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Synthesis and Anti-Inflammatory Activity of 4(3H)-Quinazolinone and Its 2-Methyl and 2-Phenyl-4 (3H)-Quinazolinone Derivatives

[1]Osarumwense P.O, [2]Edema, M.O. [3]Usifoh O.
[1]*Department of Chemical Sciences, Ondo State University of Sciences and Technology, Okitipupa, Ondo State, Nigeria.*
[2]*Provost Office, College of Education, Warri, Delta State, Nigeria.*
[3]*Faculty of Pharmaceutical Chemistry, University of Benin, Benin City, Nigeria*.
Corresponding Author: 1Osarumwense P.O

Abstract: *Some 4(3H)-quinazolinone and its derivatives with potential anti-inflammatory properties were synthesized from the reaction of anthranilamide and the proper triethyl orthoacetate, triethyl orthoformate and triethyl orthobenzoate. All 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. The quinazolinones were evaluated pharmacologically for their* ***in vivo****anti-inflammatory activities by carrageenan-induced rat paw oedema. All the investigated compounds exhibited significant anti-inflammatory activity in the range of 81-96% in comparison to control.*

Keyword: *Quinazolin-4(3H)-one,2-Methyl-4(3H)-quinazolinone,2-Phenyl-4(3H)-quinazolinone, Anthranilamide,*

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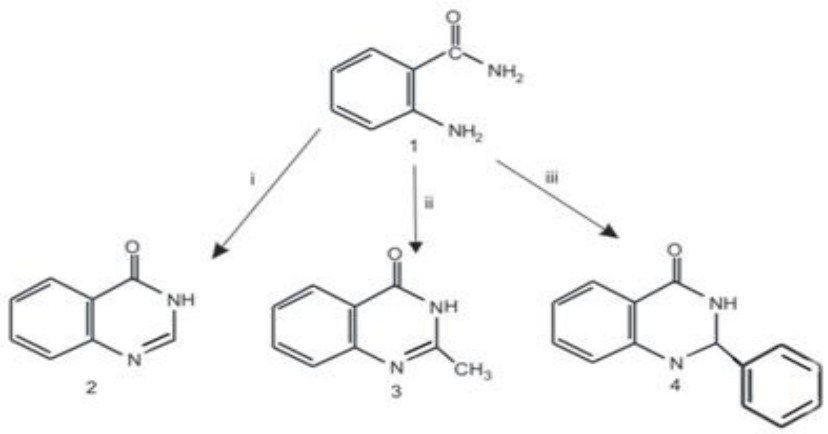
I. Introduction

Quinazoline compounds are widely used as antifungal agents (Dandia *et al.,* 2004, Bartroli *et al.,* 1998 and Aysel *et al.,* 2005). Compounds containing the 4(3H)-quinazolinone ring have been reported to posses different biological activities such as antibacterial (Nesrin *et al.,* 2009), antitubercular (Kumar *et al.,* 1983), antiviral (Corbett *et al.,* 2000), anti-convulsant (Usifoh and Scriba, 2000) and anticancer (Hour *et al.,*2000; Hamel *et al.,* 1996) activity depending on the substituents in the ring system. Since the discovery of raltitrexed (1) and thmitaq (2), interests in quinazolines as anticancer agents have further increased (Bavetsias *et al.,* 2000 and Wissner *et al.,* 2000). According to recent data, quinazoline nucleus has attracted the attention of medicinal chemists due to its well known anticancer activity and many substituted quinazoline derivatives have earned great interest in chemotherapy as antitumor drugs (Jin *etal*., 2005*).* Quinazolinesexert their antitumor activity through inhibition of the DNA repair enzyme system (Sharma, *et al.,* 2002; Thompson, 1995 and Griffin *et al.,* 1998). The present study aimed to synthesize and evaluate the biological activity of 4(3H)-quinazolinone and its 2-methyl and 2-phenyl-4(3H)-quinazolinone derivatives as potential anti-inflammatory agents.

II. Experimental

Reagents and solvents were purchased form sigma-Aldrich chemical suppliers 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 V 2.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



Scheme 1

III. Results

The condensation of anthranilamide with the proper triethyl orthoacetate, triethyl orthoformate or triethyl orthobezoate gave the corresponding 4(3H)-quinazolinone, 2-methyl-4(3H)-quinazolinone and 2-phenyl-4(3H)-quinazolinone.

Table 1: Characterization and Physical data of Synthesized compounds

Compound No	Solvent	Formula M. wt	Analysis % Cal/Found C	 H
2	Ethanol	$C_8H_6N_20$ (146.18)	66.12 67.97	4.13 4.21
3	Ethanol	$C_9H_8N_20$ (160.18)	67.42 68.96	4.99 4.77
4	Ethanol	$C_{14}H_{10}N_20$ (222.18)	75.61 75.10	4.50 4.11

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

Compound No	8(ppm) Carbon Atom No.
2	172.18 (c-2), 151.06 (c-8), 132.75 (c-1) 129.63 (c-6), 117.30 (c-4), 115.27 (c-5)115.26 (c-7, 114.63 (c-3).
3	172.18 (c-2), 151.06 (c-1), 132.75 (c-8129.63 (c-6, 117.30 (c-4), 115.27 (c-5), 115.26 (c-7), 114.63 (c-3), 21.18 (c-9).
4	162.08 (c-2), 156.67 (c-1), 147.61 (c-8), 135.79 (c-6), 135.18 (c-12), 130.49 (c-9), 130.37 (c-10), 128.29 (c-4), 128.29 (c-11), 127.64 (c-7), 126.92 (c-5), 120.97 (c-3).

Table 3: Effect of the test compounds on the carragreenan-induced rat paw oedema

Compounds No	Doses(mg/kg) (P.O)	Change in paw oedema mean ± SEM in				% Activity			
		1st h	2nd h	3rd h	4th h	1st h	2nd h	3rd h	4th h
2	10	3.28 ± 0.28	3.73 ± 0.44	2.33 ± 0.41	1.63 ± 0.48	94.82	96.78	95.71	92.64
	20	1.33 ± 0.25	2.80 ± 0.39	1.73 ± 0.39	0.73 ± 0.39	87.22	95.71	94.22	83.56
3	10	1.98 ± 0.13	1.88 ± 0.12	1.34 ± 0.23	1.50 ± 0.23	91.41	93.62	92.54	92.00
	20	1.98 ± 0.12	2.58 ± 0.38	1.18 ± 0.25	0.65 ± 0.70	91.41	95.35	91.52	81.54
4	10	1.25 ± 0.35	1.53 ± 0.34	1.20 ± 0.26	1.33 ± 0.19	86.40	92.16	91.67	90.98
	20	1.05 ± 0.30	0.70 ± 0.24	0.90 ± 0.38	1.06 ± 0.31	83.81	82.86	88.89	88.68
INDOMET	10	0.85 ± 0.30	0.93 ± 0.37	0.43 ± 0.20	0.73 ± 0.28	80.0	87.09	76.7	83.5

ACIN						0		4	6
OLIVE OIL	1.5Ml/kg	1.17 ± 0.25	0.12 ± 0.13	0.10 ± 0.15	0.12 ± 0.14	-	-	-	-

Values are mean± S.E.M; *P<0.001, significantly different from control, paired t-test (n=5), P.O= per oral.

% Activity = 100-[100x(control/drug treated]

Indomethacin (10mg/kg) was administered orally as reference drug while 5% olive oil was used as negative control. +

General procedure for the Synthesis of 4(3H)-quinazolinone and its Derivatives

Anthranilamide (0.005mol) and the proper triethyl orthoacetate, triethyl orthoformate or triethyl orthobenzoate (0.005mol) were reflexed in ethanol and stirred with the aid of a magnetic stirrer, until TLC indicated absence of the starting materials. The resulting solution was concentrated in vacuum and extracted with dimethylformamide (DMF). The organic layer was evaporated, filtered to give solid products which were recrystallised from appropriate solvents.

Pharmacological **evaluation**

Wistar rats (180-230g) of either sex kept in the laboratory animal house of the Faculty of pharmacy, University of Benin, Benin City, Nigeria were used. The animals were maintained under standard environmental conditions and had free access to standard diet and water(test compounds were administered orally by gavage in 10% olive oil suspensions at different dose levels). Ethical approval was obtained from the Animal Use and Ethics committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Anti-inflammatory Activity

Anti-inflammatory activity was measured using carrageenan induced rat paw oedema assay (Winter *et al.,* 1962; Adeyemi*et al.,* 2002). Group of 5 rats of both sexes (pregnant females excluded) were given a dose of a test compound. After one-hour 0.1ml, 1% carrageenan suspension in 0.9% NaCl solution was injected into the sub-plantar tissue of the right hind paw. The linear paw circumference was measured at hourly interval for four h two groups of drug treated rats and one control group were used each test day and the mean paw oedema value for the test group being compared with its mean value for the control group for that day.

Anti-inflammatory activity (Duffy *et al.,* 2001) was measured as the percentage reduction in oedema level when drug was present, relative to control as shown in table 3. Indomethacin (10mg/kg) was administered orally as reference drug while 10% olive oil was used as negative control.

Statistical Analysis

data were expressed as mean ±SEM; the student's t-test was applied to determine the significance of the difference between the control group and the test compounds.

4(3H)-quinazolinone(2)

Yield 87%, $^{(0.59g)}$ mp 217,IR (KBr),H-NMR (DMSO-6) :S 3.37 (S,3H,CH_3), 57.17 (ddd, H,C.), S7.51 (m,H,), δ,7.77(S,H,CH) δ,8.82 (S,H,CH) FOUND:C,67.97:14,4.21, Requires : c, 66 .12, H, 4. 13.
^{13}C.NMR (DMSO-d_6):140.12(C-l), 161.0 (161.0(C-2), 115.81(C-3), 128.66(C-4), 117.29(C.5), 134.10(C-6), 115.24 (C-7).

2-Methyl-4(3H)-quinazolinone (3)

Yield 84 %$^{(0.57g)}$ mp232^{0}C, IR (KBr), ^{1}H-NMR (DMSO-dc):3.39 (s, 3H, CH_3), δ6.51 (tt H,CH), δ7.08 (S,H,CH), δ7.7A (S,H,CH)^{13}C-NMR (DMSO-d_6):151.06(C-l)162.18(C-2),115.26(C.3),129.63(C-3),129.63(C-4),117.30(C-5),132.75(C-6),115.27(C-7),151.06(C-8),40.45(C-9).FOUND: C,68.96 H,4.77 Requires; C,67.42 H, 4.99

2-Phenyl-4(3H)-quinazolinone (4)

Yield 75% (0.51g), mp IR (KBr) IH-NMR (DMSO-d_6); S 3.40 (S, 3H, CH_3),δ 6.70(s,),$\delta\delta$7.08 (d,), δ 7.74 (s,), ^{13}C-NMR (DMSO-d_6): 151.07(C-I), 162.19(C-2), 115.28(C-3)129.64(C-4),117.30(C-5),132.76(C-6) 114.64 (C-7), 151.07 (C-8), 40.45 (C-9),130.16(C-10)127.55(C-11),130.81(C-12),
FOUND: C, 75.10 4, 4.11 Requires: C, 75.61 H, 4.50.

IV. Discussion

The Structures of the compounds were confirmed based on their elemental and spectra analyses, thus IR spectrum of the compounds. Compound 2 reveals strong absorption band at 3387, 1700,2871 and 2781,3325and 3345 attributed to Umax for NH, C=O, CH aliphatic and NH,while compound 4 reveals strong absorption band at 1699,3313, and 2331 attribution to C=0, CH aliphatic and NH.

From our results, compound 2 has a higher activity than compound 3 and compound 3 has a higher activity than compound 4. It shows that substitution of methyl and phenyl groups at position two reduces the activity. These compounds synthesized have a higher activity than indomethacin, which is a standard anti-inflammatory drug.

Carrageenan-induce paw oedema is a commonly used primary test for the screening of the news anti-inflammatory agents and is believed to be biphasic (Vinegar *et al.* 1960).The first phase (1-2hr) is due to the release of histamine or serotonin and the second phase of oedema is due to the release of prostaglandin (Britto *et al*, 1998 and Saha *et al*, 2007). The results of this study indicate that the synthesized compounds significantly reduced carrageenan induced paw oedema in rats. Therefore, the mechanism of action may be inhibition of histamine, serotonin or prostaglandin synthesis.

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