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(RESEARCH ARTICLE)

Synthesis and antibacterial activity of 3-amino-6-iodo-2-methyl quinazolin 4-(3H)-one and 6-iodo-2-methyl-4H-benzo [D] [1, 3] oxazin-4-one

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Abstract

Quinazolines and its derivatives represent one of the most active classes of compounds, which possess wide range of biological activities like anti-bacterial, analgesic, anti-microbial, anti-inflammatory, anticancer, and anti-hypertensive ,antifungal, anti-HIV, antioxidant, analgesic, anticonvulsant, antimalarial, antitumor, anti-tubercular activities. The objective of the present study was to synthesize these quinazolinone derivatives 6-iodo-2-methyl-4H-benzo[d]-[1,3]-oxazin-4-one and 3-amino-6-iodo-2—methyl-3H-quinazolin-4-one and evaluate them for their antibacterial activity. 6-lodo-4H-benzoxazin-4-one was synthesized by the reaction of 2-amino-5-Iodomethylbenzoat and acetic anhydride which reacted with nitrogen nucleophile, namely hydrazine hydrate to obtain 3-amino-6-iodo-2-methyl-3H-quinazolin-4-one. The structures of the compounds were confirmed with Infrared Spectra, Proton Nuclear Magnetic Resonance, Carbon thirteen Nuclear Magnetic Resonance, mass spectra and elemental analysis. These compounds were screen for their antibacterial activities against a number of microorganisms, *Escherichia coli*, *Klebsiella pneumonia*, Bacillius species, *Staphylococcus aurous*, *Pseudomonas aeruginosa* and *Candida albican*. The test investigated compounds exhibited significant antibacterial activity against the bacteria when compared with the control test sample. For the IR spectra, compound 1 were characterized by absence of υ $NH_2$and presence of υ C-O stretch in 1159 cm^{-1} region of the compound. Compound 2 was characterized by absence of υ C-O and presence of υNH_2 in 3284 $cm^{-1}$and 3194 cm^{-1} region of the compound. The compounds synthesized exhibited promising antibacterial activities against *Staphylococcus aureus*, *Bacillus species* and *Pseudomonas aeruginosa,* stock cultures. The compounds have high activity against the microorganisms. Compound 2 has a higher activity against *Pseudomonas aeruginosa* compared to compound 1.

Keywords: Antibacterial activity; Synthesis; Acetic anhydride; Hydrazine hydrate; Nucleophile; Quinazolin-4(3H)-one

1. Introduction

Having witnessed from literature, the enormous importance of quinazolinones [1 - 8]. Promising antimicrobial and antifungal activities have been reported in many substituted quinazoline derivatives. Earlier, Quinazoline-4-ones has been a subject of extensive pharmacological evaluation, as well as, toxicological studies for antimicrobial and antifungal activities [9]. A brief survey on the biological activities of quinazolin– 4 (3H) – one derivatives showed anti-inflammatory [10, 11], antitumor [12 – 15] anti HIV [16-17], antibacterial [18 - 19]. As well as CNS depressant and anticonvulsant activities [20 – 21].

Microbial infections cause pain and inflammation in the body. Generally two groups of agents are given for normal practice simultaneously (anti-microbial, analgesic and antiinflammatory effect). Compound with all three properties are not very common. The commercially available antimicrobial agents are having many adverse effects [22]. In view of the associated biological and pharmacological properties of heterocycles. We planned to screen these derivatives of quinazolin-4-one for their possible antibacterial activity [23].

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2. Material and methods

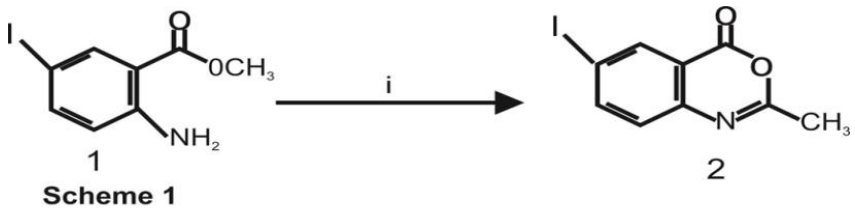
General experimental procedure

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

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 are reported in ppm relative to tetramethylsilane. Gas chromatography mass spectra were obtained on a Finingan MAT 44S mass spectrophotometer operating at 70eV. Elemental analysis was carried out with analytical Thin layer chromatography (TLC) was used to monitor the reactions.

2.1. 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.



Scheme 1

i = Acetic anhydride, ethanol

Figure 1 possible mechanism for synthesis of compound 1

Scheme 2

ii =Hydrazine hydrate, ethanol

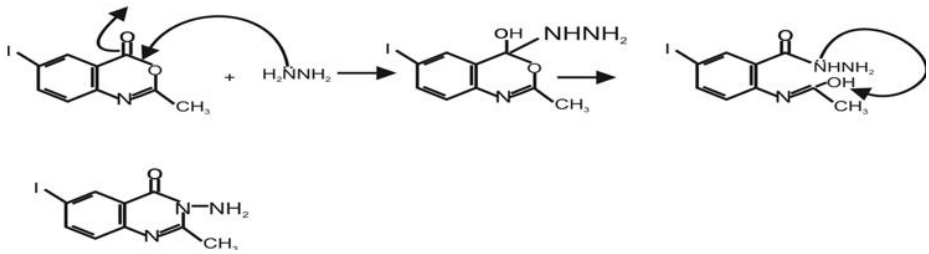


Figure 2 possible mechanism for synthesis of compound 2

2.2. Procedure for the synthesis of 6-iodo-2-methyl-4h-benzo[d]-[1,3]-oxazin-4-one(1).

Benzoxazinone has been synthesized by following the procedure of Bogert and Seil. A mixture of 1 (0.01mole, 2.77g) and acetic anhydride (0.02mole, 1.02g) was refluxed for 1-2h. The mixture was cooled, evaporated and the residue was washed with water and re-crystallized from ethanol to afford compound 2. Yield (75%), m.p 154-155^{0}C, IR (v/cm-^{1}): 3012(C-H aromatic), 2925 (C-H aliphatic), 1760 (C=0), 1620(C=N), MS: m/z 287 (M^{+}), ^{1}HNMR ($CDCL_3$): δ =7.32 - 7.10(m, 3H, ArH), 1.61 (s, 3ϭH, CH_3), Anal. Calc. for $C_9H_6N0_2I$ s: C: 37:63, H, 2.09; N, 4.88%. Found: C, 37.78, H, 2.39, N, 5.09.

2.3. Procedure for the synthesis of 3-amino-6-iodo-2—methyl-3h-quinazolin-4-one (2).

A mixture of benzoxazinone (2) (2.87g, 0.01mole) and hydrazine hydrate (1g, 0.02mole) was heated under reflux in absolute ethanol (30 ml) for 3h. The reaction mixture was concentrated. After cooling, the solid was separated out, filtered off, dried, and then re-crystallized from ethanol to afford quinazolinone (3). Yield (80%, m. p. 158^{0}C: IR (v/cm-^{1}): 3284, 3194, (NH_2), 3046 (C-H aromatic), 1660 (C=0), 1596 (C=N) MS: m/z 301 (M+), Anal. Calc. for $C_9H_6IN_30$: C. 35.90: H, 2.68; I 42.15, N.13.96.

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 2-amino-5-Iodomethylbenzoat and acetic anhydride yielded the cyclic compound 6-lodo-2-methyl-4H-benzo[*d*][1,3]-oxazin-4-one. The reaction of this compound with hydrazine hydrate yielded 3-amino-6-iodo-2-methyl-3H-quinazolin-4-one.

2.4. Evaluation of antimicrobial activity

Agar well diffusion method was utilized for the antimicrobial activity [24]. Six species: *Staphylococcus aureus* (ATCC10145), *Bacillus species* (NCTC 8236), *Escherichia coli* (ATCC 25922), *Klebsiella pneumonia* (NCTC 10418), *Pseudomonas aeriginosa* (ATCC 15692) 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) 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 ^{o}C for 24 h (for bacterial organisms) or at room temperature (28 ^{o}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% Dimethysulphuside was used as negative control. The results were assessed by measuring the zone of growth inhibition by the test compound. [25]. Activity and inactivity were observed in accordance with standard and accepted method.

2.5. Statistical analysis

All data were expressed as means ± SEM; the student's t-test was applied to determine the significance of the difference between the control group and the test compounds.

3. Results

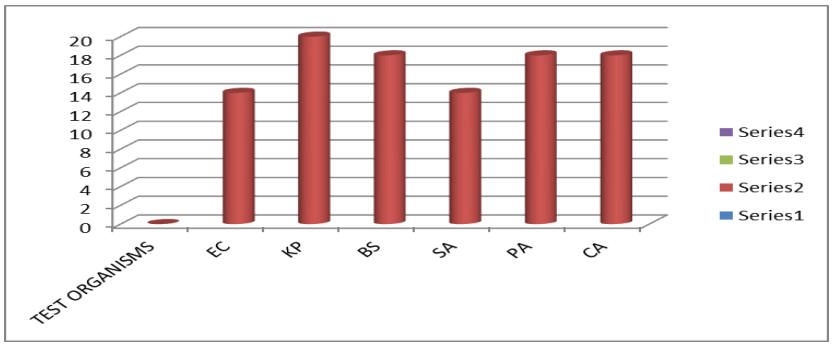


Figure 3 antibacterial activity of control drugs against tested standard organismcontrol drugs

The effect of compounds toward studied bacteria. SA = *Staphylococcus aureus,* BS = *Bacillus species,* EC = *Escherichia coli,* KP = *Klebsiella pneumonia*, PA = *Pseudomonas aeriginosa* and CA = *Candida albicans*. Significantly different from Ligand at P< 0.05, values are in mm

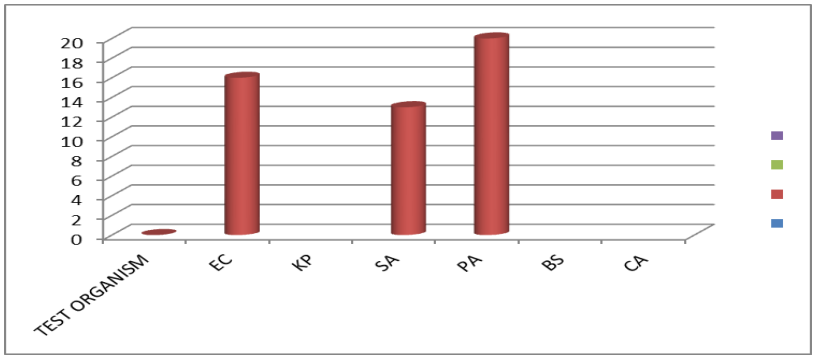


Figure 4 antibacterial activity of compound 1 against tested standard organism

The effect of compounds toward studied bacteria. SA = *Staphylococcus aureus,* BS = *Bacillus species,* EC = *Escherichia coli,* KP = *Klebsiella pneumonia*, PA = *Pseudomonas aeriginosa* and CA = *Candida albicans.* Significantly different from Ligand at P< 0.05, values are in mm

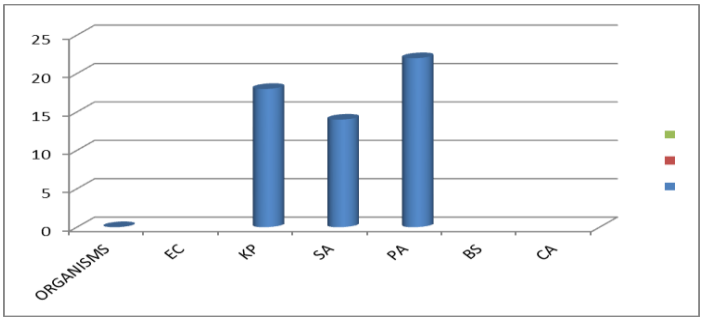


Figure 5 antibacterial activity of compound 2 against tested standard organis

The effect of compounds toward studied bacteria. SA = *Staphylococcus aureus*, BS = Bacillus species, EC = *Escherichia coli*, KP = *Klebsiella pneumonia*, PA = *Pseudomonas aeriginosa* and CA = *Candida albicans*. Significantly different from Ligand at P< 0.05, values are in mm

3.1. 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.

Table 1 characterization and physical data of synthesized compounds

Compound No	Solvent	Formula (Molecular weight)	Analysis %	C and H contents
2	Ethanol	C9H6NO2I	37.81	2.05
		(287)	37.63	2.09
3	Ethanol	C9H8lN3O	35.90	2.40
		(301)	35.88	2.66

Table 2 13C-NMR of synthesized compounds

Compound No	δ (ppm) Carbon atom number
1	168.28(C-2), 156.10(C-1), 149.23(C-8) 140.28 (C-4), 113.37 (C-5), 100.56 (C-6) 100.05 (C-3), 100.01 (C-7), 16.95 (C-9)
2	160.28 (C-2), 156.21(C-1), 154.57 (C-8) 149.07 (C-4), 143.77 (C-5), 113.65 (C-6) 108.24 (C-3), 105.64 (C-7), 22.58 (C- 9).

Table 3 1H-NMR of synthesized compounds

Compound No	δ (ppm)
1	7.32 – 7.10 (m, 3H, ArH), 1.16 (s, 3H, CH3).
2	7.52 – 7.15 (m, 3H,ArH), 5.80 (s, 2H), 2.58 (s, 3H)

Table 4 minimum inhibitory concentrations (MIC) in mg/ml of sample compounds against tested standard microorganisms

Test organism	Compound	
	1	2
Escherichia coli	6.00	-
Klebsiella pneumonia	-	7.00
Staphylococcus aureus	7.00	6.00
Pseudomonas aureus	10.00	8.00
Bacillus cereus	-	-
Candida albicans	-	-

3.2. Characterization of 7-iodo 2-methyl-4h-benzo [*d*][1,3] -oxazin-4-one (1).

^{1}H NMR (400MHz, DMSO) δ 7.32 – 7.10 (s, 3H, ArH), 1.61 (s, 3H,CH_3), ^{13}C NMR (400MHz, DMSO) δ 168.28, 156.10, 149.23, 140.28, 113.37,100.56, 100.05, 100.01, 16.95. IR (KBr, cm^{-1})3135, (NH_2), 3012 (CH aromatic), 2925, 2871, 2718 (CH aliphatic), 1760(C=0), 1620(C=N), 1159 (C-0). Anal.Cal 1159 (C-O) for $C_9H_6N0_2I$; C 55.21; H 3.07. Found: C 55.22, H 3.08.

3.3. Characterization of 3-amino-7-iodo-2-methyl-quinazoline-4(3h)-one (2).

^{1}H NMR (400 MHz, DMSO) δ 7.52 – 7.15 (m, 3H, ArH), 5.80 (s, 2H), 2.58 (s, 3H), ^{13}C NMR (400MHz, DMSO) δ 160.28, 156.21,154.57, 149.07, 143.77, 113.65, 108.24, 105.64, 22.58, IR (KBr,cm^1) 3284,3194(NH_2),3046(C-H aromatic), 1660 (C=0),1596(C-N), Anal. Cal. for $C_9H_8IN_30$; C 51. 52, H 3.82; Found, C 51.53, H 3.83.

4. Discussion

The present study reported the synthesis of two derivatives of quinazolinone, 7-iodo-2-methyl-4H-benzo [d] [1, 3]-oxazine-4-one,(1) and 3-amino-7-iodo-2-methyl 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 1.61 which was due to methyl group. Other singlets appeared at δ7.32 and 7.10 attributed to aromatic protons. Also, ^{1}H NMR spectrum of compound 2 showed acharacteristic signal at δ 2.58 (singlet) corresponding to methyl group. Multiplets appeared at δ7.52 – 7.15 attributed to aromatic protons. Another signal appeared at 5.80 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 1159cm^{-1} region of the compound. Compound 2 was characterized by absence of υ C-O and presence of υNH_2 in 3284$cm^{-1}$and 3194cm^{-1} region of the compound.

The ^{13}C NMR spectrum of compound 1, revealed signals at δ16.95, attributed to methyl group, while the aromatic carbon atoms appeared between δ values 100.05-168.28 with the carbonyl carbon atom appearing as the highest δ value of 168.28. Similarly, compound 2 showed signals at δ22.58, attributed to methyl 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. The compounds synthesized exhibited promising antibacterial activities against *Staphylococcus aureus*, *Bacillus species* and *Pseudomonas aeruginosa,* stock cultures.

5. Conclusion

The compounds have high activity against the microorganisms. Compound 2 has a higher activity against *Pseudomonas aeruginosa* compared to Compound 1. These compounds synthesized could be a potential antibiotic and a tool in Pharmaceutical drug delivery. Clinical trials need to be carried out on the compounds.

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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