ISSN: 2754-4915

Journal of Material Sciences & Manufacturing Research

SCIENTIFIC Research and Community

Research Article

Open Access

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

Osarumwense Peter Osarodion* and Omotade Treasure Ejodamen

Department of Chemical Sciences, Ondo State University of Sciences and Technology, Okitipupa, Ondo State, Nigeria

ABSTRACT

Looking at the previous studies on quinazolinones derivatives, only limited information's are available on their mass spectral along with the preparation of novel quinazolin-4-(3H)-one derivatives The condensation of Methyl-2-amino-4-Chlorobenzoate with acetic anhydride yielded the cyclic compound 2-methyl 7-Chloro-1, 3-benzo-oxazine-4-one (1) which further produce 3-Amino-2-Methyl 7-Chloro quinazolin-4(3H)-ones (2) via the reaction with hydrazine hydrate. The compounds synthesized were unequivocally 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 2show a weak molecular ion peak and a base peak of m/z 235resulting 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.

***Corresponding author**

Osarumwense Peter Osarodion, Department of Chemical Sciences, Ondo State University of Sciences and Technology, Okitipupa, Ondo State, Nigeria; Tel: +2348056350793; E-mail: osarodion.peter@yahoo.com

Received: January 07, 2021; **Accepted:** January 18, 2021; **Published:** February 27, 2021

Keywords: Mass spectroscopy, 3-amino-7-chloro-2-methyl quinazolin-4(3H)-one, 7-chloro-2-methyl-4H-benzo [d] [1, 3]-oxazin-4-one, Nucleophile, Quinazolin-4(3H)-one, Electron Impact Ionization Mass Spectra

Introduction

An introduction to Medicinal Chemistry gives us a very detailed look at the world of medicine [1]. Principles of Medicinal chemistry is necessary to consider physiochemical properties, used to develop new pharmacologically active constituents and their mechanism of action and many of them are entered to pharmacological screening for determining their biological activity. This random screening process has been inefficient, but it has resulted in identification of new lead compounds whose structures have been optimized to produce clinical agents [2]. A rich tradition of analog design strategies has evolved for creating new compounds within medicinal chemistry research for biological evaluation [3].

Heterocyclic chemistry is a chemistry involving the heterocyclic compounds, which has atoms of at least two different elements as number of ring. The heterocyclic atoms may be inorganic, though the compound contains carbon atoms in the ring. The word hetero means " different from carbon and hydrogen" Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products [4]. Heterocyclic chemistry is a potential part of the synthetic organic chemistry, covering a wide variety of bioactive molecules. Among six-membered heterocycles, quinazoline occupies significant position and is commonly found in a wide variety of natural products, synthetic pharmaceutical molecules, and other functional materials [5].

The critical role played by heterocycles in drug design cannot be denied. Even where the natural substrate or ligand for a biological target does not contain a heterocycle, drugs whether of natural or man-made origin that act on that target frequently contain heterocyclic groups [6]. Quinazolinone is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Literature studies on quinazolinones have shown that these derivatives possess a wide variety of biological activities such as antioxidant, antifungal, antibacterial, anticonvulsant, antiinflammatory, antihyperlipidemic, anticancer, antimalarial, antispasmodial analgesic, antiviral, antitubercular and antimicrobial activities [7-19].

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 3-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 and hydrazine hydrate and it was thought to synthesize this new quinazolinone derivative and

screen the compound for its electron impact (EI) mass spectral fragmentation.

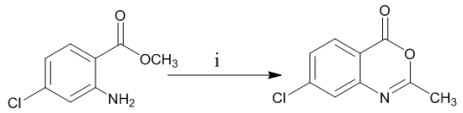
Materials and Methods

General Experimental Procedure

All reagents and solvents were products of sigma-Aldrich, Germany. Melting points were determined 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-d6 at 400 MHz with HAZ VOLATILE V2. M spectrophotometer. Chemical shifts were reported in ppm relative to tetramethylsilane. Gas chromatography-Mass spectra were obtained on a Finingan MAT 44S mass spectrometer operating at 70eV. Elemental analysis agreed favourably 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 ^{1}H and ^{13}C 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.



Scheme 1

i = Acetic anhydride, ethanol

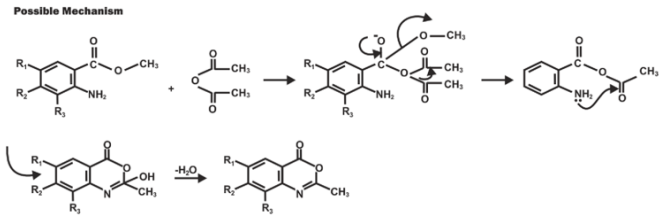
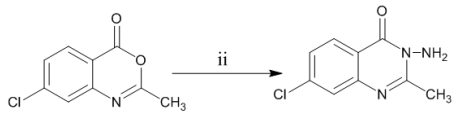


Figure1: Possible Mechanism For Synthesis of Compound 1



Scheme 2

ii = Hydrazine hydrate, ethanol

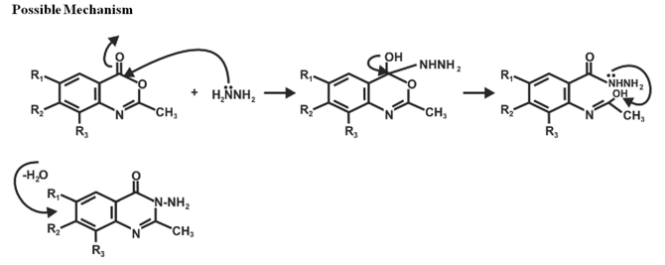


Figure 2: Possible Mechanism For Synthesis of Compound 2

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: 149-151oC).

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.

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.

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).

The molecular formula of compound 1 was $C_9H_6ClNO_2$(m/z 195.602 [M+]). The IR spectrum showed signals for carbonyl functional group at 1662 cm^{-1}, C-O and C-H stretch vibrations at 1102 cm^{-1} and 2871 cm-1respectively. The 1H NMR spectrum showed three aromatic protons at δH 7.59, 7.16 and 6.40 and a vinyl methyl protons at δ_H 2.57..In the ^{13}C NMR spectrum, the ester carbonyl resonated at δC 168.08, while the aromatic carbons resonated in the range δC 113.40 – 149.23. The resonances 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 210.033 [M^+]), had NMR data similar to1, except for an additional signal at δ_H 5.80 in the ^1H 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/Found C	H
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

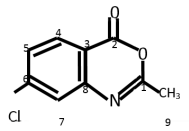
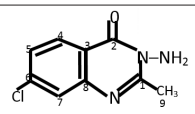
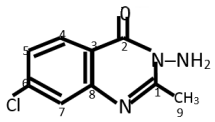
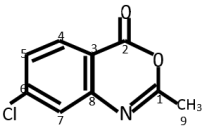
Compound No	δ (ppm) Carbon atom number
	153.13(C-1), 168.08(C-2),120.80(C-3) 128.18 (C-4), 1132.10 (C-5), 113.40 (C-6) 1122.13 (C-7), 1149.23 (C-8), 22.15 (C-9)
	154.57 (C-1), 160.28 (C-2), 120.24(C-3), 128.07(C-4), 133.60 (C-5), 113.67 (C-6), 122.12 (C-7), 148.07 (C-8), 22.58 (C- 9).

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

Compound No	δ (ppm) Carbon atom number
	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)

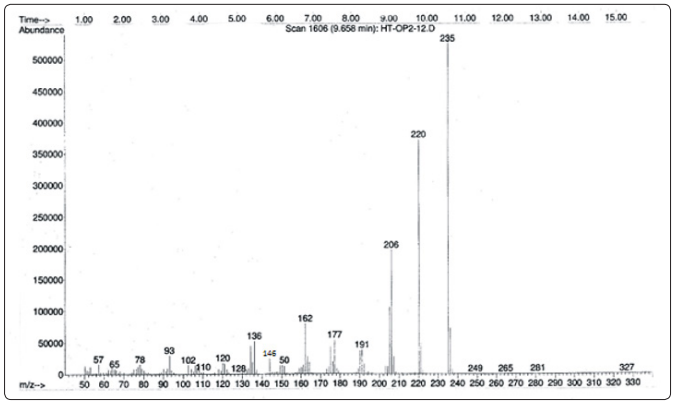


Table 4: E1 Mass Spectra (70ev) of Compound 2 m/z (relative intensity %)

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 ( )	

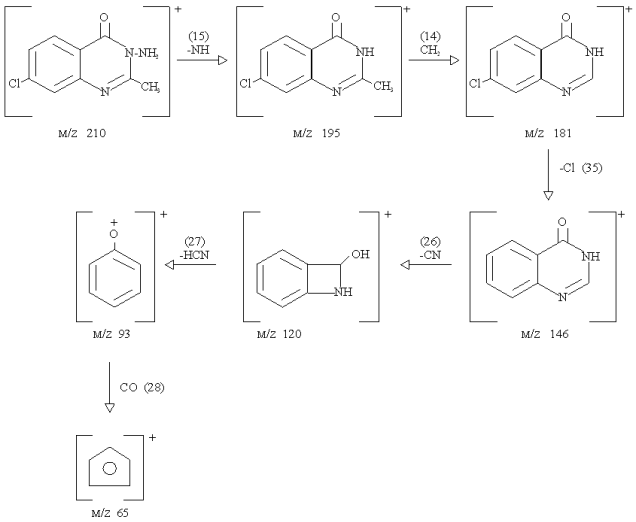


Figure 4: Main Fragmentation Pathway of Compound 2

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.

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 $C_{11}H_{13}N_30_3$; C 56.11, H 5.53; Found, C 56.40, H 5.41.

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 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 δ7.16 and 6.40 attributed to aromatic protons. Also, ^{1}H 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 δ7.41 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 υ NH_2 and presence of υ C-O stretch in 1101cm^{-1} region of the compound. Compound 2 was characterized by 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, revealed signals at δ16.95, 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 δ22.58, 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.

The molecular formula of compound 1 was $C_9H_6ClNO_2$(m/z 195.602 [M$^+$]). The IR spectrum showed signals for carbonyl functional group at 1662 cm^{-1}, C-O and C-H stretch vibrations at 1102 cm^{-1} and 2871 cm^{-1}respectively. The ^{1}H NMR spectrum showed three aromatic protons at δH 7.59, 7.16 and 6.40 and a vinyl methyl protons at δH 2.57..In the 13C 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 resonances 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 to1, 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.

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).

Acknowledgements

The author acknowledge the assistance of Baba Haruna of the Department of Pharmaceutical Chemistry of Niger Delta University, Wilberforce Island, Yenogoa and Dr. Marris, in England for running the spectra.

References

1. Kennedy John F (2007) An Introduction to Medicinal Chemistry. Carbohydrate Polymers 68: 609-610.
2. Selvam T, Kumar P, Vijayaraj P (2011) Quinazoline Marketed drugs – A Review. Research in Pharmacy 1: 1-21.
3. Stewart KD, Shirodaa M, James CA (2006) Drug Guru: A computer software program for drug design using medicinal chemistry rules. Bioorganic & Medicinal Chemistry 14: 7011-7022.
4. Maity A, Mondal S, Paira R, Hazra A, Naskar S, et al. (2011) A novel approach for the one-pot synthesis of linear and angular fused quinazolinones Tetrahedron Lett 52: 3033-3037.
5. Gundla R, Kazemi R, Sanam R, Muttineni R, Sarma JA, et al. (2008) Discovery of Novel Small-Molecule Inhibitors of Human Epidermal Growth Factor Receptor-2: Combined Ligand and TargetBased Approach. Med. Chem 51: 3367.
6. Balakumar C, Lamba P, Kishore DP, Narayan BL, Rao KV, et al. (2010) Synthesis, anti-inflammatory evaluation and docking studies of some new fluorinated fused quinazolines. Eur J Med Chem 45: 4904-4913.
7. Venakata Ramana Reddy, Nadendla Rama Rao, R Raja Reddy, R Suthakaran (2014) Microwave Assisted Synthesis, Characterization and Pharmacological Evaluation of Imidazolo Quinazoline-4-one Derivatives. J Pharm Sci Rev Res 29: 1-4.
8. Ahmed Mahal, Rajab Abu-El-Halawa, Sami A. Zabin, Mohammad Ibrahim, Mahmoud Al-Refai, et al. (2015) Synthesis, Characterization and Antifungal Activity of Some Metal Complexes Derived From Quinoxaloylhydrazone. World Journal of Organic Chemistry. 3: 1-8.
9. Nagaraju Gollapalli, J Naroop Teja, V Manjusha, M Srinivasarao, B Poornima (2013) Synthesis and Biological Evolution of Phenyl- Quinazolinone Derivatives . AJPAMC 1: 48-53.
10. Mohamed F Zayed (2014) New fluorinated quinazolinone derivatives as anticonvulsant agents. Journal of Taibah University Medical Sciences 9: 104-109.
11. Rakesh KP, Manukumar HM, D Channe Gowda (2015) Schiff's bases of quinazolinone derivatives: Synthesis and SAR studies of a novel series of potential anti-inflammatory and antioxidants. Bioorganic & Medicinal Chemistry Letters 25: 1072-1077.
12. AMR Y Esmat, Fawzia M Refaie , Soad M Abdel Gawad, Aida M Ibrahim , Mona A Mohamed (2005) The antihyperlipidemic

activities of 4(3H) quinazolinone and two halogenated derivatives in rats. Lipids in Health and Disease 4: 22.
13. Nema Rajesh Kumar (2009) Academic Journal of Cancer Research 2: 73-77.
14. Mohammed Hussen Bule (2015) IAJPR 5.
15. B Zarranz (2006) Brazilian Journal of Pharmaceutical Sciences 42.
16. CH Rajveer (2010) Int J Pharma and Bio Sci 1: 2010.
17. Ratnakar Singh (2013) IJPCBS 3: 1269-1275.
18. Kishor H Chikhalia (2012) International Journal of Drug Design and Discovery 3: 739- 730.
19. Sucheta (2012) IJPCBS 2: 97-103.