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Research Article

Fusion and Bacterialcidal Activity of 7-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one from 7-bromo,2-(o-aminophenyl)-1,3-benzoxazin-4(3H)-one

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Keywords: *Antibacterial Activity, Quinazolinone, 7-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one, 7-bromo-2-(o-aminophenyl)-1,3-benzoxazin-4(3H)-one, Nucleophile, Quinazoline-4(3H)-one.*

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Abstract

Background: Different types of Quinazolinones exhibit a wide spectrum of biological activities including anticancer, antimicrobial, anticonvulsant, antitubercular, anti-inflammatory, anlagesic, estrogenic and antiparkinsonism . Along 5-membered heterocycles thiazolidinone are found to be significant in their anticonvulsant and antimicrobial. Based on these findings the planned to synthesize the title compounds presuming that these chemical entities with thiazolidinone moiety in conjunction with Quinazolinone through imino bridge.
Methods: The compound 2-(o-thiadiaminephenyl)-3-thiadiamine-7-bromo– quinazoline-4(3H)-one (1), was produce when 2-(o-aminophenyl)-3-amino-6-bromo–Quinazolin-4(3H)-one (0.055 M) was dissolved in minimum amount of dil. HCl in a round bottom flask. Ammonium thiocyanate (0.11 M, 9.68 gm) was then added and the mixture refluxed for 7 hrs. A mixture of 2-(o-thiadiaminephenyl)-3-thiadiamine-7-bromo–Quinazolin-4(3H)-one (0.037 M, 16.095 gm) and fused sodium acetate (0.074 M, 6.068 gm) was taken in absolute alcohol (300 ml) and refluxed for 10 hours to give 7-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 – 20 mm 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.

1. Introduction

Antimicrobial drugs, including antibiotics, antivirals, and antimalarials, have been cornerstone innovations in modern medicine, dramatically improving public health outcomes. However, the rise of antimicrobial resistance (AMR) has emerged as a major global health crisis, threatening the continued effectiveness of these essential treatments. In 2019 alone, AMR was directly responsible for 1.27 million deaths

and contributed to nearly 5 million deaths worldwide, placing significant pressure on healthcare systems and economies [1]. Among AMR, bacterial pathogens, which affect a wide array of hosts from humans to plants, cause substantial morbidity, mortality, and economic losses, especially in healthcare and agriculture [2]. The excessive and improper use of antibiotics has led to the rapid development of resistant bacterial strains, reducing the effectiveness of existing treatments and underscoring the urgent need for innovative antibacterial agents [1]. Developing new drugs with unique chemical structures and mechanisms of action is essential to counteract resistance. One promising approach is to create small-molecule compounds that focus on processes unique to bacteria, like DNA topoisomerases, which are important for how bacteria copy and fix their DNA but are not found in human cells [3]. This approach offers the potential for selective, effective .treatments against resistant pathogens, addressing the growing problem of antibiotic resistance. Quinazoline derivatives, a key group of nitrogen-based compounds, have become very important in medicinal chemistry because they have many useful effects on health. These compounds are of particular interest for their broad spectrum of biological activities, which encompass antimicrobial [4], anticancer [5], antiviral [6], antiinflammatory [7], antihypertensive [8], anticonvulsant [9], antioxidant [10], anti-HIV [11], and antimalarial [12]. The quinazoline scaffold has garnered attention as a "privileged structure" in drug design, owing to its ability to interact with a variety of biological targets, including enzymes, receptors, and kinases. In the context of antimicrobial therapy, quinazoline derivatives have proven their ability to inhibit key bacterial enzymes, such as DNA gyrase and topoisomerases, placing them as potential candidates for novel antibacterial agents, especially in the face of rising antimicrobial resistance. Moreover, quinazoline-based compounds are also recognized for their minimal side effects and excellent pharmacokinetic profiles, making them highly attractive for further development. With a growing body of evidence supporting their efficacy, quinazoline derivatives are poised to play a critical role in the next generation of antimicrobial agents, as well as in the treatment of various other diseases, underscoring their importance in the ongoing quest for innovative therapeutic solutions [13].

The piperazine moiety, a six-membered nitrogen-containing heterocyclic compound, has become a highly valued structural motif in drug discovery due to its unique physicochemical properties. Piperazine has two nitrogen atoms that face each other, which provides important benefits like a large polar surface area, a strong structure, and the ability to accept and donate hydrogen bonds. These features improve how well the drug binds to its target, how specific it is, and how well it dissolves in water, while also making it easier for the body to absorb and use, which is important for creating effective medicines. Over the years, piperazine and its substituted derivatives have been incorporated into a wide range of marketed pharmaceuticals, demonstrating their versatility across various therapeutic areas, including antibiotics [14] anticancer agents [14], antimicrobials [15], antipsychotics [16], antiviral agents [17], antiinflammatory [18], antimycobacterial [19], antiparasitic [20], anticonvulsant [21], antituberculosis effects [22], as well as acetylcholinesterase inhibition [23] and more. With a growing body of evidence supporting their efficacy, quinazoline derivatives are poised to play a critical role in the next generation of antimicrobial agents, as well as in the treatment of various other diseases, underscoring their importance in the ongoing quest for innovative therapeutic solutions [24]. Piperazine helps connect different active parts of drugs, like quinazoline or phosphonamidate, which leads to the creation of new molecules that work better against bacteria. This wide range of biological effects highlights the great potential of piperazine-based compounds in finding new drugs, making them an important part of creating new treatments that work against a variety of infections, especially those caused by resistant germs [25].

Quinazolinone peptides were reported for their anti-inflammatory, antioxidant, anthelminthic, antibacterial and antifugal activities [23].

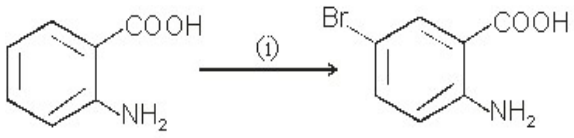
Chemistry

The introduction of 2-amino substituent is a successful strategy to improve the chemical stability of benzoxazinone. Due to the 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. The reaction of 4, 5-disubstituted derivatives of methylanthranilate and acetic anhydride yielded the cyclic compound 6-bromo,2-(o-aminophenyl)-3,1-benzoxazin-4(3H)-one. The reaction of this compound with hydrazine hydrate yielded 6-bromo-2-(o-aminophenyl)-3-amino-Quinazolin-4(3H)-one.

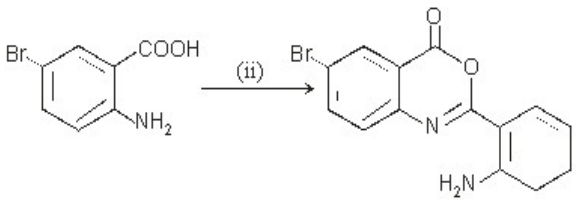
2. Materials

2.1. Experimental

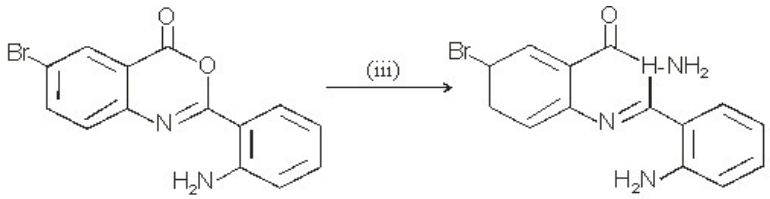
All reagents and solvents were purchased from sigma-Aldrich, in Germany. Melting points were determined on a kofler hot stage apparatus and were uncorrected. IR spectra were recorded on a Buck scientific IR M500 instrument. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO – d_6 at 400 MHz with HAZ VOLATILE V2. M Chemical shifts Sare reported in ppm relative to tetramethylsilane. Gas chromatography mass spectra were obtained on a Finingan MAT 44 S mass spectrophotometer operating at 70 eV. Elemental analysis agreed favourably with the calculated values. Analytical thin layer chromatography (TLC) was used to monitor the reactions.



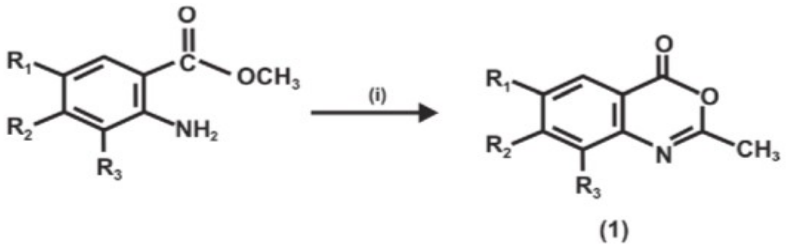
Scheme 1: CH_3COOH/Br)



Scheme 2: Pyridine/o-aminobenzybylchloride

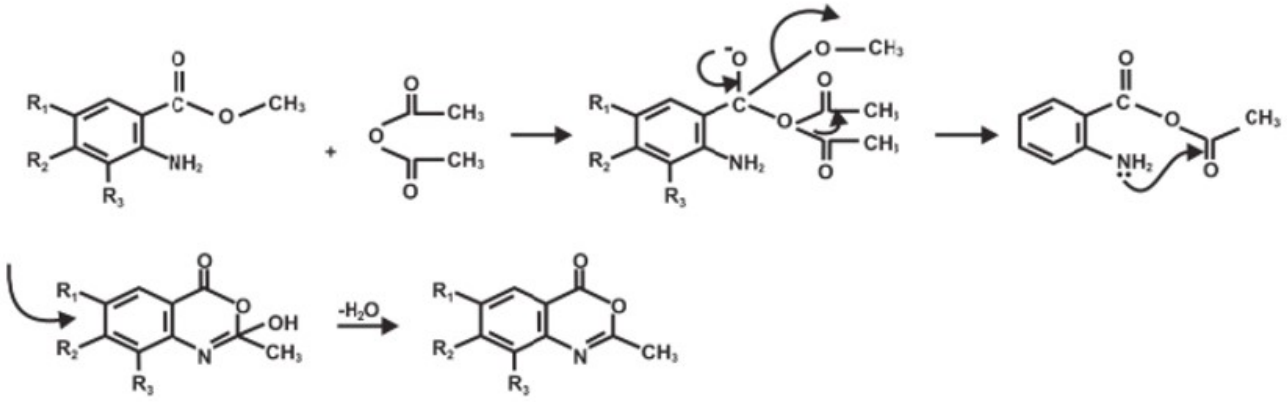


Scheme 3: Reflux/$NH_2NH_2H_2O$

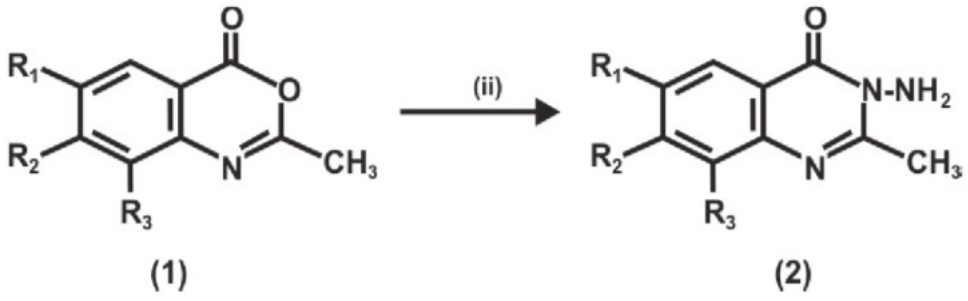


Scheme 4: Where: R_1 = Br, R_2 = H, and R_3 = H

Possible Mechanism

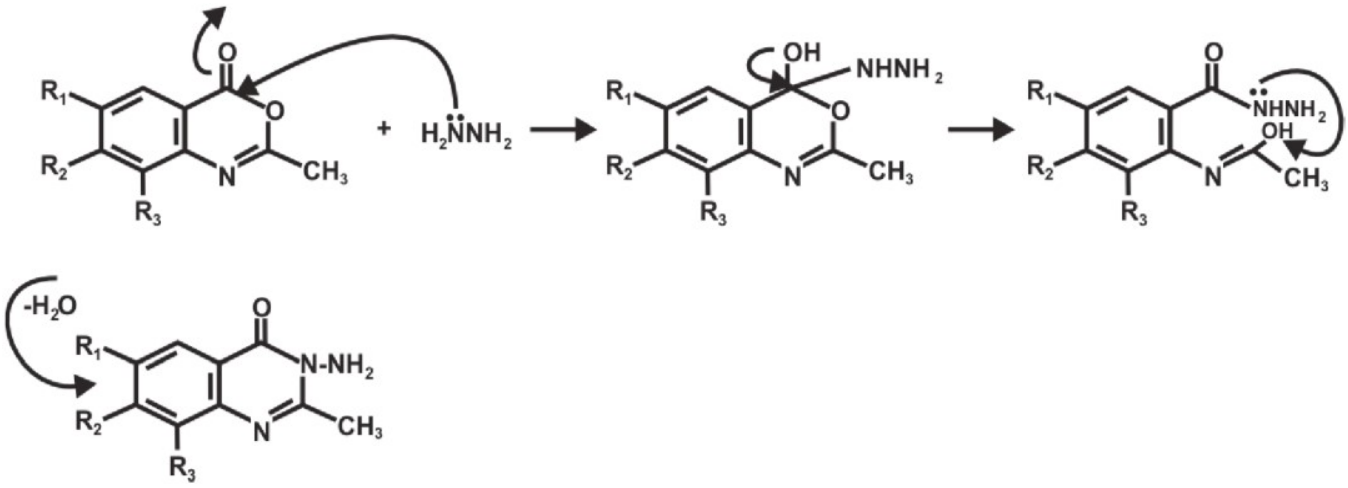


Diagram



Scheme 5: Where: R_1 = Br, R_2 = H, and R_3 = H

Possible Mechanism



Diagram

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 7-bromo,2-(o-aminophenyl)-1,3-benzoxazin-4(3H)-one, (1)

5-bromo anthranillic acid (.16 M, 34.72 gm) was dissolved in 100 ml of pyridine. To this reaction mixture o-amino benzoyl chloride (.16 M, 24.8 gm) 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.- 191°C, yield- 80%, Rf – 0.65, IR (cm^{-1}): 3069 υ (C-H str. of the aromatic ring), 1696 υ (C=O str. of the ring), 3364 3346 υ (N-H str. of the ring). ^{1}H NMR: 7.7-7.8 (d, 2H of $–NH_2$), 7.18-7.25 (dd, 2H of-ArH), 6.71 (d, 1H of -ArH).

Synthesis Of 7-bromo,2-(o-aminophenyl)-1,3-benzoxazin-4(3H)-one (2)

7-bromo-2-(o-aminophenyl)-1-,3-benzoxazin-4(3H)-one (0.075 M, 23.775 gm) 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-81%, Rf- 0.68, IR (cm^{-1}): 3048 υ (C-H str. of the aromatic ring), 3361, 3351 υ (N-H str. of the ring), 1706 υ (C=O str. of the ring), 1316 υ (C-N str. of the ring). ^{1}H NMR: 7.71-7.81 (dd, 2H of –ArH), 7.45-7.87 (m, 5H of –ArH), 5.66 (s, 2H of NH_2), 6.15 (s, 2H of $–NH_2$).

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. Antibacterial evaluation

Antibacterial activities of control drugs and tested compounds against tested standard organism

Control drugs
Ciprofloxacin (CPX) for bacteria
Ketonaxol (PEF) for fungus
Compound 1 (1)
Compound 2 (2)

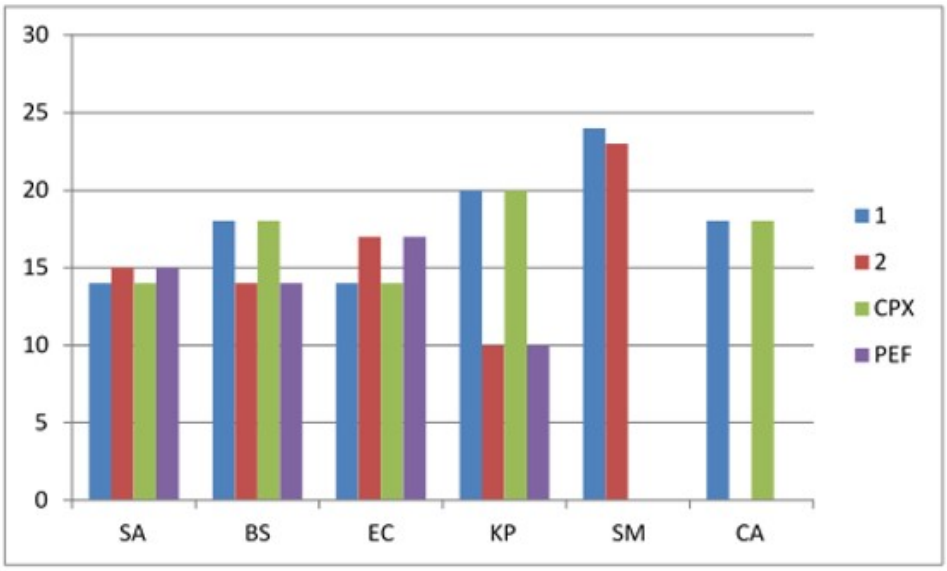


Figure 1: The effect of Compounds toward studied bacteria

Where,
SA = Staphylococcus aureus, BS = Bacillus species, EC = Escherichia coli, KP = Klebsiellapneumonia, SM = Serratiamarcescens and CA = candida albicans.
Significantly different from Ligand at P <0.05, values are in mm.

4. Results and Discussion

Table 1: Characterization and Physical Data of Synthesized Compounds

Compound No	Solvent	Formula Molecular Weight	Analysis% Calc/Found C	 H
1	Ethanol	$C_{14}H_9BrN_20_2$ (317)	55.22 55.21	3.08 3.07
2	Ethanol	$C_{14}H_{11}BrN_30$ (331)	51.53 51.52	3.83 3.82

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

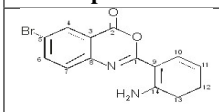
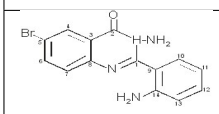
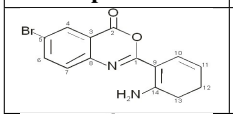
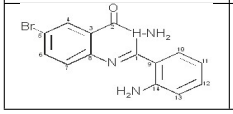
Compound No	δ (ppm) Carbon atom number
	155.15(C-1), 160.45(C-2), 120.10(C-3), 128.05(C-4), 112.70(C-5), 112.62(C-6), 122.10 (C-7), 148.15 (C-8), 24.10 (C-9), 113.70(C-10), 113.60(C-11), 121.10 (C-12), 24.15 (C-13), 148.11 (C-14)
	154.51(C-1), 160.14 (C-2), 120.28(C-3), 128.21 (C-4), 112.41 (C-5), 112.14 (C-6), 122.20 (C-7), 148.05(C – 8), 24.15 (C-9). 111.70(C-10), 114.60(C-11), 122.10 (C-12), 25.10 (C-13), 143.15 (C-14)

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

Compound No	δ (ppm)
	7.7-7.8 (d, 2H of –NH_2), 7.18-7.25 (dd, 2H of-ArH), 6.71 (d, 1H of -ArH).
	7.71-7.81 (dd, 2H of –ArH), 7.45-7.87 (m, 5H of –ArH), 5.66 (s, 2H of NH_2), 6.15 (s, 2H of –NH_2).

5. Discussion

The present study reported the synthesis of two derivatives of quinazolinone, 2-(o-aminophenyl)- 7-bromo–3,1-benzoxazin-4(3H)-one (1) and 2-(o-aminophenyl)-3-amino-7-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 1H NMR spectra of the compounds synthesized, compound 1 displayed a duplet at δ 7.7-7.8, and at 6.71 attributed to aromatic protons. Also, ^{1}H NMR spectrum of compound 2 showed a characteristic duplet at δ 7.71-7.81. Multiplets appeared between δ 7.45 - 7.87 attributed to aromatic protons. For the IR spectra, compound 1 were characterized by the presence of IR (cm^{-1}): 3048 υ (C-H str. of the aromatic ring), 3361, 3351 υ (N-H str. of the ring), 1706 υ (C=O str. of the ring), 1316 υ (C-N str. of the ring). 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 24.15, attributed to phenyl group, while the aromatic carbon atoms appeared between δ values 112.62 – 160.45 with the carbonyl carbon atom appearing as the highest δ value of 160.18. Similarly, compound 2 showed signals at δ 25.10, attributed to phenyl group, while the aromatic carbon atoms appeared between δ values 112.14 - 160.14, with the carbonyl carbon atom appearing as the highest δ value of 160.14.

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, 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.

6. 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, 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 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.

Article Information

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Conflict of Interest: The author declares no conflict of interest.

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.

Informed Consent: Written informed consent was obtained from all participants.

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.

Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

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