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Fusion and Anti–inflammatory Activity of 6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one from 6-bromo,2-(o-aminophenyl)-3,1-benzoxazin-4(3H)-one.

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Abstract:

Quinazolinone spin–off disclose various medicinal valuables such as analgesic, anti-inflammatory and anticancer activities, as well as antimicrobial activity. These heterocycles are beneficial intermediates in organic synthesis. Methods/Experimental: The compound, 6-bromo,2-(o-aminophenyl)-3,1-benzoxazin-4(3H)-one(1) was synthesized by dissolving 5-bromo anthranillic acid in 100 ml of pyridine. To this reaction mixture o-amino benzoyl chloride stirring at room temperature for 30 minutes this was refluxed with 75 mL of hydrazine hydrate for 3 hrs at 120-130^{0}C. the reaction mixture was allowed to cool to room temperature to give 6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one **(2).** These Compounds were appraise for their anti–inflammatory activity and the paw volume of each rat was dignified before 1 h and after 3 h of carrageenan treatment with the help of a plethysmometer. Study Design: This study was experimentally design and the synthesized compounds were masked and extimated pharmacologically for their in-vivo anti-

inflammatory activity. Compound 1 had antiinflammatory activity of 61.75% and 71.53% at 20 mg/kg and 10 mg/kg respectively, while compound 2 had anti-inflammatory activity of 69.52% and 83.55% at 20 mg/kg and 10 mg/kg respectively. Result: The result shows that compound 2 synthesized had a higher anti-inflammatory activity than indomethacin which is a standard anti-inflammatory drug. Compound 2 had a higher antiinflammatory activity than Compound 1. Conclusions: From our findings, compound 2 synthesized had a higher anti-inflammatory activity than Compound 1 and Indomethacin, a standard anti-inflammatory drug.

Keywords: Anti–inflammatory activity; Quinazolinone derivatives; 6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one; 6-bromo,2-(o-aminophenyl)-3,1-benzoxazin-4(3H)-one.

Introduction

Quinazolinones are fascinating class of heterocyclic compounds that have great importance in medicinal chemistry and reported to possess a diverse range of pharmacological activities such as antimicrobial [1–5], anti-inflammatory [6], antioxidant [7], anticonvulsant [8], antihypertensive [9], bronchodilator [10], and anticancer activities [11]. The quinazoline-4-one moiety has shown versatile pharmacodynamic action in many of its synthetic analogues as well as in many isolated derivatives of naturally occurring alkaloids [12].

Quinazolinones are one of the fused heterocyclic compounds that are of considerable interest because of diverse range of biological activities [13, 14]. This fused bicyclic compound was earlier known as benzo-1,3-diazine [15]. Imines (Schiff bases) and their reaction products are an important class of the most widely used organic compounds and have been studied over the years and reported to possess a wide range of biological activities such as anti-inflammatory [16], anticonvulsant [17], antimicrobial [18], antioxidant [19], cytotoxic [20], and antitubercular [21].

This research was aimed at synthesis and to pharmacologically investigate these compounds for their anti–inflammatory activity and to obtain more precise information about the course of reaction.

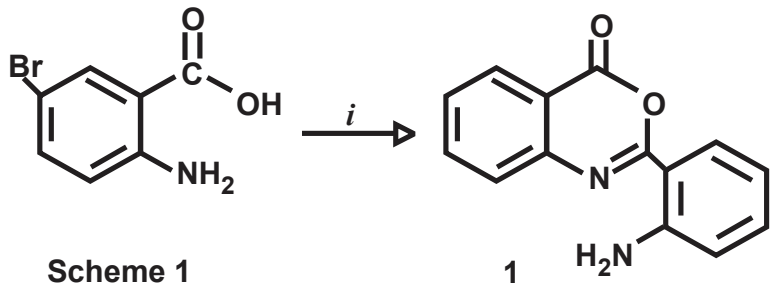
Chemistry.

The introduction of 2-amino substituent is a successful strategy to improve the chemical stability of benzoxazinone. Due to the antibacterial and 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 pricise information about the course of the reaction and some interesting pharmaceutical compounds. Dissolving 5-bromo anthranillic acid in 100 ml of pyridine in o-amino benzoyl chloride stirring at room temperature for 30 minutes produce the cyclic compound 6-bromo,2-(o-aminophenyl)-3,1-benzoxazin-4(3H)-one(1). The reaction of this compound with 75 mL of hydrazine hydrates for 3 hrs at 120-130^{0}C. the reaction mixture was allowed to cool to room temperature to give 6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one **(2).**

Materials and methods

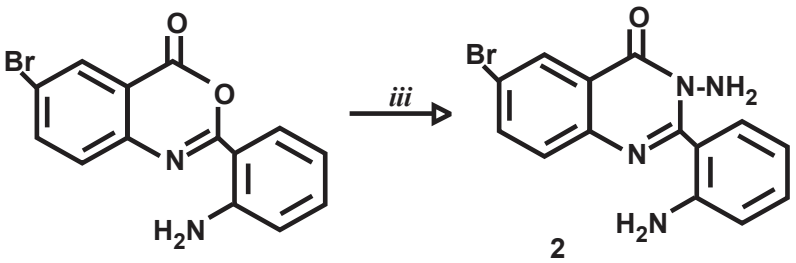
2. Experimental

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.



Scheme 1 **1**

***i* = Pyridine/ o-Aminobenzoyl Chloride**



Scheme 2

***iii* = $NH_2NH_2H_2O$ / Reflux (3 hours)**

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.

Synthesis of 6-bromo,2-(o-aminophenyl)-3,1-benzoxazin-4(3H)-one(1).

5-bromo anthranillic acid (.16M, 34.72gm) was dissolved in 100 ml of pyridine. To this reaction mixture o-amino benzoyl chloride (.16M, 24.8gm) was added with stirring at room temperature. Stirring continued for 30 mins at the same temperature. This reaction mixture was filtered out and collect the precipitate, which was washed with distilled water and Pet.ether 60/80 to remove the traces of pyridine. The pale creamish crystals obtained were dried at 60^0C. m.p.-190^0C, yield- 75%,

Synthesis of 6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one (2).

6-bromo-2-(o-aminophenyl)-3-,1-benzoxazin-4(3H)-one (0.075M, 23.775gm) was refluxed with 75 mL of hydrazine hydrate for 3 hrs at 120-130^0C. the reaction mixture was allowed to cool to room temperature. Pale creamish crystals developed were recrystallized from super dry ethanol. m.p.-178-180^0C, yield-75%,

3. 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; Adeyemiet 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.

4. Results and Discussion

Table 1: Characterization AndPhysical Data Of Synthesized Compounds

Compound No	Solvent	Formula M. wt	Analysis% Calc/Found	
			C	H
1	Ethanol	$C_{14}H_9BrN_20_2$	42.40	2.27
		(396.8)	42.50	2.28
2	Ethanol	$C_{14}H_9BrN_40$	39.50	2.11
		(424.8)	39.70	2.12

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

Compound No	δ (ppm) Carbon atom number

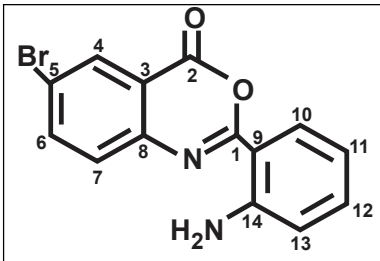
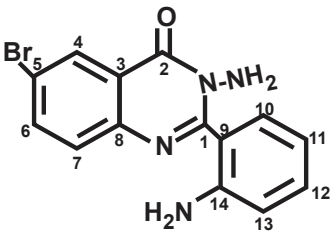
 1	157.14(C-1), 160.18(C-2), 121.13(C-3), 127.19(C-4), 112.62(C-5), 112.31(C-6), 121.11 (C-7), 145.06 (C-8), 24.02 (C-9) 112.64(C-10), 112.41(C-11), 112.22 (C-12), 116.07 (C-13), 112.14(C-14).
 2	155.32(C-1), 161.12 (C-2), 121.17(C-3), 127.33 (C-4), 112.11 (C-5), 112.12 (C-6), 122.22 (C-7), 147.14(C – 8), 24.12 (C- 9), 112.51 (C-10), 112.31 (C-11), 121.11 (C-12), 116.09(C – 13), 112.21(C – 14).

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

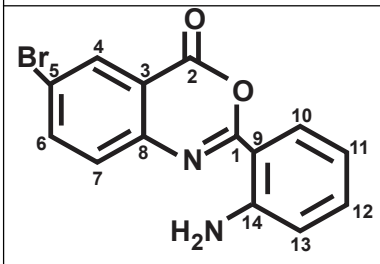
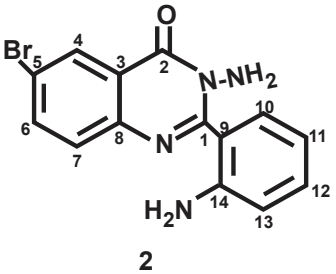
Compound No	δ (ppm)
 1	5.64 (d, 2H of –NH_2), 7.18-7.25 (dd, 1H of-ArH), 7.43-7.86 (m, 5H of –ArH), 6.71 (d, 1H of -ArH).
 2	7.72-7.80 (m, 5H of –ArH), 5.65 (s, 2H of NH_2), 6.18 (s, 2H of –NH_2).

Table4: Effect Of The Synthesized Compounds On Carrageenan Induced Paw Edema (Anti–inflammatory Activity Of The Compounds Synthesized Relative To Control)

ANTI–INFLAMMATION ACTIVITY

TABLE 1: CARRAGEENAN INDUCED PAW EDEMA

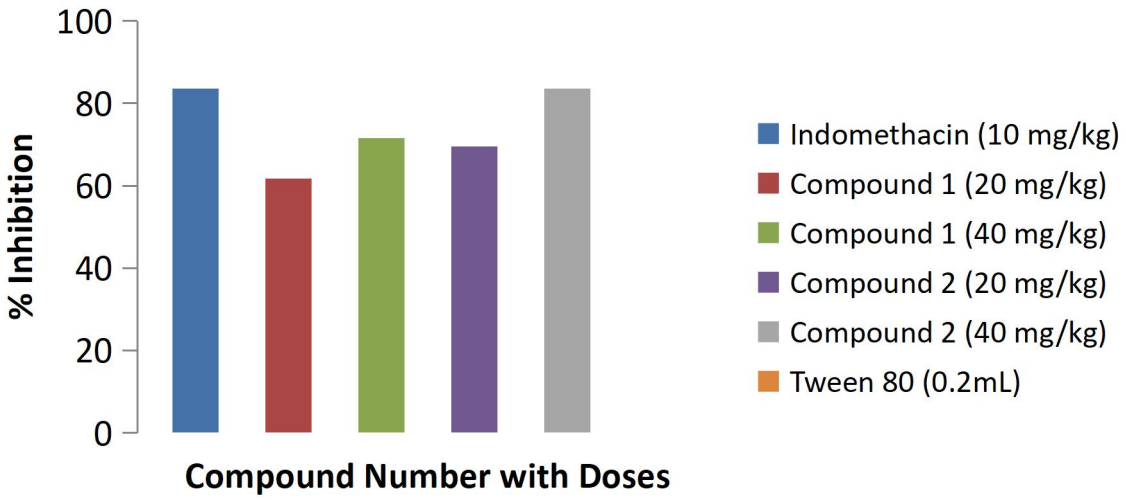


Figure 1: Percentage Inhibition of Graded Doses of Test Compound 1 and 2 against Carrageenan-Induced Paw Edema

Values are mean ± S.E.M. where number of replicates, n=4 per group, (*p<0.05, ***p<0.001).

4. Discussion

The present study reported the synthesis of two derivatives of quinazolinone, 6-bromo,2-(o-aminophenyl)-3,1-benzoxazin-4(3H)-one(1) and 6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one (2) . The compounds were investigated for their Antiinflammatory activity. 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 duplet at δ 5.64 which was due to amino, –NH_2 group. Other duplet appeared at δ 7.18 and 7.25 attributed to aromatic protons. Also, ^{1}H NMR spectrum of compound 2 showed a characteristic signal at δ 5.65 and 6.18 (singlet) corresponding to the two amino, –NH_2 groups. Two singlets appeared at δ7.41 and 7.10 attributed to aromatic protons. Another signal appeared at 5.80 which is attributed to the protons of the amino group. For the IR spectra, compound 1 were characterized by the presence of 3068 υ C-H str. of the aromatic ring, 1698 cm^{-1} υ C=O str. of the ring, 3365 cm^{-1}

3345 cm^{-1} υ N-H str. of the ring in the region of the compound. Compound 2 was characterized by presence of υ 3048 cm^{-1} υ (C-H str. of the aromatic ring), 3361 cm^{-1} , 3351 cm^{-1} υ (N-H str. of the ring), 1706 cm^{-1} υ (C=O str. of the ring), υ 1316 cm^{-1} region of the compound.

The ^{13}C NMR spectrum of compound 1, revealed signals at δ24.02, attributed to phenyl group, while the aromatic carbon atoms appeared between δ values 112.31 – 160.18 with the carbonyl carbon atom appearing as the highest δ value of 160.18. Similarly, compound 2 showed signals at δ24.12, attributed to phenyl group, 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.

These compounds synthesized exhibited promising Anti–inflammatory activities. The in-vivo anti–inflammatory activity of compounds synthesized were determined using carrageenan induced paw edema and the results obtained are summarized in *Figure* 1. Compound 1 shows at dose level 20mg/kg the % inhibition was 61.75% and at dose level of 40mg/kg, the % inhibition was 71.73%. For Compound 2, the % inhibition at dose level 20mg/kg was 69.52% and at dose level 40mg/kg, the % inhibition was 83.55%. The % inhibition for the indomrthacin drug used was 83.50%. Compound 2 showed the highest activity at 40mg.kg compared to the other compound 1, and indomethacin a standard drug. . These compounds synthesized have a higher activity than indomethacin, which is a standard anti–inflammatory drug.

5. Conclusion

The present study has showed that the quinazolinone derivatives 1 and 2 have high anti–inflammatory activity. Compound 1 has Anti–inflammatory activity of 61.75% and 71.53% at 20mg/kg and 40mg/kg dose levels, while Compound 2 has Anti–inflammatory activity of 69.52% and 83.55% at 20mg/kg and 40mg/kg dose levels. Compound 2 has a higher Anti–inflammatory activity compared to Compound 1 and Indomethacin a standard Anti–inflammatory drug. From this result, Compound 2 could be a potential Anti–inflammatory and a tool to pharmaceutical drug delivery.

Conflict of interest

The author declares no conflict of interest.

Funding

No fund was obtained during the research.

Author declaration

The author hereby declares 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 me.

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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Declaration statement

The author declares there is no conflict of interest.

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