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Synthesis and Analgesic 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).

Osarumwense Peter Osarodion

Department of Chemical Science, Ondo State University of Science and Technology, Okitipupa, Ondo State, Nigeria.

***Corresponding Author**: Osarumwense Peter Osarodion, Department of Chemical Science, Ondo State University of Science and Technology, Okitipupa, Ondo State, Nigeria.

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Abstract

4(3H)-quinazolinone rings have been reported to possess different biological activities such as antibacterial, antifungal, antitubercular, antiviral, anticancer. These activities also include antihypertensive, diuretic, antimicrobial, pesticidal, anticonvulsant, anaesthetic and sedative activities, anti-malarial, and anti-diabetic. 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. When tested for their in vitro analgesic activity using acetic acid induced induced writhing in mice, the compounds had Analgesic activity. The compounds exhibited significant analgesic activity in the range of 74.67 - 83.80% in comparison to control. From our findings, the compounds synthesized have higher analgesic activities as compared to the standard analgesic drug.

Keywords: *Recurrent diabetic foot ulcer, expert opinion*

Introduction

Quinazolinones and quinazolines are noteworthy in medicinal chemistry, because of wide range of their antibacterial, antifungal [1,2,3,4,5.6], antiinflammatory [7,8], antimalarial [9], anti-HIV [10], antiviral [10,11], antituberculosis [1, 12], (1,12) properties and also their inhibitory effects on thymidylate synthase [1,2,3,4,5.6], poly-(ADP-ribose) polymerase (PARP) [15, 16, 17], and thyrosine kinase [18, 19]. There are several approved drugs with quinazoline structure in the market such as, prazosin hydrochloride, doxazosine mesylate and terazosine hydrochloride [20, 21].

In the early 1900s, Paul Ehrlich, the legendary German chemist, initiated the use of drugs for infectious diseases. He developed methods for screening a series of chemicals for their potential activity against diseases. The term ‘‘chemotherapy’’, which means the use of chemicals to treat disease, was also coined by him [22].

The synthetic drugs were hugely used in early twentieth century (1900-1930s). But the use of synthetic drugs for treating microbial diseases reduced after the discovery and development of antibiotics. A paradigm shift in therapeutics for treating bacterial diseases took place after the industrial production of penicillin and succeeding development of other antibiotics. There was extraordinary decline in encumber of disease due to large-scale use of these antibiotics [23].

Hence, a general opinion was generated among citizens and policy-makers that infectious diseases would not produce significant problem in the future. But to everyone’s surprise, in the last few decades the historical statement, made by the surgeon-general William H. Stewart in the US Congress (1969)- “It is time to close the book on

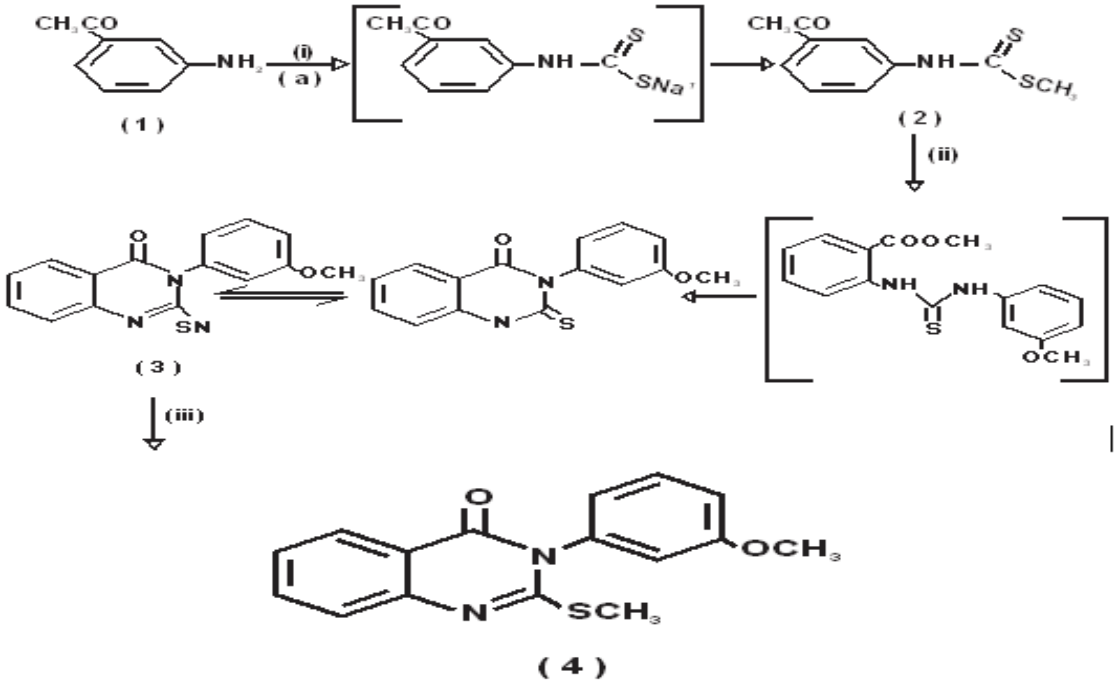
infectious diseases", has not only been reversed but left least possibility of the closure of the said book [24].

These findings prompted the author to synthesis these quinazolinone derivatives with the aim of obtaining more precise information about the course of the reaction and determine the Analgesic properties.

Materials and Methods

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 1H 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.



Scheme 1

i = CS2/NaOH

a = DMSO

ii = Methyl Anthranilate / EtOH, Δ

iii = NaOH / EtOH, (CH3)2SO4

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+].

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.

Pharmacological evaluation

Swiss mice (30 - 40 g) of both sexes were used. The animals were maintained under standard diet and water. Test compounds were administered orally at dose levels. Ethic approval of animal use was obtained from ethics committee of the faculty of pharmacy, University of Benin, Benin City Nigeria.

Acetylsalicylic acid (100 mg/kg) was used as standard in the analgesic assay. There was a dose dependent decrease in writhing which was significant ($p < 0>$

Analgesic activity

The acetic acid induced abdominal constriction method is widely used for the evaluation of peripheral antinociceptive activity [21]. Swiss albino mice (30 – 40 g) were divided into five groups of 5 animals per group of both sexes (pregnant females excluded) and were given a dose of a test compound. Animals in group I received distilled water per oral to serve as control. Group II, III and IV were administered the compounds at doses of 100 mg/kg body weight respectively per oral. Group V animals were treated with acetylsalicylic acid (100 mg/kg body weight) by same route. After one hour of treatment, animals were administered 0.6

Results

Table 1: Characterization and physical data of synthesized compounds

Compound No	Solvent	Formula M. wt	Analysis% Calc/Found	
			C	H
3	Ethanol	$C_{15}H_{12}N_20_2S$ (284)	62.20 62.10	5.18 4.98
4	Ethanol	$C_{16}H_{14}N_2O_2S$ (298)	64.41 64.40	4.73 4.71

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

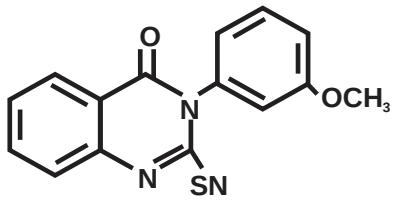
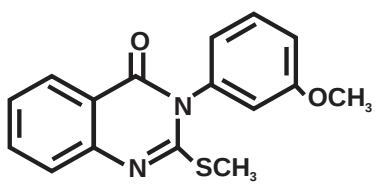
Compound No	δ (ppm)
 (3)	3.10 (s, 3H, OCH3), 7.30-7.91 (m, 8H, ArH), 10.52 (br s, 1H, NH)
 (4)	2.85 (s, 3H, SCH3), 3.34 (s, 3H, OCH3), 7.23-7.72 (m, 8H ArH)

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Table 3: ^{13}C-NMR of Synthesized compounds

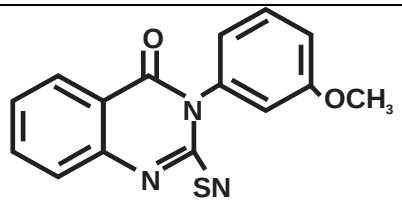
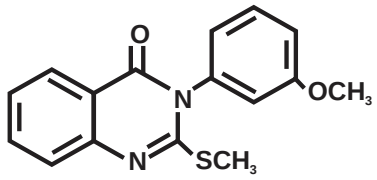
Compound No	δ (ppm)
 (3)	51.92(CH3), 100.04 (CAr), 168.27 (CAr), 3311 (NH), 1691 (C=O), 1211 (C=S)
 (4)	22.57(CH3), 56.81(CH3), 105.65(CAr), 160.26(CAr), 169.02 (C=O), 3313 (NH), 1212 (C=S)

Table 5: Effect of the test compounds on acetic acid induced writhing in mice.

Compound No	Does mg/kg p.o)	Numbers of writhing (per 20 min)	% Inhibition
3	*20* *40*	*47.41 ± 0.11* *32.40± 0.22*	*35.78* *57.54*
4	*20* *40*	*31.05± 2.14* *22.16± 0.15*	*59.49* *72.38*
TWEEN 80	*0.2ML*	*69.00 ± 0.12*	
Acetylsalicylic acid		*22.50 ± 3.07*	*67.39*
Indomethacin	*10*	*14.80 ± 4.95*	*78.55*

Values are meant ± S.E.M; P<0.001, significantly different from control, paired t-test (n=5), P.O = per oral.

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 singlets 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 analgesic activity. The compounds synthesized exhibited promising analgesic activity In addition, compound 3 showed higher activity than compound 4. Table 3

Conclusions

In summary, synthesis of new series of 1-(4-oxo-3-(3- methoxyphenyl)-3H-dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazides has been described. These derivatives have exhibited significant analgesic activity. The compounds exhibited the analgesic activity and offers potential for further optimization and development to new antitubercular agents.

The present study has showed that the quinazolinone derivatives 3 and 4 have analgesic activity. Compounds 3 showed higher activity compared to the control drugs, indomethacin and acetylsalicyclic acid, which is a standard analgesic drug.

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Conflicts 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 me.

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