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(RESEARCH ARTICLE)

Synthesis and Antibacterial Activity of 3-(3-methoxyphenyl)-2-methylsulfanyl-3Hquinazolin-4-one (4) and 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro1H-quinazolin-4-one (3) Via N-(3- methoxyphenyl)-methyl dithiocarbamic acid (2)

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Abstract

Introduction: Heterocyclic compounds have already provided a platform for the rapid swap of research in the areas of organic, pharmaceutical, analytical, and medicinal chemistry. In the pharmaceutical industry, among the top two hundred branded drugs, more than 75% have heterocyclic fragments in their structures.

Methods/Experimental: The compound, 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro1H-quinazolin-4-one (3) was synthesized by dissolving Methyl anthranilate and N-(3- methoxyphenyl)-methyl dithiocarbamic acid in ethanol and anhydrous potassium carbonate and refluxed for 23 h and re-precipitated by treating with dilute hydrochloric. The 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro-1Hquinazolin-4-one was dissolved in 40 mL of 2% alcoholic sodium hydroxide solution and dimethyl sulphate was added drop wise with stirring for 1 h, the reaction mixture was then poured into ice water to get 3-(3-methoxyphenyl)-2-methylsulfanyl-3Hquinazolin-4-one (4). The synthesized compounds were screened against various strains of microorganism; *Staphylococcus aureus*, *Bacillus species, Escherichia coli*, *Klebsiella pneumonia*, Enterococcus Feacalis, *Pseudomonas aeriginosa*, and *candida albicans*. Compounds 3 and 4 showed significant activity against *Staphylococcus aureus*, *Bacillus species, Escherichia coli*, *Klebsiella pneumonia*, *Enterococcus Feacalis*, *Pseudomonas aeriginosa*, and *candida albicans*, MIC ranging from 6 – 12 mg/mL.

Result: The compounds exhibited significant antibacterial activity in comparison to control.

Conclusions: From our findings, the compounds synthesized have higher antibacterial activities as compared to the standard antibacterial drug.

Keywords: Antibacterial activity; Quinazolinone; 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro1H-quinazolin-4-one; N-(3- methoxyphenyl)-methyl dithiocarbamic acid; 3-(3-methoxyphenyl)-2-methylsulfanyl-3Hquinazolin-4-one

1. Introduction

Quinazolinones are pharmacophoric scaffold ubiquitous in various biologically active natural products, synthetic compounds, pharmaceutical drugs, agrochemicals and veterinary products [1]. The chemical structure of quinazolinones constitute a crucial scaffold of compounds with various therapeutic and biological activities such as antimalarial [2], antimicrobial [3, 4], antitubercular [5], anticonvulsant [6], anticancer [7], antihypertensive [8], anti-diabetic [9], anti-inflammatory [10], anti-cholinesterase [11], cellular phosphorylation inhibition [12], dihydrofolate reductase inhibition [13], kinase inhibitory activities [14], inhibitors of tubuline polymerization [15], diuretic [16], antipsychotic [17], dopamine agonists [18] and anti-HIV [19].

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Malaria is a parasitic disease caused by Plasmodium species parasite. It is widespread in several regions in Africa, Asia and South America. These parasites have developed a drug resistance to almost all the commercially available antimalarial drugs. The good antimalarial potency and the less side effects of quinazolinone compounds promote the researchers for the development of new antimalarial compounds [20].

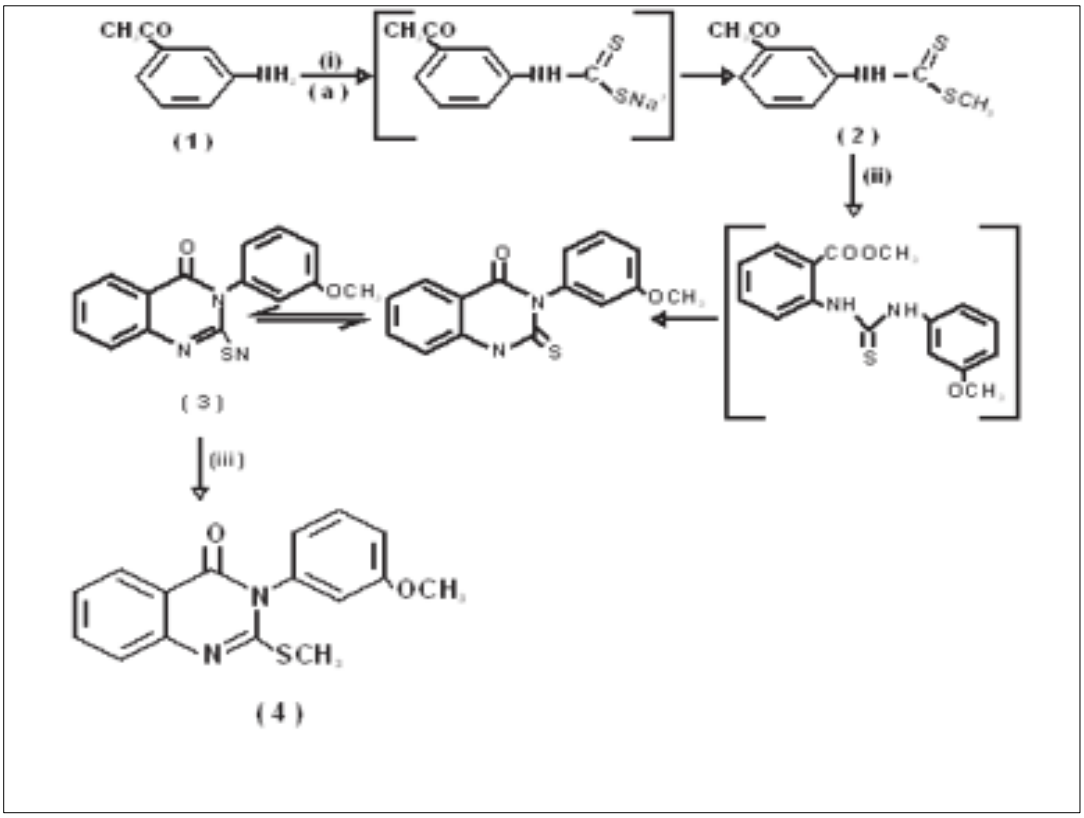
Quinazolines and quinazolinones (Figure 1) are main classes of fused heterocycles rings for a great importance in medicinal chemistry [21].Many substituted quinazoline and quinazolinone derivatives possess a broad spectrum of bioactivities such as bactericidal [22], fungicidal [23], anti-tuberculosis [24], antiviral [25], muscle relaxant [26], antimalarial [27], diuretic agents [28], antiprotozoal [29], CNS depressant [30] more other biological activities. Various synthetic drugs molecules such as nolatrexate [31], albaconazole [32], afloqualone (Arofuto) [33] and proquazone (Biarison) [34] are also contain derivatives of quinazoline and quinazolinone as active functional materials.

These findings prompted the author to synthesis these quinazolinone derivatives via the interaction of the benzoxazinone derivatives with different nitrogen nucleophiles, with the aim of obtaining more precise information about the course of the reaction and determine the Antibacterial properties.

2. Material and methods

2.1. General Experimental Procedure

The whole reagent and solvent that were used for the study were bought from sigma-Aldrich chemical company in Germany. Melting points were established using the Kefler hot stage apparatus and were not alter. The Buck scientific IR M500 instrument was used for the recording of the IR spectra. The ^{1}H and ^{13} C N M R spectra were recorded in D M S O at 400 MHz with HAZ VOLATILE V2.M. As generally known, chemical shifts are reported in ppm relative to tetramethylsilane. Gas chromatography Mass (GC/MS) spectra were obtained on a Finingem MAT 44S mass spectrometer operating at electron impact energy of 70eV. Elemental analysis data were fully related to the calculated values. Analytical Thin Layer Chromatography (TLC) was used to monitor the reactions.



i = CS2/NaOH a = DMSO; ii = Methyl anthranilate / EtOH, Δ; iii = NaOH / EtOH, (CH3)2SO4

Figure 1 General Experimental Procedure

2.1.1. Synthesis of 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro1H-quinazolin-4-one (3)

A solution of 3-methoxy aniline 1 (0.02 mol) in dimethyl sulphoxide (10 mL) was stirred vigorously. To this solution carbon disulphide (1.6 mL; 0.026 mol) was added and aqueous sodium hydroxide 1.2 mL (20 molar solution) was added drop wise during 30 min with stirring. Dimethyl sulphate (0.02 mol) was added gradually keeping the reaction mixture stirring in freezing mixture for 2 h. The reaction mixture was then poured into ice water. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol. Methyl anthranilate (0.01 mol) and the above prepared N-(3- methoxyphenyl)-methyl dithiocarbamic acid (0.01 mol), were dissolved in ethanol. To this, anhydrous potassium carbonate was added and refluxed for 23 h. The reaction mixture was cooled in ice and the solid separated was filtered and purified by dissolving in 10% alcoholic sodium hydroxide solution and re-precipitated by treating with dilute hydrochloric acid. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol. Yield = 86 %, mp 256-257 °C. IR: 3311 (NH), 1691 (C=O), 1211 (C=S) cm-1. 1 H NMR (CDCl3): 3.10 (s, 3H, OCH3), 7.30-7.91 (m, 8H, ArH), 10.52 (br s, 1H, NH); MS (m/z): 284 [M+].

2.1.2. Synthesis of 3-(3-methoxyphenyl)-2-methylsulfanyl-3Hquinazolin-4-one (4)

The 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro-1Hquinazolin-4-one 4 (0.01 mol) was dissolved in 40 mL of 2% alcoholic sodium hydroxide solution. To this dimethyl sulphate (0.01 mol) was added drop wise with stirring. The stirring was continued for 1 h, the reaction mixture was then poured into ice water. The solid obtained was filtered, washed with water, dried and recrystallized from ethanolchloroform (75:25) mixture. Yield = 86%, mp 155-156 °C; IR: 1690 (C=O) cm-1; 1 H NMR (CDCl3): 2.85 (s, 3H, SCH3), 3.34 (s, 3H, OCH3), 7.23-7.72 (m, 8H ArH); MS (m/z): 298 [M+]; Anal. Calcd. for C16H14N2O2S: C, 64.41; H, 4.72; N, 9.38. Found: C, 64.45; H, 4.74; N, 9.33.

2.2. Evaluation of antimicrobial activity

Agar well diffusion method was utilized for the antimicrobial activity. [35] Seven species: *Staphylococcus aureus* (ATCC10145), *Bacillus species* (NCTC 8236), *Escherichia coli*(ATCC 25923),*Klebsiella pneumonia* (NCTC 10418), *Enterococcus Feacalis* (NCTC 6571)*, Pseudomonas aeriginosa* (ATCC 101145), 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) andallowed to dry. The various concentrations of the compounds (20 – 640 mg/mL) were introduced. The culture plates were incubated at 37℃ for 24 h (for bacterial organisms) or at room temperature (28 ^{0}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. [36]

2.3. Minimum inhibitory concentration

The microdilution susceptibility test was used for the determination of antibacterial and antifungal activity. The nutrient broth was prepared and added in microiter plates except first well in which inoculum was not added and considered as negative control. A stock solution of test compounds was prepared in DMSO (200 µg/ml) followed by twofold dilution at concentrations of (100, 50, 25….3.125 µg/ml). The 75 µl inoculums were added to the other all wells containing test compounds ranging from 100, 50, 25….3.125 µg/ml. The microtitre plates were then incubated at 37 °C for 48 h, and minimal inhibitory concentration was measured in the growth in the form of turbidity. The ciprofloxacin was used as reference drugs for the antibacterial study while ketonaxol was used for antifungal study [37].

2.4. Statistical analysis

All Data were expressed as the means ± SEM (standard error of mean), of triplicate determination. Student's t-test was applied to determine the significance of the difference between the control group and the test compounds.

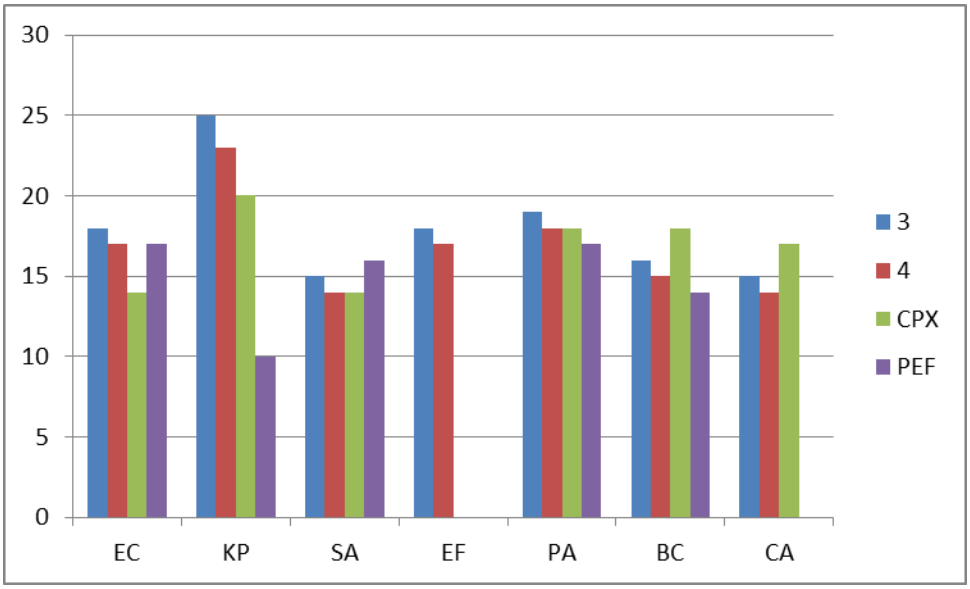
3. Results

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

3.1.1. Control drugs

- Ciprofloxacin (CPX) for bacteria
- Ketonaxol (PEF) for fungus
  - Compound 3 (3)

- Compound 4 (4)



The various Microorganism used in X–axis, SA = *Staphylococcus aureus*, BS = *Bacillus species*, EC = *Escherichia coli,* KP = *Klebsiella pneumonia,* EF = *Enterococcus feacalis*, PA= *Pseudomonas aeriginosa* and CA = *candida albicans.* The Zone of inhibition of the Microorganism in the Y–axis.

Figure 2 The effect of Compounds toward studied bacteria

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**
3	Ethanol	$C_{15}H_{12}N_2O_2S$ (284)	62.20	5.18
			62.10	4.98
4	Ethanol	$C_{16}H_{14}N_2O_2S$ (298)	64.41	4.73
			64.40	4.71

Table 2 ^{1}H-NMR of Synthesized compounds

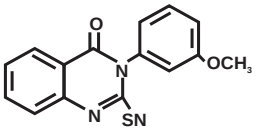
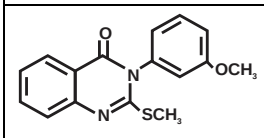
Compound No	**δ (ppm)**
 (3)	3.10 (s, 3H, OCH3), 7.30-7.91 (m, 8H, ArH), 10.52 (br s, 1H, NH)
 (4)	2.85 (s, 3H, SCH3), 3.34 (s, 3H, OCH3), 7.23-7.72 (m, 8H ArH)

Table 3 13C-NMR of Synthesized compounds

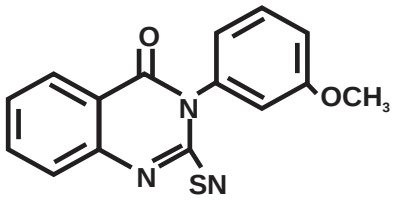
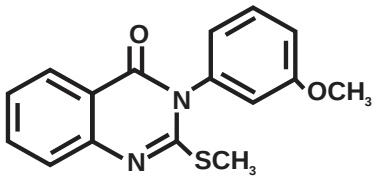
Compound No	δ (ppm)
 (3)	51.92(CH3), 100.04 (CAr), 168.27 (CAr), 3311 (NH), 1691 (C=O), 1211 (C=S)
 (4)	22.57(CH3), 56.81(CH3), 105.65(CAr), 160.26(CAr), 169.02 (C=O), 3313 (NH), 1212 (C=S)

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

Test Organism	Compound 3	Compound 4
Escherichia coli	12.00	11:00
Biscillus Species	7.00	6.00
Staphylococcus Avreces	7:00	6:00
Klebsiella pneumonia	12:00	11.00
Enterococcus Feacalis	8:00	7:00
Pseudomonas aeriginosa	12.00	10.00
Candida albicans	–	–

4. Discussion

Synthetic route depicted in Scheme (1) outline the chemistry part of the present work. The key intermediate 3-(3-methoxyphenyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (4) was obtained by reacting 3-methoxy aniline (1) with carbon disulphide and sodium hydroxide in dimethyl sulphoxide to give sodium dithiocarbamate, which was methylated with dimethyl sulfate to afford the dithiocarbamic acid methyl ester (2). Compound 2 on reflux with methyl anthranilate (3) in ethanol yielded the desired 3-(3- methoxyphenyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (4) via the thiourea intermediate in good yield (82%).

The synthesized compounds were screened for their in vitro antibacterial activity against *Staphylococcus aureus*, *Bacillus species, Escherichia coli*, *Klebsiella pneumonia*, *Enterococcus Feacalis, Pseudomonas aeriginosa* and *Candida albicans*.. The results of antibacterial activity depicted in Table. 1 indicates that the test compounds inhibited the growth of the bacterial in varying degree. Compounds with proton substituents to the sulphur showed higher antibacterial activity over the methyl substituents to sulphur.

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 3 displayed a

singlet signal at: δ 3.10 attributed to methoxy group. Other singlet appeared at δ7.30 and 7.91 attributed to aromatic protons. Two singlet appeared at δ7.41 and 7.10 attributed to aromatic protons. Another signal appeared at 10.52 which were attributed to the protons of the amino group.

The ^{13}C NMR spectrum of compound 3, revealed signals at δ51.92 attributed to the methoxy group, while the aromatic carbon atoms appeared between δ values 100.04 -168.27 with the carbonyl carbon atom appearing as the highest δ value of 1691.01. Similarly, compound 4 showed signals at δ22.57, and 56.81 attributed to methyl and the methoxy groups respectively, while the aromatic carbon atoms appeared between δ values 105.65-160.26, with the carbonyl carbon atom appearing as the highest δ value of 169.02.

The ^{13}C 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.

The compounds were investigated for their antimicrobial activity. The compounds synthesized exhibited promising antimicrobial activity against *Staphylococcus aureus*, *Bacillus species, Escherichia coli*, *Klebsiella pneumonia*, *Enterococcus Feacalis, Pseudomonas aeriginosa* and *Candida albicans*. In addition, compound 1 showed activity against *Escherichia coli* while compound 3 was active against all the compounds synthesized. Table 3 Showed the MIC of both compounds against the susceptible organisms. Compound 4 had a slightly lower MIC (6 and 11 mg/mL) than compound 3 (6 and 12 mg/kg) against *Staphylococcus aureus*, *Bacillus species, Escherichia coli*, *Klebsiella pneumonia*, *Enterococcus Feacalis, Pseudomonas aeriginosa,* and *candida albicans*. respectively (table 4). This indicated that compound 3 is slightly more active against *Staphylococcus aureus*, *Bacillus species, Escherichia coli*, *Klebsiella pneumonia*, *Enterococcus Feacalis, Pseudomonas aeriginosa,* and *candida albicans* to compound 4.

5. Conclusion

The present study has showed that the quinazolinone derivatives 3 and 4 have antibacterial activities. Compounds 3 and 4 showed activity against: *Staphylococcus aureus*, *Bacillus species, Escherichia coli*, *Klebsiella pneumonia*, *Enterococcus Feacalis, Pseudomonas aeriginosa,* and *candida albicans*. Compound 3 has a higher activity against all the synthesized compounds compared to compound 4. Compound 3 has a higher antibacterial activity compared to Compound 4 and the control drugs, Ciprofloxicin (CPX) and Ketonaxol (PEF).

Compliance with ethical standards

Acknowledgment

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Disclosure of Conflict of interest

The author declares no conflict of interest.

Authors' 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 them.

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