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(RESEARCH ARTICLE)

Synthesis and antibacterial activity of newly synthesized 7-chloro–2–methyl-4h–benzo[d] [1, 3]–oxazin–4–one and 3–amino-7-chloro-2–methyl-quinazolin-4(3h)–one

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Abstract

The current study is aimed at the synthesis of these quinazolinone derivatives 7-Chloro-2-Methyl-4H-benzo[d]-[1,3]-Oxazin-4-one and 3-Amino-7-Chloro-2—Methyl-3H-Quinazolin-4-One and evaluate them for their antibacterial activity.The condensation of 2-amino-methyl-4-methoxybenzoate with acetic anhydride yielded the cyclic compound 2-methyl-4, 5-disubstituted-1, 3-benzo-oxazine-4-one which further produce a novel 2,3-disubstituted quinazolin-4 ones via the reaction with hydrazine hydrate The quinazolinone derivatives 7-chloro-2-methyl-4H-benzo[d][1,3]-oxazin-4-one and 3-amino-7-chloro-2-methyl-quinazolin-4(3H)- One were evaluated pharmacologically for their in vivo analgesic activities by acetic acid induced writhing in mice. The compounds synthesized were unequivocally confirmed by means of Infrared, Nuclear Magnetic Resonance (^{1}H and ^{13}C), Gas Chromatography Mass Spectrophotometer and Elemental analysis.The synthesized compounds were screened against various strains of microorganism; *Klebsiella pneumonia, Staphylococcus aureus*, *Bacillus species*, *Escherichia coli*, *Klebsiella pneumonia*, , and *Candida albicans*. Compounds 1and 2 showed significant activity against *Klebsiella pneumonia, Staphylococcus aureus and Pseudomonas aeruginosa* with MIC ranging from 6 – 9 mg/mL. The test investigated compounds exhibited significant antibacterial activity against the bacteria when compared with the control test sample. The IR spectra of compound 1 were characterized by absence of υ $NH_2$and presence of υ C-O stretch in 1157 cm^{-1} region of the compound. Compound 2 was characterized by absence of υ C-O and presence of υNH_2 in 3285 $cm^{-1}$and 3184 cm^{-1} region of the compound. The compounds synthesized exhibited promising antibacterial activities against *Klebsiella pneumonia, Staphylococcus aureus* and *Pseudomonas aeruginosa,* stock cultures. The compounds have high activity against the microorganisms. Compound 2 has a higher activity against *Klebsiella pneumonia, Styphylococcus aureus, Pseudomonas aeruginosa,* and *Bacillus cereus* compared to Compound 1.

Keywords: 3-amino-7-chloro-2-methyl-quinazolin-4(3H)-one; 7-chloro-2-methyl-4H-benzo[d][1,3]-oxazine-4- one, quinazolin-4(3H)-one; antibacterial activity; Nucleophile, Synthesis; Reaction mixture; *Klebsiella pneumonia*; *Staphylococcus aureus*

Abbreviations

TLC	Thin Layer Chromatography
SEM	Standard error mean
IR	Infrared Spectra
UV/Visible	UV-Visible Spectra

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^{1}H NMR	Proton Nuclear Magnetic Resonance
^{13}C NMR	Carbon thirteen Nuclear Magnetic Resonance
GCMS	Gas Chromatography Mass Spectroscopy
CPX	Ciprofloxicin
PEF	Ketonaxol

1. Introduction

Quinazolinone derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals. Several reports have been published on the biological activities of quinazolinone derivatives, including their anti-inflammatory [1–7], antimalarial [8, 9], antimicrobial, anti-fungal, antibacterial [10–16], anticonvulsant [17– 20], and antitumor [21, 22].

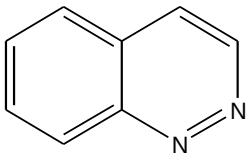
Quinazolinone derivatives with 2, 3- substitution are reported to possess significant analgesic and anti- inflammatory activity [23, 24]. Looking at the biological significance of quinazolinone nucleus, it was thought to synthesize new quinazolinone derivatives and screen them for their analgesic activity.

One of the medicinally important heterocyclic compounds is the quinazoline. Quinazoline is a compound made up of two fused six-membered simple aromatic rings, benzene ring and a pyrimidine ring. Quinazoline, earlier known as benzo-1, 3-diazine was first prepared in the laboratory by Gabriel in 1903, although one of its derivatives was known much earlier [25].

The name quinazoline (German; Chinazolin) was first proposed for this compound by Weddige, on observing that this was isomeric with the compounds Cinnolin and Quinoxaline. Paal and Bush suggested the numbering of quinazoline ring system, which is currently used. The other less commonly used names for this ring system are phemiazine and 5,6-benzopyrimidine. However, the name quinazoline is now universally accepted [26].

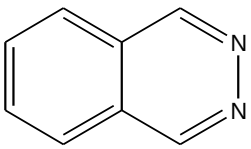
There are four isomers of Quinazoline which are identified by nitrogen positions;

Cinnoline [1,2 – Benzodiazine],



1

Phthalazine [2,3- Benzodiazine],



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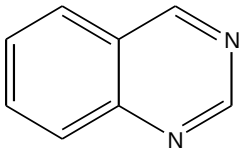
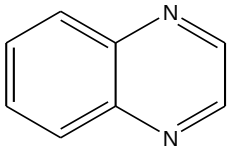
Quinazoline [1,3-Benzodiazine],



3

Quinoxaline [1,4-Benzodiazine]



4

Taking into consideration the use of quinazolinone derivatives in the treatment of some diseases, mentioned above, we have tested the antibacterial activity of the synthesized compounds 1 and 2 using strains of Staphylococcus aureus, *Pseudomonas aeruginosa*, Bacillus species, *Escherichia coli, Klebsiella pneumonia*, , and *Candida albicans* stock cultures.

2. Material and methods

2.1. General experimental procedure

Reagents and solvents were purchased from sigma-Aldrich chemical supplier in Germany. Melting points were determined on a Kofler hot stage apparatus and are 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 400MH_z with HAZ VOLATILE V2.M. Chemical shifts are reported in ppm relative to tetramethylsilane period. Gas chromatography mass (GC/MS) spectra were obtained on a Finingan MAT 44S mass spectrometer operating at electron impact energy of 70eV. Elemental analysis data agreed with the calculated values. Analytical thin layer Chromatography (TLC) was used to monitor the reactions.

2.1.1. Synthesis of 7-chloro-2-methyl-4H-benzo[d][1,3]-oxazine-4- one, quinazolin-4(3H)-one, (1)

This involved the condensation of Methyl-2-amino-5-methoxyl-benzoate "2.11g" (0.01mol) and 1.02g (0.01mol) acetic anhydride in 30ml ethanol medium were reacted. The reaction was heated under reflux with stirring using a magnetic stirrer until the reaction mixture showed no trace of starting material when the TLC was developed (2 hours).

At the end of the reaction, work up was done. Ethanol was removed in vacuum and the crude mixture was poured into 50ml of ice water on a cold water bath. The mixture was stirred for 30 minutes filtered and extracted into ethyl acetate and allowed to evaporate at room temperature to give solid products which were recrystallized from hexane or dichloromethane-hexane mixture. Yield was "2.01g" (95%), mp: "148-150"C.

2.1.2. Synthesis of 3-amino-7-Chloro 2-Methyl quinazoline-4-(3H)-One. (2)

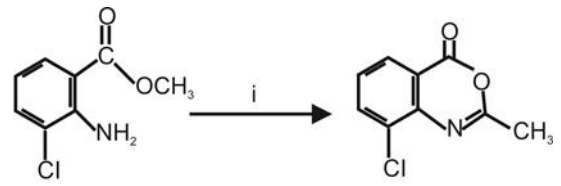
The condensation of equimolar amounts of 2-methyl, 6-methoxyl-4H-benzo [D] [1, 3] –oxazine-4-one "1.06g", ("0.005" mol) and hydrazine hydrate "0.93g",("0.01" mol) were added to 30ml boiling ethanol with stirring using a magnetic stirrer until the reaction mixture showed no trace of starting material when the TLC was developed (3 hours).

At the end of the reaction, the reaction mixture was concentrated in vacuum under reduced pressure using rotary evaporator. The white precipitate formed was then filtered, washed three times with 20ml of distilled water [20ml x 3]. The white crystals were dried and recrystallized from dimethylformamide (DMF) to give pure 3-amino-7-Chloro 2-Methyl quinazoline-4-(3H)-one. Yield was "1.00g" (94%) mp: "97-99"C.

2.2. Evaluation of antimicrobial activity

Agar well diffusion method was utilized for the antimicrobial activity [27]. Six species: *Staphylococcus aureus* (ATCC10145), *Bacillus species* (NCTC 8236), *Escherichia coli* (ATCC 25923), *Klebsiella pneumonia* (NCTC 10418), *Serratia marcescens* (ATCC 14756) and *Candida albicans* (ATCC24433) stock cultures were used. The test organisms were obtained from the Pharmaceutical Microbiology Department of the University of Benin, Benin City, Nigeria. The test organisms were cultured overnight in nutrient broth, diluted to the turbidity of 0.5 McFarland standard. Broth

culture (0.2 mL) were seeded on nutrient agar (for bacterial organisms) or Sabouraud dextrose agar (for the fungus) and allowed to dry. The various concentrations of the compounds (20 – 640 mg/mL) were introduced. The culture plates were incubated at 37°C for 24h (for bacterial organisms) or at room temperature (28°C) for 48 h (for the fungus). The results were taken by considering the zones of inhibition by the test compounds. Ciprofloxacin (20 mg/mL) was used as positive control while the vehicle (10% DMSO) was used as negative control. Activity and inactivity were observed in accordance with standard and accepted method [28].



2

Scheme 1

i=Acetic anhydride, ethanol

Figure 1 Where: R_1 = H, R_2 = H, and R_3 = Cl

Possible Mechanism

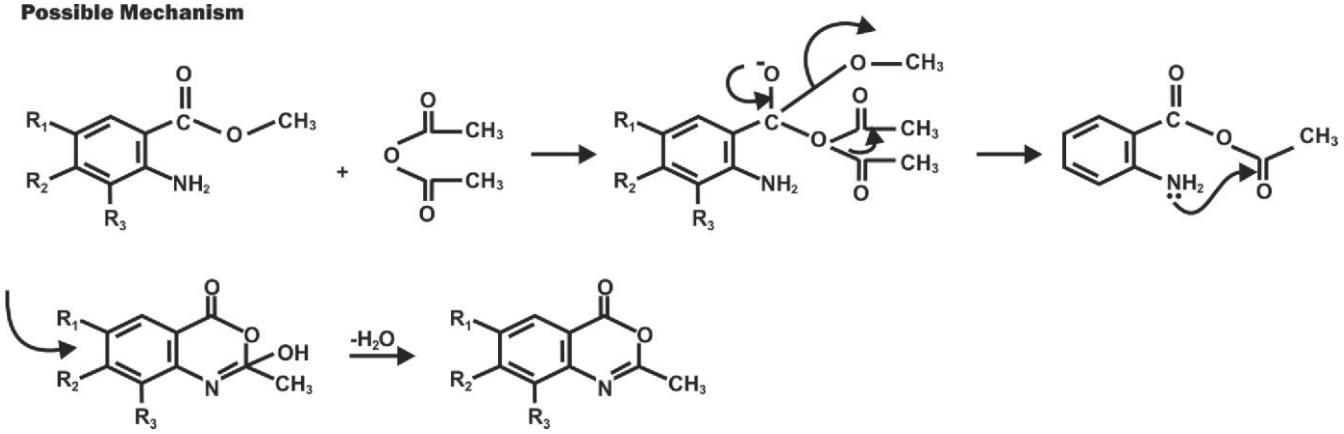
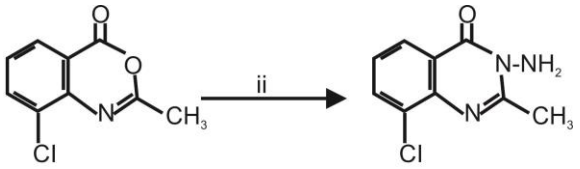


Figure 2 Where: R_1 = H, R_2 = H, and R_3 = Cl

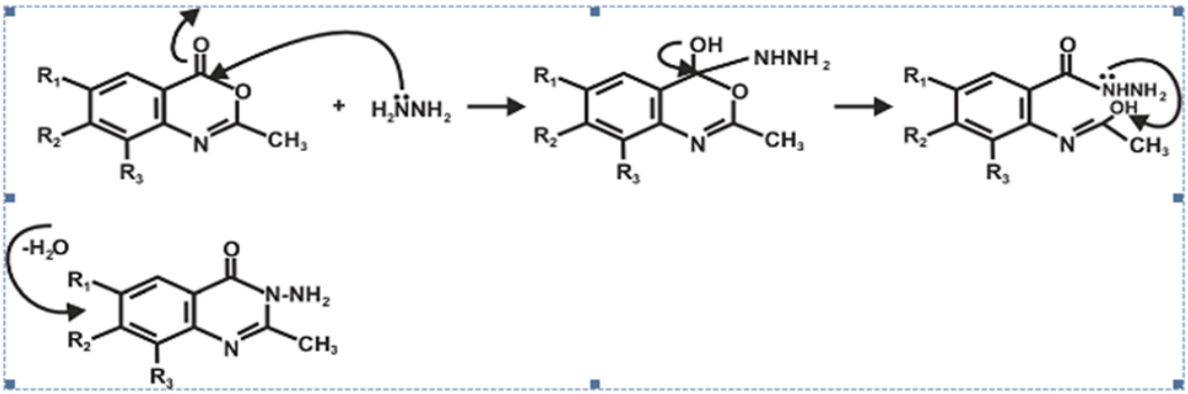


3

Scheme 2

ii = Hydrazine Hydrate, ethanol

Possible Mechanism



2.3. 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.

3. Results

3.1. Antibacterial activity of control drugs andtested compounds against tested standard organism

3.1.1. Control Drugs

Ciprofloxicin (CPX) For Bacteria

Ketonaxol (PEF) For Fungus

Compound 1 (1)

Compound 2 (2)

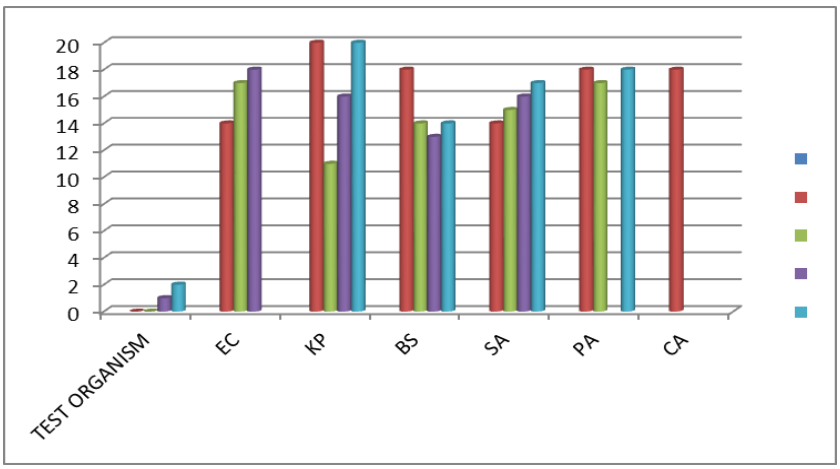


Figure 3 The effect of Compounds toward studied bacteria. SA=Staphylococcus aureus, BS=Bacillus species, EC=Escherichia coli, KP=Klebsiellapneumonia,SM= Serratiamarcescens and CA=*Candida albicans*

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

3.2. Characterization of 7-Chloro-2-Methyl-4H–benzo[d] [1,3]–oxazine–4–one (1)

^{1}H NMR (400MHz, DMSO) δ 7.49 (s, 1H), 7.14 (s, 1H), 6.30 (s, 1H), 2.53 (s, 3H), ^{13}(NMR (400MHz, DMSO) δ 168.05, 140.10, 149.40, 153.07, 141.33, 134.40, 127.03, 114.40, 23.42. IR (KBr, cm^{-1}) 3381, 3203, 3135, (NHz), 3018 (CH aromatic), 2951, 2871, 2718 (CH aliphatic), 1662 (C=0). Anal. Cal 1159 (C-0) for $C_9H_6ClN0_2$; C 61.10; H 4.13. Found: C 61.20, H 4.76.

3.3. Characterization of 3-amino-7-Chloro 2-Methyl quinazoline-4-(3H)-One (2).

^{1}H NMR (400 MHz, DMSO) δ 7.48 (s, 1H), 7.31 (s, 1H), 7.04 (s, 1H), 5.79 (s, 2H), 2.56 (s, 3H) ^{13}C NMR (400MHz, DMSO) δ 161.20, 142.50, 154.10, 148.20, 134.60, 121.30, 114.10, 127.60, 148.20, 23.10. IR (KBr, cm^{-1}) 3301 (NH_2), 1622 (C=0), Anal. Cal. for $C_9H_8N_30$; C 54.21, H 4.43; Found, C 54.30, H 4.31.

Table 1 Characterization and physical data of synthesized compounds

Compound No	Solvent	Formula M. wt	Analysis% Calc/Found	
			C	H
1	Ethanol	C9H6NCl02	61.10	4.13
		(195.602)	61.20	4.76
2	Ethanol	C9H8N3Cl0	54.21	4.43
		(209.633)	54.30	4.31

Table 2 ^{13}C-NMR of synthesized compounds

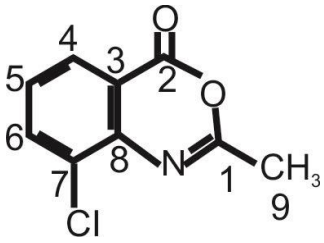
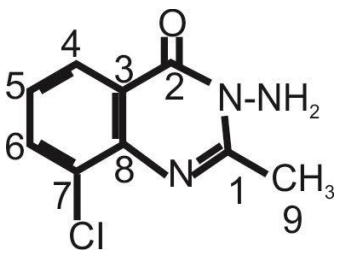
Compound No	δ (ppm) Carbon atom number
	168.05(C-2), 140.10(C-6), 149.40(C-8) 153.07(C-1), 141.33 (C-5), 134.40 (C-4) 127.03 (C-3), 114.40 (C-7), 23.42(C-9).
	161.20(C-2), 142.50 (C-6), 154.10 (C-1) 148.20 (C-8), 134.60 (C-5), 121.30 (C-3), 114.10 (C-7), 127.60 (C-4), 148.20(C-8), 23.10 (C-9)

Table 3 ^{13}C-NMR of synthesized compounds

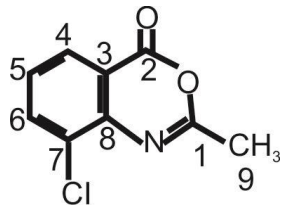
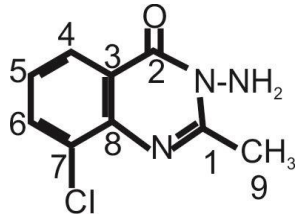
Compound No	δ (ppm)
	7.49 (s, 1H), 7.14 (s, 1H), 6.30 (s, 1H), 2.53 (s, 3H)
	7.48 (s, 1H), 7.31 (s, 1H), 7.04 (s, 1H), 5.79 (s, 2H), 2.56 (s, 3H)

Table 4 Minimum inhibitory concentrations (MIC) in mg/mL of tested compounds against tested standard microorganisms

TEST ORGANISM	COMPOUND	
	1	2
Escherichia coli	6.00	-
Klebsiella pneumonia	-	7.00
Staphylococcus aureus	6.00	6.00
Pseudomonas Aeuriginosa	9.00	8.00
Bacillus species	-	-
Candida albicans	-	-

4. Discussion

The present study reported the synthesis of two derivatives of quinazolinone, 3-amino-7-chloro-2-methyl-quinazolin-4(3H)-one (1) 7-chloro-2-methyl-4H-benzo[d][1,3]-oxazine-4- one, quinazolin-4(3H)-one, (2). The compounds were investigated for their Antimicrobial 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 2.53 which was due to methyl group. Other singlets appeared at δ7.49 and 7.14 attributed to aromatic protons. Also, ^{1}H NMR spectrum of compound 2 showed a characteristic signal at δ 2.56 (singlet) corresponding to methyl group. Two singlets appeared at δ7.48 and 7.31 attributed to aromatic protons. Another signal appeared at 5.79 which was attributed to the protons of the amino group. For the IR spectra, compound 1 were characterized by absence of υ $NH_2$and presence of υ C-O stretch in 1662cm^{-1} region of the compound. Compound 2 was characterized by absence of υ C-0 and presence of υNH_2 in 3301cm^{-1} region of the compound.

The ^{13}C NMR spectrum of compound 1, revealed signals at δ23.40, attributed to methyl group, while the aromatic carbon atoms appeared between δ values 114.40-168.50 with the carbonyl carbon atom appearing as the highest δ value of 168.50. Similarly, compound 2 showed signals at δ23.10, attributed to methyl group, while the aromatic carbon atoms appeared between δ values 114.10 – 161.20, with the carbonyl carbon atom appearing as the highest δ value of 161.20. The compounds synthesized exhibited promising antimicrobial activities against *Klebsiella pneumonia*, *Staphylococcus aureus*, *and Pseudomonas aeuriginosa* stock cultures.

5. Conclusion

The present study has showed that the quinazolinone derivatives 1 and 2 have antibacterial activity. Compound 2 has a higher activity against *Klebsiella pneumonia, Staphylococcus aureus*, and *Pseudomonas aeuriginosa,* compared to Compound 1.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The author declares no conflict of interest.

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