Conglomerate and Analgesic 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.

Osarumwense Peter Osarodion¹,*

¹Department of Chemical Science, Ondo State University of Science and Technology, Okitipupa, Ondo State, Nigeria.

*Corresponding Author:
Email: Osarodion.peter@yahoo.com, po.osarumwense@oaustech.edu.ng
Tel: 08056350793

Abstract:

Introduction: Quinazolinone by–product disclosed various curative characteristics 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 integrated by dissolving 5-bromo anthranillic acid in 100 ml of pyridine. To this reaction mixture o-amino benzyol chloride stirring at room temperature for 30 minutes this was refluxed with 75 mL of hydrazine hydrate for 3 hrs at 120-130°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 evaluated for their analgesic activity using Acetic acid induced model. Study Design: This study was experimentally design and the analgesic activity was evaluated.
using Acetic acid induced model. **Result:** The compounds synthesized were evaluated pharmacologically for their in-vivo analgesic activities by acetic acid induced writhing in mice. The two scrutinized compounds exhibited significant analgesic activity in the range of 61.33 - 83.18% in comparison to control. **Conclusions:** From our findings, compound 2 synthesized have higher analgesic activities as compared to indomethacin a standard analgesic drug.

**Keywords** Analgesic activity; Coglomerate; 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**

Different types of Quinazolinones disclose a capacious spectrum of organic activeness including anticancer[1], antimicrobial[2,5], anticonvulsant[3], antitubercular[4], anti-inflammatory[6], analgesic[6], estrogenic7 and antiparkinsonism[8]. The chemistry of heterocyclic composites has been a fascinating field of study for interminability. The conglomerate of novel oxadiazole derivatives and investigation of their chemical and biotic behavior have gained more importance in contemporary decades for biotic, medicinal and agricultural reasons. 1,3,4-Oxadiazoles represent a crucial class of heterocyclic compounds. Their derivatives possess a comprehensive spectrum of biotic activity in both agrochemicals and pharmaceuticals such as insecticidal, herbicidal, antibacterial, antifungal, analgesic, anti-inflammatory, antimalarial, antiviral, anti-HBV, antianxiety, anticancer, anti-HIV, antitubercular and anticonvulsant [9–24].

Quinazolinone nucleus has been getting distinction due to the fact that its derivatives have been found to own wide spectrum of pharmacological properties. Quinazolin-4(3H)-one outgrowth are advantageous heterocycles, possessing potent pharmacognosy activities such as antibacterial, antifungal, analgesic, anti-inflammatory, anthelminthic, anticancer, anticonvulsant, antihistaminic, anti-HIV, antiproliferative, antitubercular, antiviral, CNS depressant, cytotoxicity, diuretic and hypolipidemic [25–40].

This investigation was aimed at synthesis and survey of these compounds for their analgesic activity and to acquire more precise information about the course of reaction.
Chemistry.

The presentation of 2-amino substituent is a successful master plan to improve the chemical solidity of benzoxazinone. Due to the microbicidal and pharmacological activities of 4(3H)-quinazolinone derivatives, 2,3-disubstituted derivative of quinazoline-4-one were conglomerated via the interaction of the benzoxazinone derivative with nitrogen nucleophile with the aim of obtaining more accurate information about the course of the reaction and some captivating 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-benzoxin-4(3H)-one(1). The reaction of this compound with 75 mL of hydrazine hydrates for 3 hrs at 120-130°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

Experimental

All testing agents and cleaners were acquired from sigma-Aldrich, in Germany. Melting points were resolved 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 MHz 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 concord favourably with the calculated values. Analytical thin layer chromatography (TLC) was used to praepostor the reactions.

![Scheme 1](image-url)
Scheme 2

\[ iii = \text{NH}_2\text{NH}_2\text{H}_2\text{O} / \text{Refux (3 hours)} \]

**Elemental Analysis**

Summary of the structure of the compounds is shown 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 anthranilic 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°C. m.p.-190°C, 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°C. the reaction mixture was allowed to cool to room temperature. Pale creamish crystals developed were recrystallized from super dry ethanol. m.p.-178-180°C, yield-75%,

**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 orchestrated orally by gavage in 10% olive oil suspensions at different dose levels). Ethical approval was procued from the Animal Use and Ethics committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria.
Results and Discussion

Table 1: Characterization And Physical Data Of Synthesized Compounds

<table>
<thead>
<tr>
<th>Compound No</th>
<th>Solvent</th>
<th>Formula</th>
<th>M. wt</th>
<th>Analysis% Calc/Found</th>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethanol</td>
<td>C_{14}H_{9}BrN_{2}O_{2}</td>
<td>(396.8)</td>
<td>42.40</td>
<td>42.50</td>
<td>2.27</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>C_{14}H_{9}BrN_{4}O_{0}</td>
<td>(424.8)</td>
<td>39.50</td>
<td>39.70</td>
<td>2.11</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Compound No</th>
<th>δ (ppm) Carbon atom number</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>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).</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>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).</td>
</tr>
</tbody>
</table>
Table 3: $^1$H-NMR Of Synthesized Compounds

<table>
<thead>
<tr>
<th>Compound No</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image 1" /></td>
<td>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).</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image 2" /></td>
<td>7.72-7.80 (m, 5H of –ArH), 5.65 (s, 2H of NH$_2$), 6.18 (s, 2H of –NH$_2$).</td>
</tr>
</tbody>
</table>

**FIGURE 1**: Analgesic Activity of Compound 1 and 2 Against Acetic Acid-Induced Writhing in mice.

**Figure 1**: Effects of Test Compounds 1 and 2 on Acetic Acid-Induced Writhing in Mice.
Figure 1: Compound 1 Acetic acid induce writhing in mice Values are mean ± S.E.M. where number of replicates, n=4 per group, ASP= Aspirin. (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001)

FIGURE 2: Analgesic Activity of Compound 2 Against Acetic Acid-Induced Writhing in mice.

Figure 1: Compound 1 and 2 Acetic acid induce writhing in mice Values are mean ± S.E.M. where number of replicates, n=4 per group, ASP= Aspirin. (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001)

Discussion

The present investigation reported the conglomerate of two outgrowth of quinazolinones, 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 examined for their Analgesic activity. 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 duplet at δ 5.64 which was due to amino, –NH2 group. Other duplet appeared at δ 7.18 and 7.25 attributed to aromatic protons. Also, 1H NMR spectrum of compound 2 showed a characteristic signal at δ 5.65 and 6.18 (singlet) corresponding to the two amino, –NH2 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 ν C-H str. of the aromatic ring, 1698 cm⁻¹ ν C=O str. of the ring, 3365 cm⁻¹ 3345 cm⁻¹ ν N-H str. of the ring in the region of the compound. Compound 2 was characterized by presence of ν 3048 cm⁻¹ ν (C-H str. of the aromatic ring), 3361 cm⁻¹ , 3351 cm⁻¹ ν (N-H str. of the ring), 1706 cm⁻¹ ν (C=O str. of the ring), ν 1316 cm⁻¹ region of the compound.

The 13C 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 Analgesic activities. The in-vivo analgesic activity of compounds synthesized were determined using carrageenan induced paw edema and the results obtained are summarized in *Figure 1*. Compound 1 has Analgesic activity of 61.33% and 83.18% at 20mg/kg and 40mg/kg dose levels, while Compound 2 has Analgesic activity of 69.49% and 83.18% at 20mg/kg and 40mg/kg dose levels. Compound 2 showed the highest activity at 40mg/kg compared to the other compound 1, and indomethacin a standard Analgesic drug. These compounds synthesized have a higher activity than indomethacin, which is a standard analgesic drug.

**Conclusion**

The present investigation has showed that the quinazolinone derivatives 1 and 2 have high analgesic activity. Compound 1 has Analgesic activity of 61.33% and 71.14% at 20mg/kg and 40mg/kg dose levels, while Compound 2 has Analgesic activity of 69.49% and 83.18% at 20mg/kg and 40mg/kg dose levels. Compound 2 has a higher Analgesic activity compared to Compound 1 and Indomethacin a standard Analgesic drug. From this result, Compound 2 could be a potential Analgesic and a tool to pharmaceutical drug delivery.

**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 him.

**Ethics approval and consent to participate**

Ethic approval, permission 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.

**Acknowledgements**

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


El-Essawy FA, Khattab AF, Abdel-Rahman AAH. Synthesis of 1,2,4-triazol-3-ylmethyl-, 1,3,4-oxa-, and -thiadiazol-2-ylmethyl-1H-[1,2,3]-triazolo[4,5-d]pyrimidininediones. Monatsh Chem. 2007;138:777–785. doi:10.1007/s00706-007-0649-7.


