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Synthesis And Antibacterial 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 derivatives reveal various medicinal properties such as analgesic, anti-inflammatory and anticancer activities, as well as antimicrobial activity. These heterocycles are valuable 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 120-1300C. 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 bacterialrial activity (against some gram positive and gram- negative microorganism) and antifungal activity (against Candida albicans). Study Design: This study was experimentally design and the antibacterial activity was evaluated against some microorganism, Staphylococcus aureus, Bacillus species, Aspergillus Species, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumonia, and candida albicans Result: The compounds exhibited significant antibacterial activity with a zone of inhibition in the range of 10 – 16mm in comparison to control. Conclusions: From our findings, the compounds synthesized have higher antibacterial activities as compared to Ciprofloxicin (CPX) and Ketonaxol (PEF) standard antibacterial drugs.

Keywords: *Antibacterial 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

Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer [1–4], anti-inflammation [5, 6], anti-bacterial [7–10], analgesia [5, 9], anti-virus [11], anti-cytotoxin [12], anti-spasm [9, 13], anti-tuberculosis [14], anti-oxidation [15], anti-malarial [16], anti-hypertension [17], anti-obesity [18], anti-psychotic [19], anti-diabetes [20], etc.

Quinazolinone derivatives have been attracting growing attention from medicinal and agricultural chemists, owing to their diverse biological activities, such as antibacterial [21–27], antifungal [28–30], antiviral [31,32], antitumor [33,34] and anticonvulsant [35] activities.

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. Among a wide variety of nitrogen heterocycles that have been explored for developing role in medicinal chemistry and subsequently have emerged as a pharmacophore [36].

This research was aimed at synthesis of 6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one and 6-bromo,2-(o-aminophenyl)-3,1-benzoxazin-4(3H)-one and investigating them for their antibacterial activity and to obtain more precise information about the course of reaction.

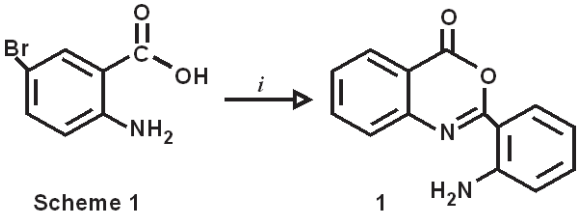
Chemistry

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 120-1300C. 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

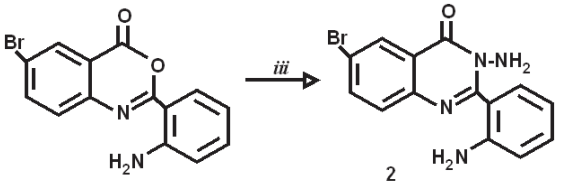
All reagents and solvents were purchased from sigma-Aldrich, in Germany. Melting points were determined on a kofler hot stage apparatus and were uncorrected. IR spectra were recorded on a Buck scientific IR M500 instrument. The 1H and 13C NMR spectra were recorded in DMSO-*d*6 at 400 MHz with HAZ VOLATILE 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 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

1



Scheme 2 2

iii = $NH_2NH_2H_2O$ / Reflux (3 hours)

2

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 600C. m.p.-1900C, 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 120-1300C. the reaction mixture was allowed to cool to room temperature. Pale creamish crystals developed were recrystallized from super dry ethanol. m.p.-178-1800C, yield-75%,

Antimicrobial activities

Determination of zone of inhibition

The microbial growth inhibitory activities of the powdered crude drug obtained were determined by the agar well plate method where the compounds were initially dissolved in distilled water (1:1). Those compounds with activities were later tested at concentrations of 10, 15, 20, 60 mg/mL against clinical isolated *Staphylococcus aureus, Bacillus species, Escherichia coli, Aspergillus Species*, *Klebsiella pneumonia, Pseudomonas aeuriginosa and Candida albicans* using the standard microbiological method. Sterile nutrient and Sabouraud dextrose agar plates were prepared for bacteria and fungi respectively and standardized inoculum of test organisms was spread uniformly.

We used a sterile borer (8 mm) and 100µL of the test concentrations, to bored six wells, standard antibiotic, and the solvent control were added to each well. The plates were left on the table for 1 h for the test solution to diffuse into the medium and then incubated at 37°C for 18-24 h. The resultant zone of inhibitions of microbial growth around the well was measured in mm. The test was performed in triplicate. Standard antibiotics ciprofloxacin (30 mg/mL), and Ketonaxol (50 mg/mL) were tested against bacteria and fungi respectively as the positive control [37].

Determination of MIC

The minimum inhibitory concentration (MIC) values of the powdered crude drug obtained were determined using the agar dilution method. Four different concentrations range of 100 µL of the synthesized compounds were incorporated into their respective molten agar and allowed to set. This was also repeated for ciprofloxacin and itraconazole as positive control and the diluent as a negative control. Each of the standardized test microorganisms was radially streaked onto the prepared plates. The plate was left to stand for 1 h at room temperature, incubated at 37°C for 18-24 h. The MIC was recorded as the lowest concentrations that inhibited the growth of each of the test organisms [37].

Results and Discussion

Table 1: Characterization and Physical Data of Synthesized Compounds

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

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

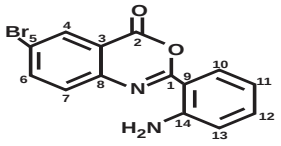
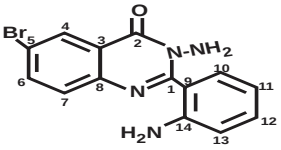
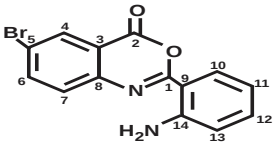
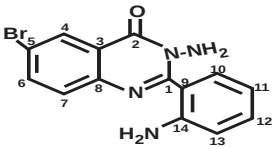
Compound No	δ (ppm) Carbon atom number
 1	157.14(C-1), 160.18(C-2), 121.13(C-3), 127.19(C-4), 112.62(C-5), 112.31(C-6), 121.11 (C-7), 145.06 (C-8), 24.02 (C-9) 112.64(C-10), 112.41(C-11), 112.22 (C-12), 116.07 (C-13), 112.14(C-14).
 2	155.32(C-1), 161.12 (C-2), 121.17(C-3), 127.33 (C-4), 112.11 (C-5), 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).

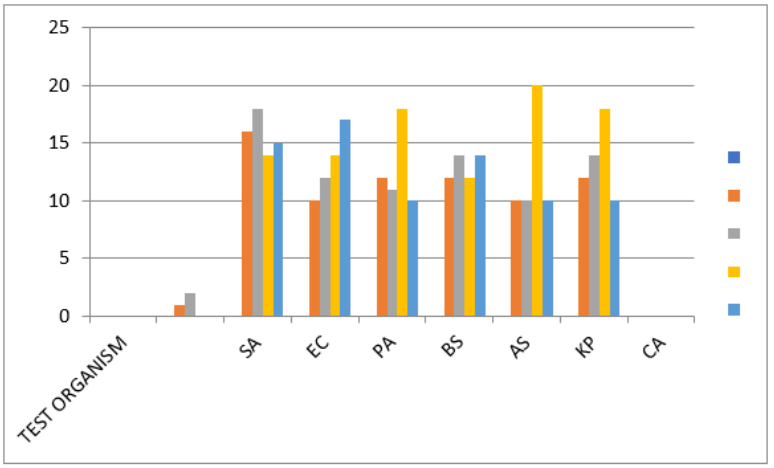


Figure 1: The effect of the Synthesized Compounds and Standard drugs toward studied bacteria. SA = *Staphylococcus aureus, BS* = *Bacillus species*, AS = *Aspergillus Species*, PA = *Pseudomonas aeruginosa*, EC = *Escherichia coli,* KP=*Klebsiella pneumonia*, and CA=*candida albicans*.
Control drugs- Ciprofloxicin (CPX) for bacteria, Ketonaxol (PEF) for fungus, Compound 1 (1), Compound 2 (2)
Significantly different from Ligand at P< 0>

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 Antibacterial 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 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 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 Antibacterial activities. The antibacterial activity of compounds synthesized were determined using the agar well plate method and the results obtained are summarized in Figure 1. Compound 2 showed the highest activity against *Staphylococcus aureus, Bacillus species*, *Escherichia coli, Klebsiella pneumonia* compared to the other compound 1. It may be that the substitution of amino group at position three increases the activity. These compounds synthesized have a higher activity against *Staphylococcus aureus,* than **Ciprofloxacin (CPX) and Ketonaxol (PEF)**, which are standard antibacterial drugs.

Conclusion

The present study has showed that the quinazolinone derivatives 1 and 2 have high antibacterial activity. Compound 2 showed the highest activity against *Staphylococcus aureus, Bacillus species*, *Escherichia coli, Klebsiella pneumonia* compared to the other compound 1. It may be that the substitution of amino group at position three increases the activity. These compounds synthesized have a higher activity against *Staphylococcus aureus,* than **Ciprofloxacin (CPX) and Ketonaxol (PEF)**, which are standard antibacterial drugs. This study has confirmed that the antibacterial analysis shows that the compounds synthesized have high activity against *Staphylococcus aureus, Bacillus species*, *Aspergillus Species*, *Pseudomonas*

aeruginosa, *Escherichia coli,* and *Klebsiella pneumonia*, with no activity against *Candida albicans*. From this result, Compound 2 could be a potential Antibacterial and a tool to pharmaceutical drug delivery.

Declarations

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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