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(RESEARCH ARTICLE)

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Synthesis and antibacterial activities of quinazolin-4(3h)-one, 2-methyl-4(3h)-quinazolinone and 2–phenyl-4(3h)-quinazolinone

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Abstract

Background: Quinazoline and quinazolinone scaffolds represent an important class of biologically active nitrogen heterocyclic compounds. Many marketed drugs are based on these moieties. A diverse range of molecules with quinazoline/quinazolinone moieties have been reported to exhibit broad spectrum of biological activities

Objective: This study is aimed at the synthesis of these quinazolinone derivatives, quinazolin-4(3H)-One, 2-Methyl-4(3H)-quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one and evaluate them for their antibacterial activities. Method: The consolidation of 2-amino-methyl-4-methoxybenzoate with acetic anhydride produced the cyclic compound 2-methyl-4, 5-disubstituted-1, 3-benzo-oxazine-4-one which also produce a novel 2,3-disubstituted quinazolin-4 ones via the reaction with hydrazine hydrate. The quinazolinone derivatives quinazolin-4(3H)-One, 2-Methyl-4(3H)-quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one were evaluated pharmacologically for their in vivo analgesic activities by acetic acid induced writhing in mice. The compounds synthesized were assuredly validated by means of Infrared, Nuclear Magnetic Resonance (1H and 13C), Gas Chromatography Mass Spectrophotometer and Elemental analysis. The synthesized compounds were tested for their antibacterial activity.Compounds 1,2 and 3 showed significant antibacterial activities. Discussion: Compound 1 was identified by the absence of methyl group and the presence of methyl group for compound 2. The test analysed compounds exhibited significant antibacterial activities. The compounds synthesized exhibited promising antibacterial activities against the tested organisms. Conclusion: The compounds have high antibacterial activities. Compound 2 has a higher activity compared to Compound 1 and 3. Compound 2 has a higher antibacterial against Escherichia coli, Klebsiella pneumonia and *Pseudomonas aeuriginosa*.

Keywords: Quinazolin-4(3H)-One; 2-Methyl-4(3H)-quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one quinazolin-4(3H)-one, Antibacterial activity

1. Introduction

Quinazolinones and their derivatives constitute an important class of heterocyclic compounds. Many of them show insecticidal [1], analgesic [2], antifungal [3], antibacterial [4], anticancer [5], anti-inflammatory [5] activities.

For example, the widely known quinazolinone drug, methaqualone was first synthesized in India in 1951 and was used world-wide as a sedative-hypnotic agent. [6] Also, structural activity relationship studies on 3-phenylsulfonylquinazoline-2,4-dione derivatives reveal that the 1- pyridylmethyl and 1-(N-pyridylacetamide) derivatives showed inhibitory concentration (IC50) in the order of 108 M as human heart chymase inhibitors [7].

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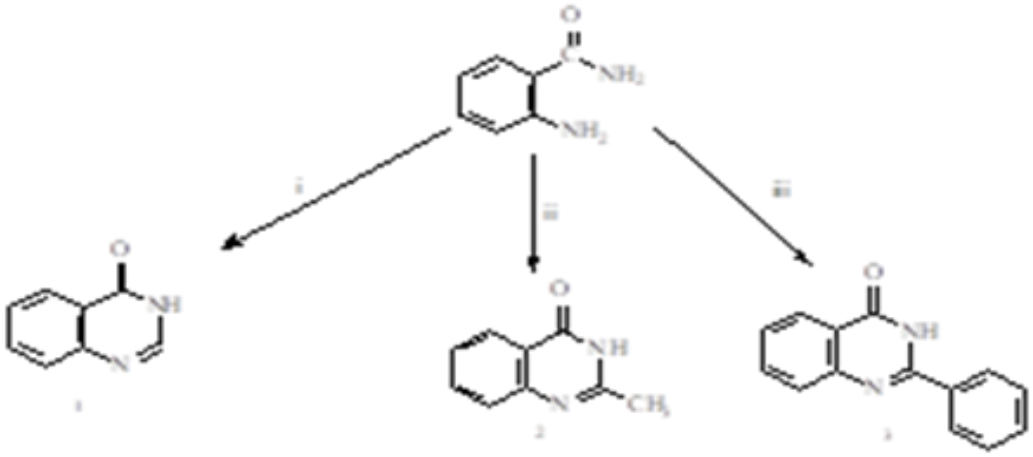
Molecular modeling studies on the interaction of one of the derivatives, 7-chloro-3- (4-chlorophenylsulfonyl) quinazoline-2,4(1H, 3H)-dione (2), with the active site of human heart chymase shows good fitting and interaction[7].

Literature survey revealed the versatile biological activities of quinazolinone derivatives [8]. It has been established that quinazolinones possess antiviral [9], antifungal [10], antiallergic [11], antitumor [12], and antidiabetic activities [13]. In the recent past, quinazolinones were reported to exhibit pronounced coronary vasodilatory [14] and histamine receptor type 3 inverse agonism [15]. Various researchers have reported the antibacterial activity of quinazolinone derivatives [15 –19].

Quinazolinone and their derivatives are building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganisms and animals. In light of the growing number of applications in recent years, there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazolinone derivatives. Compounds containing 4(3H)-quinazolinone ring system have showed antitumor, anticonvulsant, antitubercular activities, anti-inflammatory, analgesic, antimicrobial and anticoccidal activities [20 - 24].

Quinazolinones have been frequently used in medicine [25 - 27], such as quinethazone and metolazone and are used in medicine as diuretics while prazosin is a vasodilator, which is also used as asn antihypertensive drug. Quinazolinones are also a class of drugs which function as hypnotic/sedatives that contain a 4-quiazolinone core. Their use has also been proposed in the treatment of cancer [28]. Examples include afloqualone, cloroqualoneanddiproqualone.

The synthesized compounds were screened for their analgesic activity using the agar well plate method which is widely used for the evaluation of antibacterial activity. The compounds synthesized display antibacterial activities. Compounds 1, 2, and 3 showed significant antibacterial activities.



Scheme 1 i=HCl $(OC_2H_5)_3$, ethanol, ii=$CH_3C(OC_2H_5)_3$, ethanol, iii=$C_6H_5C(OC_2H_5)_3$, ethanol**.**

2. Material and methods

2.1. General Experimental Procedure

All chemicals were analytical grade and were purchased from sigma-Aldrich chemical supplier in Germany. Thin layer chromatography (TLC) were performed on aluminum plate silica gel coated with florescent indicator F254 (0.25 mm Kieselgel 60) in a solvent system.FT-IR spectra were recorded using a CARY 630 product. Proton and carbon nuclear magnetic resonance (1H and 13C NMR) spectra were recorded on a BrukerAvance 500 MHz spectrometer. DEPT 135 NMR spectra were recorded to determine the presence of CH2. Chemical shifts for protons and carbons were reported in parts per million downfield from tetramethylsilane and were referenced to residual deuteratedprotium and the carbon resonance in the NMR solvent (CDCl3 = δ 7.26 and 77.22 or CD3OD = δ 4.70). Chemical shift data of multiplicity were presented as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration.

2.2. Method

2.2.1. Synthesis of 4-(3h)-Quinazolinone (1)

Anthranilamide 0.68g (0.005mol) and triethylorthoformate 0.74g (0.005mol) were refluxed in 20ml ethanol with stirring using a magnetic stirrer until TLC indicated complete disappearance of the starting material (2 hours). The resulting solution was concentrated in vacuum and extracted into dichloromethane. The organic layer was dried over anhydrous sodium sulphate filtered and evaporated to give solid products which were recrystallized from Dimethylformamide (DMF), 0.66g (97%), mp 215-217^{o}C.

2.2.2. Synthesis of 2-Methyl-4(3h)-Quinazolinone (2)

Anthranilamide 0.68g (0.005mol) and triethylorthoacetate 0.81g (0.005mol) were reacted following the procedure for 1 above. Yield was 0.64g (94%), mp: 231-233oC.

2.2.3. Synthesis of 2-Phenyl-4 (3H)-Quinazolinone (3)

Anthranilamide 0.68g (0.005mol) and triethylorthobenzoate 1.12g (0.005mol) were were reacted following the procedure for 1 above. Yield was 0.57g (83%), mp: 198-2000C.

2.3. Antimicrobial activities

2.3.1. Determination of zone of inhibition

The microbial growth inhibitory activities of the synthesized sulfonylphenoxides were determined by the agar well plate method where the compounds were initially dissolved in dichloromethane and 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, 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.

Six wells were bored using a sterile borer (8 mm) and 100μL of the test concentrations, 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 thenincubated 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 itraconazole (50 mg/mL) were tested against bacteria and fungi respectively as the positive control [29].

2.4. Determination of MIC

The minimum inhibitory concentration (MIC) values of the sulfonylphenoxides 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 [29].

2.5. Statistical analysis

All data were expressed as the mean + SEM, the students't-test was applied to determine the significance of the difference between the control group and the test compounds.

3. Results

Table 1 Characterization and physical data of synthesized compounds.

Compound No	Solvent	Formula M. wt	Analysis% Calc/Found C	H
1	Ethanol	$C_{11}H_{11}N0_4$ (221.209)	62.20 62.10	5.18 4.98
2	Ethanol	$C_{11}H_{13}N_30_3$ (235.239)	56.11 56.40	5.53 5.41
3	Ethanol	$C_{11}H_{13}N_30_3$ (235.239)	56.11 56.40	5.53 5.41

Table 2 13C-NMR of Synthesized compounds.

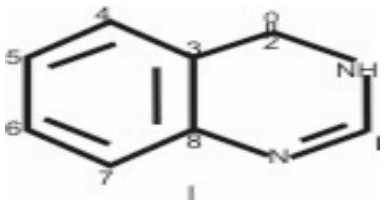
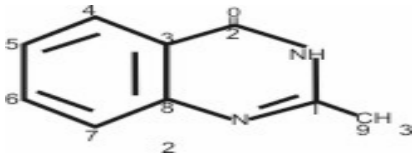
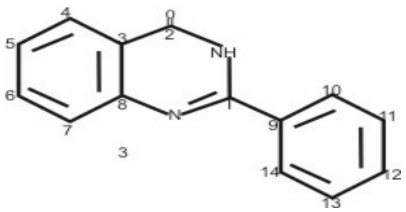
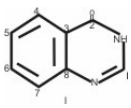
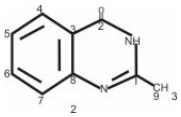
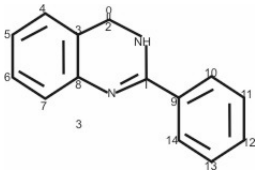
Compound No	δ (ppm) Carbon atom number
1 	168.28(C-2), 155.80(C-6), 149.23(C-8) 140.28 (C-1), 113.37 (C-5), 100.56 (C-4) 100.05 (C-3), 100.01 (C-7), 16.95 (C-9) 56.13 (C-10), 51.93 (C-11)
2 	160.28 (C-2), 155.29 (C-6), 154.57 (C-1) 149.07 (C-8), 143.77 (C-5), 113.65 (C-1) 108.24 (C-3), 105.64 (C-7), 56.80 (C-10) 56.63 (C-11), 22.58 (C-9)
3 	168.28(C-2), 155.80(C-6), 149.23(C-8) 140.28 (C-1), 113.37 (C-5), 100.56 (C-4) 100.05 (C-3), 100.01 (C-7), 16.95 (C-9) 56.13 (C-10), 51.93 (C-11)

Table 3 1H-NMR of Synthesized compounds.

Compound No	δ (ppm) Carbon atom number
1 	7.74 (s, 1H), 7.55 (d, 1H), 7.16 (t 1H), 7.08 (s, 1H), 6.70 (d 1H), 6.40 (s, 1H), 3.78 (t 1H) 3.68 (s, 1H).

2 	7.41 (s, 1H), 7.10 (d, 1H), 7.09 (t 1H), 7.08 (s, 1H), 6.70 (d 1H), 6.58 (s, 1H), 5.80 (t 1H) 2.56 (s, 1H),
3 	8.22 (d, 1H), 7.88 (t, 1H), 7.76 (d, 1H), 7.60 (t, 1H), 7.53 (d, 3H), 5.71 (s, 2H), 3.38

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

3.1.1. Control drugs

Ciprofloxicin (CPX) for bacteria
Ketonaxol (PEF) for fungus
Compound 1 (1)
Compound 2 (2)
Compound 3 (3)

Figure 1 The effect of Compounds toward studied bacteria. SA=*Staphylococcus aureus*, BS=*Bacillus species*, EC=*Escherichia coli*, KP=*Klebsiellapneumonia*,PA= *Pseudomonas aeuriginosa* and CA=*Candida albicans*

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

3.2. Characterization of 4-(3H)-Quinazolinone (1)

^{1}H NMR (400 MHz, DMSO) δ 7.74 (s, 1H), 7.55 (d, 1H), 7.16 (t 1H), 7.08 (s, 1H), 6.70 (d 1H), 6.40 (s, 1H), 3.78 (t 1H) 3.68 (s, 1H), ^{13}C NMR (400 MHz,) δ 172.18, 151.06, 132.75, 129.63, 117.30, 115.26, 114.63, 40.43, 1R (KBr,cm^{-1}), 3387 (NH_2), 2871, 2781 (CH aliphatic), 1700 (C=0). Anal Cal. for $C_8H_6N_20$: C 66.12, H 4.13, Found: C 67.42 H 4.99.

3.3. Characterization of 2-Methyl-4(3h)-Quinazolinone (2)

^{1}H NMR (400 MHz, DMSO) δ 7.41 (s, 1H), 7.10 (d, 1H), 7.09 (t 1H), 7.08 (s, 1H), 6.70 (d 1H), 6.58 (s, 1H), 5.80 (t 1H) 2.56 (s, 1H), ^{13}C NMR (400 MHz,) δ 168.28, 151.06, 132.75, 129.63, 117.30, 115.26, 100.5, 56.13, 51.93, 16.92. 1R (KBr,cm^{-1}), 3252, 3325, 3345 (NH_2),1641 (C=N), 3015 (CH, aromatic), 1693 (C=0). Anal Cal. for $C_9H_8N_20$: C 67.42, H 4.99, Found: C 68.96 H 4.77.

3.4. Characterization of 2-Phenyl-4 (3H)-Quinazolinone(3)

^{1}H NMR (400 MHz, DMSO) δ 8.22 (d, 1H), 7.88 (t, 1H), 7.76 (d, 1H), 7.60 (t, 1H), 7.53 (d, 3H), 5.71 (s, 2H), 3.38 (s, 1H) ^{13}C NMR (101 MHz, DMSO) δ 162.08, 156.67, 147.61, 135.79, 120.97, 1R (KBr,cm^{-1}), 3387 (NH) 1697 (C=0). Anal Cal. for $C_{14}H_{10}N_20$: C 75.61, H 4.50, Found: C 75.10 H 4.11.

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

Test Organism	**Compound**		
	1	2	3
Escherichia Coli	6.00	6:00	6.00
Bacillus Species	12.00	12.00	12.00
Staphylococcus Avreces	6:00	7:00	7:00
Klebsiela Pneumonia	7:00	7.00	7:00
Pseudomonas aeuriginosa	12.00	12:00	12:00
Candida Albicans	8:00	7.00-	7.00

4. Discussion

The reaction of Anthranilamide and triethylorthoformate (1), triethylorthoacetate (2) and triethylorthobenzoate (3) yielded the quinazolinone derivatives quinazolin-4(3H)-One (1) 2-Methyl-4(3H)-quinazolinone (2) and 2–Phenyl-4(3H)-quinazolin-4(3H)–one (3). These compounds were evaluated pharmacologically for their in vivo analgesic activities by acetic acid induced writhing in mice.

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 2 displayed a singlet signal at: δ 3.68 attributed to methyö group which was absent in compound 1. Other singlets appeared at δ 7.74, 7.55, 7.16, and 7.08 for compound 1, attributed to aromatic protons. The 13C NMR spectrum for compound 1 showed 11 peaks that represented the C atoms in the compound. This confirmed the structure of the compound as there were 11 non-equivalent carbon atoms in the compound. All the carbon atoms appeared at a high chemical shift values, and occurred between 100.01-168.28 confirming that they are unsaturated C. The >C=O is characteristically at 168.28.

The 1HNMR of compound 1 revealed seven protons. One of the protons at chemical shift 2.54ppm is attributed to the solvent DMSO. All the peaks were singlets. The singlet at position 11.45ppm is attributed to NH proton, while the signals at positions 7.78 ppm, 7.55 ppm, 7.16 ppm, and 7.08 ppm are all due to aromatic protons.

Also, 1H NMR spectrum of compound 2 showed a characteristic signal at δ 2.56 (singlet) corresponding to methyl group. Two singlets appeared at δ7.41 and 7.10 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 2 was characterized by absence of υ C-0 and presence of υ NH_2 in 3301cm^{-1} and 3300 region of the compounds.

The 13C NMR spectrum of compound 1, revealed signals at δ16.95, 51.93 and 56.13 attributed to methyl groups respectively, 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, 56.63 and 56.80 attributed to methyl and the two methoxy groups respectively, 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 13C nuclear magnetic resonance revealed low δ values for the aliphatic carbons. This is because the alkyl group is electron donating and hence produces a shielding effect which makes the carbon atom to resonate at low δ values. The aromatic and the carbonyl carbon atoms appeared at high δ values. This is because the aromatic ring is electron withdrawing and the aromatic carbons are highly deshielded and resonate at high frequency. The electronegative effect of the oxygen atom on the carbonyl group makes the carbonyl carbon to appear at higher δ value.

This present study reported the synthesis of these three compounds and they were investigated for their antibacterial activities. The compounds synthesized exhibited promising antibacterial activities. Compound 1, 2 and 3 have antibacterial activities against all the microorganisms while compound 2 has the highest antibacterial activities against *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeuriginosa* Compared to Compound 1 and 3 with a higher zone of inhibition. It may be that the substitution of the methyl group at position one increase the activity. These compounds synthesized have a higher antibacterial activity. These three compounds exhibited promising antibacterial activities. This indicated that compound 2 has a higher activity against *Escherichia coli, Klebsiella pneumonia and Pseudomonas aeuriginosa* microorganisms compared to compound 1 and 3.

5. Conclusion

Although numerous classes of quinazolinones have been synthesized their syntheses have the disadvantage of being multiple step reactions and time taken which are in hours and sometimes in days. However, the synthetic pathways in this study have numerous benefits for performing synthesis in organic compounds including reduced pollution, increased reaction rates, yield enhancement and cleaner chemistries. The in vitro antimicrobial studied of Quinazolin-4(3H)-One, 2-Methyl-4(3H)-Quinazolinone and 2–Phenyl-4(3H)-quinazolinone showed good activities against C. albicans. All the quinazolinone derivatives had good activities against Gram-positive and Gram-negative. The present study has shown that the quinazolinone derivatives 1, 2 and 3 have antibacterial activities with Compound 2 showing a higher activity compared to compound 1 and 3.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Authors' declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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