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Synthesis and Antibacterial Activity of 2-[o-imino-(4-thiazolidinone)-phenyl]-3-imino-(4-thiazolidinone)- 6-bromo Quinazolin-4(3H)-one from 2-(o-thiadiaminephenyl)-3-thiadiamine-6-bromo–quinazoline-4(3H)-one

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Abstract: Introduction: Broad range of quinazolinone biological properties including: antibacterial, anticancer, and anti-inflammatory activities motivate us to synthesis some quinazolinone derivatives. These heterocycles are profitable intermediates in organic synthesis. Methods/Experimental: The compound 2-(o-thiadiaminephenyl)-3-thiadiamine-6-bromo–quinazoline-4(3H)-one (1), was produce when 2-(o-aminophenyl)-3-amino-6-bromo–Quinazolin-4(3H)-one (0.055M) was dissolved in minimum amount of dil. HCl in a round bottom flask. Ammonium thiocyanate (0.11M, 9.68gm) was then added and the mixture refluxed for 7 hrs. A mixture of 2-(o-thiadiaminephenyl)-3-thiadiamine-6-bromo–Quinazolin-4(3H)-one (0.037M, 16.095gm) and fused sodium acetate (0.074M, 6.068gm) was taken in absolute alcohol (300ml) and refluxed for 10 hours to give 6-bromo-2-[o-imino-(4-thiazolidinone)-phenyl]-3-imino-(4-thiazolidinone)-Quinazolin-4(3H)-one(2). These Compounds were evaluated for their antibacterial 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 – 20mm in comparison to control. Conclusions: From our findings, the compounds synthesized have higher antibacterial activities against *Staphylococcus aureus, Aspergillus Species*, as compared to Ciprofloxicin (CPX) and Ketonaxol (PEF) standard antibacterial drugs.

Keywords: Antibacterial Activity, Quinazolinone Derivatives,
2-[o-imino-(4-thiazolidinone)-phenyl]-3-imino-(4-thiazolidinone)- 6-bromo–Quinazolin-4(3H)-one,
2-(o-thiadiaminephenyl)-3-thiadiamine-6-bromo–quinazoline-4(3H)-one

1. Introduction

Quinazoline subordinates, which are associated to the N-containing chemical compounds, have caused all–embracing concerns due to their extensively and definite biopharmaceutical activities. Investigators have already determined many therapeutic activities of quinazoline by products, 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.

Quinazolines and quinazolinones are a fortunate class of nitrogen heterocyclic scaffolds that have been found to exhibit a wide spectrum of pharmacokinetics activities, including anti-inflammatory, antitubercular, and antiviral activities [21] [22]. A number of quinazoline-root drugs such as prazocin and doxazosine have been approved to treat

benign prostatic hyperplasia and post-traumatic stress disorder [23] [24], while both erlotinib and gefitinib have been used for the cure of lung and kidney cancers [25].

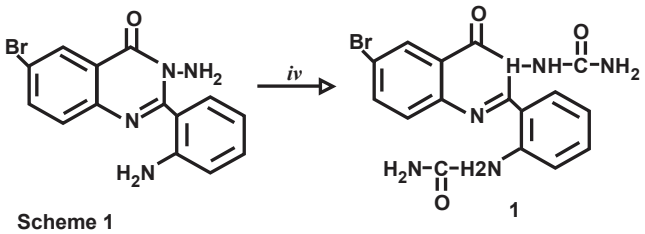
This examination was focus at synthesis of 2-[o-imino-(4-thiazolidinone)-phenyl]-3-imino-(4-thiazolidinone)-6-bromo–Quinazolin-4(3H)-one; 2-(o-thiadiaminephenyl)-3-thiadiamine-6-bromo–quinazoline-4(3H)-one and investigating them for their antibacterial activity and to obtain more precise information 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 120-130°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).

2. Materials and Methods

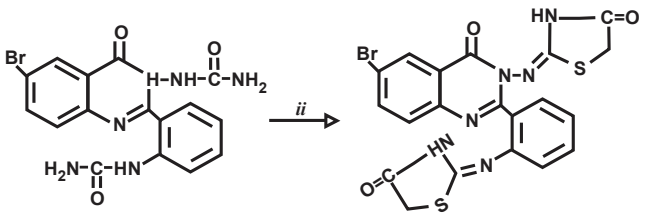
2.1. Reagents



Scheme 1

iv = NH_4SCN / Reflux (7 hours)

Figure 1. *Synthesis of 2-(o-thiadiaminephenyl)-3-thiadiamine-6–bromo–quinazoline-4(3H)-one(1).*



Scheme 2

ii = $ClCH_2COOH$ / CH_3COONa

Reflux (10 hours)

Figure 2. *Synthesis of 2-[o-imino-(4-thiazolidinone)-phenyl]-3-imino-(4-thiazolidinone)-6–bromo–Quinazolin-4(3H)-one (2).*

All reagents and solvents were procured from sigma-Aldrich, in Germany. Melting points were resolved on a kofler hot stage apparatus and were uncorrected. IR spectra were documented 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.

2.2. 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 2-(o-thiadiaminephenyl)-3-thiadiamine-6–bromo–quinazoline-4(3H)-one(1).

6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one (0.055M,) was dissolved in minimum amount of dil. HCl in a round bottom flask. Ammonium thiocyanate (0.11M, 9.68gm) was then added and the mixture refluxed for 7 hrs. After cooling the product separated out as crystals which were separated and washed with cold distilled water for several times and dried. Recrystallized effected with rectified spirit. m.p.-161-165°C, yield- 90%.

Synthesis of 2-[o-imino-(4-thiazolidinone)-phenyl]-3-imino-(4-thiazolidinone)-6–bromo–Quinazolin-4(3H)-one (2).

A mixture of 6-bromo-2-(o-thiadiaminephenyl)-3-thiadiamine-Quinazolin-4(3H)-one (0.037M, 16.095gm) and fused sodium acetate (0.074M, 6.068gm) was taken in absolute alcohol (300ml) and refluxed for 10 hrs. The bulk of the solvent was reduced to about one third by distilling off the solvent under reduced pressure. Ice cold water was then added to the content. The precipitate so obtained was filtered and washed with distilled water. Rectified spirit was used for recrystallization. m.p.- 202-208°C, yield-85%.

2.3. 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 [26].

2.4. 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 [27].

3. Results

Figure 3. Antibacterial Activity of Control Drugs and Tested Synthesized Compounds Against Tested Standard Organism.

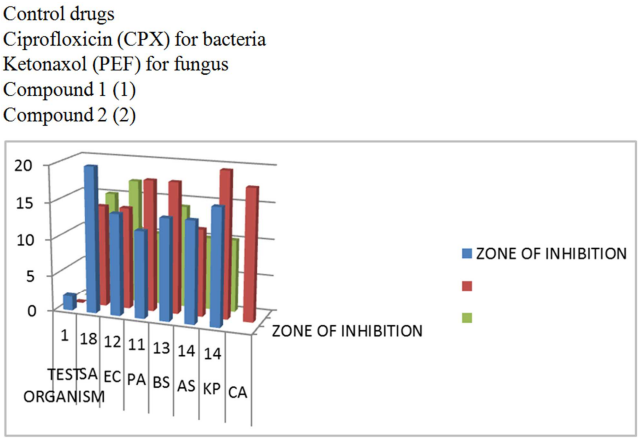


Figure 3. *The effect of the Synthesized Compounds and Standard drugs toward studied bacteria. SA = Staphylococcus aureus, BS = Bacillus species, AS = Aspergillus Species, PA = Pseudomonas aeruginosa, EC = Escherichia coli, KP=Klebsiella pneumonia, and CA=candida albicans.*

Significantly different from Ligand at P< 0.05, values are in mm.

Table 1. *Characterization And Physical Data Of Synthesized Compounds.*

Compound No	Solvent	Formula M. wt	Analysis% Calc/Found	
			C	H
1	Ethanol	$C_{16}H_{15}BrN_6O_3$ (496.8)	38.63 38.65	2.62 2.63
2	Ethanol	$C_{19}H_{11}BrN_6O_3$ (530.7)	42.94 42.95	2.07 2.08

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

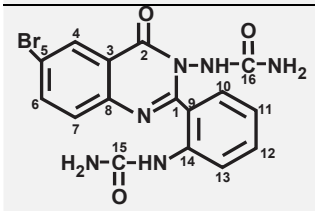
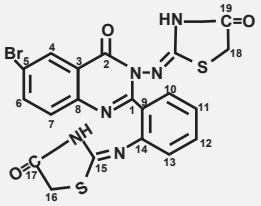
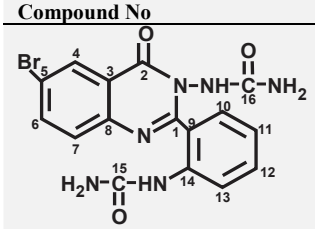
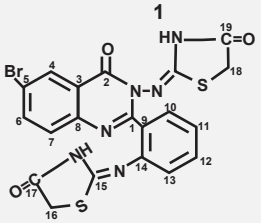
Compound No	δ (ppm) Carbon atom number
 1	157.14(C-1), 160.18(C-2), 121.13(C-3), 127.19(C-4), 112.62(C-5), 112.31(C-6), 121.11 (C-7), 145.06 (C-8), 24.02 (C-9) 112.64(C-10), 112.41(C-11), 112.22 (C-12), 116.07 (C-13), 112.14(C-14), 160.12(C-15), 160.13(C-16).
 2	155.32(C-1), 161.12 (C-2), 121.17(C-3), 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). 161.10 (C-15), 112.13 (C-16), 161.11 (C-17), 112.12 (C-18), 161.13 (C-17)

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

Compound No	δ (ppm)
 1	8.35 (d, 1H of –ArH), 7.65-7.80 (dd, 2H of –ArH), 7.39-7.79 (m, 5H of –ArH), 2.21 (s, 1H of –NH), 12.45(s, 1H of –NH), 9.53 (s, 2H of NH_2).
 2	11.78 (s, 1H of –NH), 5.42 (s, 2H of -NH), 3.75 (s, 2H of –CH_2), 7.36-7.80 (m, 5H of –ArH), 8.08-8.18 (d, 2H of –ArH).

Characterization Of 2-(o-aminophenyl)-6–bromo–3,1-benzoxazin-4(3H)-one(1).

Rf- 0.62. IR (cm^{-1}): 3077 υ (C-H str. of the aromatic ring), 1562 υ (C=S str. of the ring), 3363, 3353 υ (N-H str. of the ring), 1698 υ (C=O str. of the ring), 1319 υ (C-N str. of the ring). ^{1}H NMR: 8.35 (d, 1H of –ArH), 7.65-7.80 (dd, 2H of –ArH), 7.39-7.79 (m, 5H of –ArH), 2.21 (s, 1H of –NH), 12.45(s, 1H of –NH), 9.53 (s, 2H of NH_2). ^{13}CNMR (400MHz, DMSO) δ 157.14, 160.18, 121.13, 127.19, 112.62, 112.31, 121.11, 145.06, 24.02, 112.64, 112.41, 112.22, 116.07, 112.14, 160.12, 160.13. m.p.-161-165°C, yield- 92%.

Characterization Of 2-(o-aminophenyl)-6–bromo–3-amino-Quinazolin-4(3H)-one (2).

Rf = 0.69, IR (cm^{-1}): 1506 υ (C=N str. of the ring), 679 υ (C-S-C str. of the ring). ^{1}H NMR: 11.78 (s, 1H of –NH), 5.42 (s, 2H of -NH), 5.42 (s, 2H of –NH), 7.36-7.80 (m, 5H of –ArH), 8.08-8.18 (d, 2H of –ArH). ^{13}CNMR (400MHz, DMSO) δ 155.32, 161.12, 121.17, 127.33, 112.11, 112.12, 122.22, 147.14, 24.12, 112.51, 112.31, 121.11, 116.09, 112.21. 161.10, 112.13, 161.11, 112.12, 161.13. m.p.- 202-208°C, yield-89%.

4. Discussion

The present study reported the synthesis of two derivatives of quinazolinone, 2-(o-aminophenyl)- 6-bromo–3,1-benzoxazin-4(3H)-one(1) and 2-(o-aminophenyl)-3-amino-6-bromo–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 ^{1}H NMR spectra of the compounds synthesized, compound 1 displayed a singlet at δ 2.21, 12.45, and 9.53 which was due to amino, $-NH_2$ group. Duplet appeared between δ 7.65-7.80, 7.39-7.79 and at 8.35 attributed to aromatic protons. Also, ^{1}H NMR spectrum of compound 2 showed a characteristic signal at δ 11.78 and 5.42 (singlet) corresponding to the two amino, $-NH_2$ groups. Two duplets appeared between δ 8.08 - 8.18 and a multiplets appeared between 7.36-7.80 attributed to aromatic protons. For the IR spectra, compound 1 were characterized by the presence of 3077 υ C-H str. of the aromatic ring, 1698 cm^{-1} υ C=O str. of the ring, 3363 cm^{-1} 3353 cm^{-1} υ N-H str. of the ring in the region of the compound. Compound 2 was characterized by presence of υ 679 cm^{-1} υ (C-S-C str. of the ring, 1506 cm^{-1} υ (N-H str. of the ring) region of the compound.

The ^{13}C NMR spectrum of compound 1, revealed signals at δ 24.02, attributed to phenyl group, while the aromatic carbon atoms appeared between δ values 112.14 – 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 112.11 - 161.12, with the carbonyl carbon atom appearing as the highest δ value of 161.12.

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 specie*s, *Escherichia coli, Pseudomonas Aeuriginosa, 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,* and *Aspergillus Species* than Ciprofloxacin (CPX) and Ketonaxol (PEF), which are standard antibacterial drugs.

5. 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 specie*s, *Escherichia coli, Pseudomonas Aeuriginosa, 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,* and *Aspergillus Species* 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 specie*s, *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.

Conflict of Interest

The author declares no conflict of interest.

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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