N_2O]^+$ 146 (1.5)	
		CN	$[C_7H_6NO_2]^+$ 136(10)	
		O	$[C_7H_6NO]^+$ 120 (4)	
		HCN	$[C_6H_5O]^+$ 93(10)	
		CO		

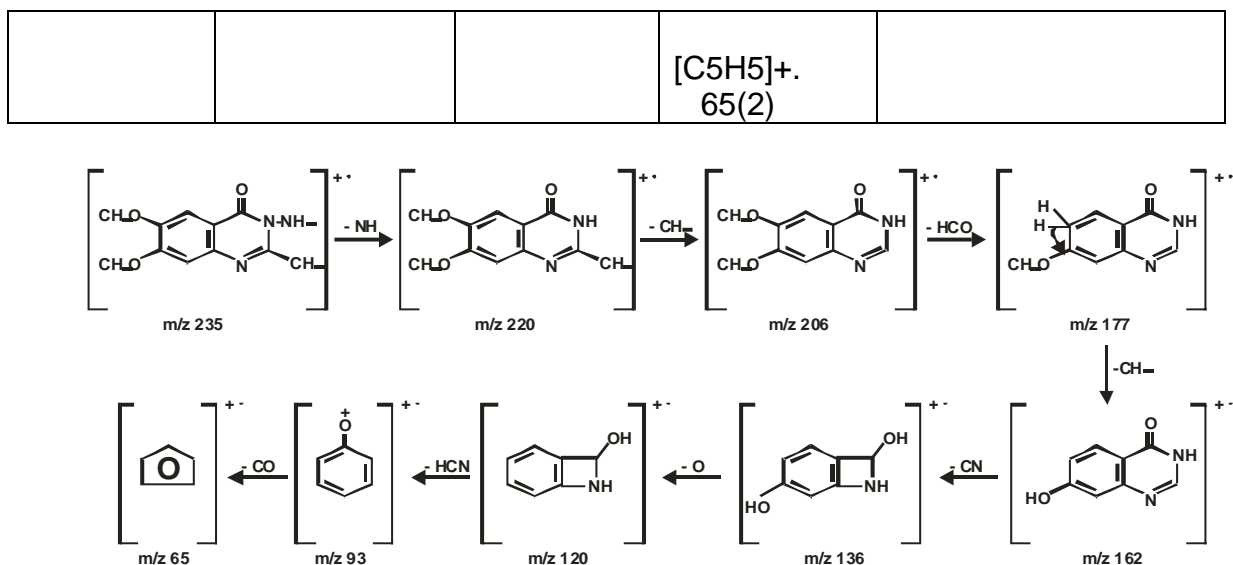


Fig.4. Main fragmentation pathway of compound 2

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

1H NMR (400MHz, DMSO) δ 7.16 (s, 1H), 6.40 (s, 1H), 3.78 (s, 6H), 3.68 (s, 3H), ^{13}C 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, (NH₂), 3018 (CH aromatic), 2951, 2871, 2718 (CH aliphatic), 1662 (C=O). Anal. Cal 1159 (c-0) for C₁₁H₁₁N₂O₄; C 62.20; H 5.18. Found: C 62.10, H 4.98.

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

1H 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 (NH₂), 1622 (C=O), Anal. Cal. for C₁₁H₁₃N₃O₃; C 56.11, H 5.53; Found, C 56.40, H 5.41.

Discussion

Structural elucidations of compounds synthesized were characterized by correct elemental analysis and careful inspections of spectral data. Looking at the 1H NMR spectra of the compounds synthesized, compound 1 displayed a singlet signal at: δ 3.78 attributed to methoxy group and singlet at δ 3.68 which was due to methyl group. Other singlets appeared at δ 7.16 and 6.40 attributed to aromatic protons. Also, 1H NMR spectrum of compound 2 showed a characteristic signal at δ 2.56 (singlet) corresponding to methyl group and duplet at: δ 3.90 for methoxy group. Two singlets appeared at δ 7.41 and 7.10 attributed to aromatic protons. Another signal appeared at 5.80 which was attributed to the protons of the amino group. For the IR spectra, compound 1 was characterized by absence of ν NH₂ and presence of ν C-O stretch in 1101 cm^{-1} region of the compound. Compound 2 was characterized by absence of ν C=O and presence of ν NH₂ in 3301 cm^{-1} region of the compound.

The ^{13}C NMR spectrum of compound 1, revealed signals at δ 16.95, 51.93 and 56.13 attributed to methyl and the two methoxy groups respectively, while the aromatic carbon atoms appeared between δ values 100.05-168.28 with the carbonyl carbon atom appearing as the highest δ value of 168.28. Similarly, compound 2 showed signals at δ 22.58, 56.63 and 56.80 attributed to methyl and the two methoxy groups respectively,

while the aromatic carbon atoms appeared 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.

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 235 corresponding to the molecular mass of the compound. The molecular ion of m/z 235 fragment to give m/z 220 by loss of $-\text{NH}$ 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 $-\text{CH}_3$ 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 $-\text{HCN}$ and finally gave m/z 65 by loss of CO group.

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/z 235).

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