Synthesis Of 3-Substituted-6, 8-Dibromo-2-Methyl Quinazolin-4(3H)-One Derivatives Via 6, 8-Dibromo-2-Methyl-4h-Benzo [D] [1,3] –Oxazin-4-One.

Osarumwense, P.O, Edema, M.O, Usifoh, O, Marvis, E.

Abstract: The condensation of methyl 3, 5-dibromoanthranilate with acetic anhydride yielded the cyclic compound 2-Methyl-6, 8-dibromo-4H-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 (^{1}H and ^{13}C), Gas chromatography Mass Spectrophotometer and Elemental analysis.

Keywords: benzoxazinone, cylization, 3, 5-dibromoanthranilate, 6, 8-dibromo-2-Methyl-4H-benzo[d] [1, 3] –oxazine-4-one, nitrogen nucleophile, synthesis, 3-substituted-6,8-dibromo-2-Methyl-quinazoline4(3H)-one.

Introduction

4(3H)-quinazolinone is a frequently encountered unit in natural products such as L-vasicinone [1] isolated from justicia adhatoda leaves [1] and drugs such as methaqualone [2] a hypnotic and anticonvulsive drug [2]. The inhibition of chymotrypsin-like and elastase-like serine proteases by 4H-3, 1-benzoxazinones were investigated [3] such compounds have recently been shown to be active in vivo after intratracheal administration [4]. Introduction of 2-amino substituent is a successful strategy to improve the chemical stability of benzoxazinones. Many fused pyrimidines such as quinazolines have been reported, anti-inflammatory [5], antimicrobial [6], and anticancer activities [7], [8]. Moreover, several quinazolinone derivatives were synthesized as potential antimicrobial [9] anticancer [10] and antimalarial agent [11]. These findings prompted the authors to synthesis a varieties of quinazolinone derivatives via the interaction of the benzoxazinone derivatives with different nitrogen nucleophiles, with the aim of obtaining more precise information about the course of the reaction and some interesting pharmaceutical compounds.

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 quinazolin-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 methyl 3, 5-dibromoanthranilate and acetic anhydride yielded the cyclic compound 2-Methyl-6, 8-dibromo-4H-benzo-oxazine-4-one. The reaction of this compound with hydrazine hydrate yielded the novel 2, 3-disubstituted quinazoline-4-one.

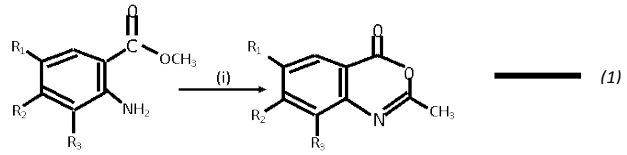
Materials and methods

General Experimental Procedure

All reagents and solvents were purchased from sigma-Aldrich, in 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-*d*6 at 400 MH_z with HAZ VOLATILE V2. M Chemical shifts Sare reported in ppm relative to tetramethylsilane. Gas chromatography mass spectra were obtained on a Finingan MAT 44S mass spectrophotometer operating at 70eV. Elemental; analysis agreed favourably with the calculated values Analytical thin layer chromatography (TLC) was used to monitor the reactions.

Elemental Analysis

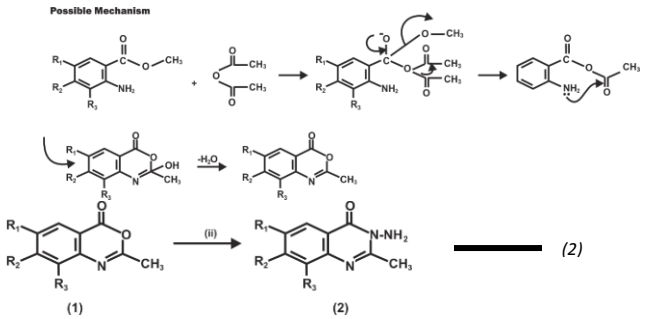
The compositions of the compounds are summarized in table 1. The C and H contents (both theoretically calculated values and actual values) are indicated.



Scheme 1

Wahere : R_1 = Br , R_2 = H , R_3 = Br

***i* = Acetic anhydride, Ethanol**

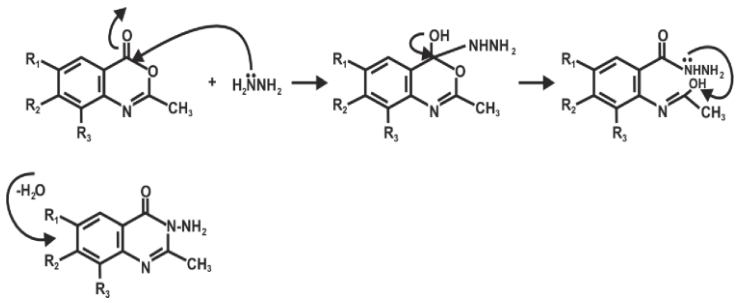


Scheme 2

Wahere : R_1 = Br , R_2 = H , R_3 = Br

***ii*= Hydrazine hydrate, Ethanol**

Possible Mechanism



General Procedure for the Synthesis of 6, 8-dibromo-2 Methyl-4h-benzo [d] [1, 3] –Oxazine-4-One (1)

3.09g (0.01mol) of methyl 3, 5-dibromoanthranilate with 10ml 1.02g (0.01mol) acetic anhydride in 30ml ethanol medium were reacted 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).At the end of the reaction, work up was done. Ethanol was removed in vacuum and the crude mixture was poured into 50ml of ice water on a cold water bath. The mixture was stirred for 30 minutes filtered and extracted into ethyl acetate and allowed to evaporate at room temperature to give solid products which were recrystallized from hexane or dichloromethane-hexane mixture. Yield was 2.95g (95%), mp: 84-86^{o}C.

General Procedure for the Synthesis of 3-Substituted 6, 8-dibromo-2-Methyl-Quinazoline4(3H)-One (2)

The condensation of equimolar amounts (1.59, 0.005mol) of 2- methyl-6, 8-dibromo-4H-benzo [1, 3]-oxazine-4-one and hydrazine hydrate (0.93g, 0.01mol) in 30ml boiling ethanol were heated under reflux in 30ml ethanol with stirring using a magnetic stirrer until the reaction mixture showed no trace of starting material when the TLC was developed (3 hours).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 three times with 20ml of distilled water [20ml x 3]. The white crystals were dried and recrystallized from dimethylformamide (DMF) to give pure 3-amino-2-methylquinazolin-4 (3H) –one. Yield was 1.48g (93%) mp: 75-77^{o}C.

Results And Discussion

Table 1: *Characterization and Physical data of synthesized compounds*

Compound No	Solvent	Formula M.wt	Analysis % Cal/Found C	H
1	Ethanol	$C_9H_5NBr_2O_2$ (318.95)	33.86 33.65	1.57 1.46
2	Ethanol	$C_9H_7N_3Br_2O$ (393)	45.71 44.53	2.54 3.10

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

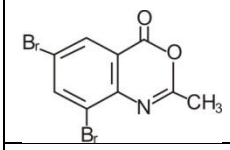
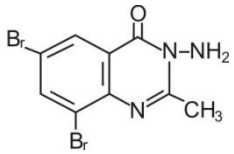
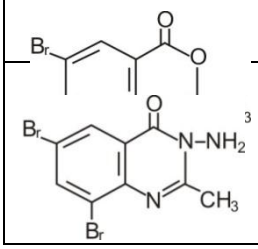
Compound No	Δ (ppm) Carbon atom number
	168.31(C-2), 167.19 (C-1), 143.52 (C-8), 136.69 (C-6), 131.29 (C-4), 123.95 (C-3),122.01 (C-5), 119.57 (C-7), 25.43 (C-9)
	169.09 (C-2), 156.86 (C-1), 140.20 (C-8),139.72 (C-6), 129.50 (C-4), 123.81 (C-5)119.86 (C-7), 153.19 (C-3), 24.85 (C-9)

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

Compound No	Δ (ppm) Carbon atom number
	7.91 (s,1H), 6.87 (s,1H), 3.87 (s, 3H)
	9.94 (s, 1H), 7.59 (s, 1H), 5.57 (s, 2H), 2.57 (s,3H)

Characterization of 2-Methyl-6, 8-dibromo-4H-benzoxazin-4-one(1)

^{1}H NMR(400 MHz, DMSO) δ 7.91 (s, 1H), 6.87 (s, 1H), 3.87 (s,3H), ^{13}C NMR (400 MH_z, DMSO) δ 168.31, 167.59, 143.52, 136.69, 133.29, 123.05, 122.01, 119.57, 25.43, 1R (KBr, cm^{-1}), 3356 (CH aromatic), 2945, 2767 (CH, aliphatic), 1699 (C=O), 1665 (C-O). anal Cal for $C_9H_5Br_2NO_2$ C 33.85, H 1.57, Found: C 33.65, H 1.46

Characterization of 2-Methyl, 6, 7-dibromo-4(3H)-quinazolin-4-one (2)

^{1}H NMR (400 MHz, DMS0) δ 9.94 (S, 1H), 7.59 (S, 1H), 5.57 (S, 2H), 2.57 (S, 3H), ^{13}C NMR (400MH_z DMSO), δ 169.09, 156.86, 140.20, 139.72, 129.50, 123.81, 119.86, 113.19, 24.86. 1R (KBr, cm^{-1}), 3344, 3227 (NH_2), 3000 (CH aromatic),2834 (CH, aliphatic), 1616 (C=N), 1070 (C-O)Anal Cal for $C_9H_7Br_2N_3O$ C 32.43, H 2.10,Found C 32.10, H 2.15.

Discussion

Structural elucidations of compounds synthesized were characterized by correct elemental analysis and careful inspections of spectral data. The ^{1}HNMR spectra of the compounds, compound 1 displayed a singlet signal at δ3.87 attributed to methyl group. Other singlets appeared at δ7.91 and 6.87 attributed to aromatic protons. Also, ^{1}HNMR spectrum of compound 2 showed characteristic signal at 2,57 (singlet) corresponding to methyl group. Another signal appeared at 5.57 which was attributed to the protons of the amino group. The ^{13}CNMR spectrum of compound 1, revealed signal at 25.43 attributed to methyl group, between δ values 119.57-168.31 with the carbonyl carbon atom appearing as the highest δ value of 168.31. Similarly, compound 2 showed signals at δ24.85 attributed to methyl group; while the aromatic carbon atoms appeared between

δ values 153.19-169.09, with the carbonyl carbon atom appearing as the highest δ value of 169.09. The ^{13}C nuclear magnetic resonance revealed low δ values for the aliphatic carbon. 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 high frequency. The electronegative effect of the oxygen atom on the carbonyl group makes the carbonyl carbon to appear at higher δ value.

Acknowlegments:
The authors appreciate the assistance of Dr. Marvis E in England for running the spectra.

Conclusion:
Looking at the IR spectrum of compound 1 and compound 2. Compound 1 reveals the presence of a Sharp peak at 1665 attributed to C-O which was absence in compound 2, and the presence of a sharp peak at 3227 in compound 2, attributed to NH_2, which was absent in compound 1.

References
[1] Bitterroot Restoration. (2011). Herbal Medicine. Justicia adhatoda for Asthma. File///c:/Documents and setting/CST Tadmin/ Desktop/New folder/.

[2] Electrophoresis. (2011). Capillary Electrophoresis-Mass spectrometry Therapeutic Protein Characterization Springer ISBN 978–3–319-46238-7.DOI 10.1007/978-3-319-46240-0.

[3] Neumann, V.; Schechter, N.; and Gitschow, M. (2001). Pharmacological activities of 4H-3, -1-benzoxazinones derivatives Bioorganic and Medicinal Chemistry 9, 947.

[4] Mitsushashi, H.; Nonaka, T.; Hamamura, I; Kishimoto,T.; Muratani, E.; and Fuji, K. (1999). Pharmacological activities of 4H-3, 1-benzoxazinones derivatives Pharmacol, J. 127, 1147.

[5] Gineinah, M.M.; Nasr, M.N.; Abdela, M.M.; El. Emam. A.A.; and Said, S.A. (2002). Synthesis and anti-inflamatory properties of some quinazolinone derivaties. Med. chem. Res. 10, 243-252.

[6] Meligie, S.; El-Ansury, A.K..; Said, M.M.; and Hussein, M.M.M. (2001). Antimicrobial activities of some quinazolinone derivaties Indian J. Chem. 40B, 62-69.

[7] Corresponding Author; E-mail address; osarodqion.peter@yahoo.com

[8] Partin, J.V.; Anglin, I.E.; and Kyprianou, N.Br. J. (2003). Synthesis and anticancer activities of some quinazolinone derivatives Br. J. Cancer 88(10).

[9] Huron, D.R.; Gorre, M.E.; Kraker, A.J.; Sawyers, C.L.; Rosen, N.; Moasser, M.M. (2003).. Anticancer activities of some quinazolinone derivaties. Clin Cancer Res. 9(4). 1267-1273.

[10] Farghaly, A.M.; Soliman,R.; Khalil, M.A.; Bekhite, A.A.; El-Din, A.; Bekhit, A. (2002). Antimicrobial properties of some quinazolinone derivatives. Boll.Chem. Farm 141(5), 372-378.

[11] Parkanyi, C.; and Schmidt, D.S.J. (2000). Synthesis and anticancer activities of some quinazolinone derivatives Heterocycl. Chem. 37, 725-729.

[12] Kikuchi, H.; Tasaka, H.; Hirai, S.; Takaya, Y.; Lwabuchi, Y.; Ooi, H.; Hatakeyama, S.; Kim, HS.; Wataya, Y.; and Oshima, YJ.(2002). Synthesis and antimalarial agent of some quinazolinone derivaties. Med. Chem. 45(12), 2563-2570.