Synthesis And Anagesic activities of Quinazolin-4(3H)-One, 2-Methyl-4(3H)-Quinazolinone and 2-Phenyl-4(3H)-quinazolin-4(3H)-one

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ABSTRACT

Background: Objective: The current study is aimed at the synthesis of these quinazolinone derivatives quinazolin-4(3H)-one, 2-Methyl-4(3H)-quinazolinone and 2-Phenyl-4(3H)-quinazolinone and evaluate them for their anagesic activity. Method: The condensation of 2-amino-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 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 unequivocally confirmed by means of infrared, Nuclear Magnetic Resonance (1H and 13C), Gas Chromatography Mass Spectrophotometer and Elemental analysis. The synthesized compounds were screened for their analgesic activity. Compounds 1, 2 and 3 showed significant analgesic activity. Discussion: Compound 1 was characterized by the absence of methyl group and the presence of methyl group for compound 2. The test investigated compounds exhibited significant analgesic activity when compared with the control test sample. The compounds synthesized exhibited promising analgesic activities against . Conclusion: The compounds have high analgesic activity. Compound 3 has a higher activity compared to Compound 2 and compound 2 has a higher analgesic activity compared to compound 1. Compound 3 has a higher analgesic activity compared to the standard drugs Aspirin and Indomethacin.

Keywords: quinazolin-4(3H)-One, 2-Methyl-4(3H)-quinazolinone and 2-Phenyl-4(3H)-quinazolin-4(3H)-one

1. INTRODUCTION

Pain in community-dwelling adults is a major public health problem. Epidemiologic studies estimate that the prevalence of chronic pain in the general population ranges from 7% to 55%.[1-4] Regrettably, people in pain must often make difficult choices about pain relief therapy, because most treatment options for pain management include the use of analgesics and adjuvant medications that may have adverse side effects, are often unavailable or costly, or trigger fears of addiction. A few studies have examined the attitudes of the public toward pain in general, but research on the factors contributing to the undertreatment of pain is lacking.[1-4]

An analgesic, or painkiller, is any member of the group of drugs used to achieve analgesia-relief from pain.[5] Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from anesthetics, which reversibly eliminate sensation, and include Paracetamol [known in the US as Acetaminophen or simply APAP], the non-steroidal anti-inflammatory drugs [NSAIDs] such as the salicylates, and opioid drugs such as morphine and opium. In choosing analgesics, the severity and response to other medication determines the choice of agent; the World Health Organization [WHO] pain ladder.[6] Analgesia due to blockade of pain nerve sensitizing mechanism induced by bradykinin, TNFα, ILs.[7]

Literature survey revealed the versatile biological activities of quinazolinone derivatives.[8] It has been established that quinazolines possess antiviral[9], antifungal[10], antiallergic[11], antitumor[12], and anti-diabetic activities.[13] In the recent past, quinazolines were reported to exhibit pronounced coronary vasodilatory.[14] and histamine receptor type 3
invers agonist. Various researchers have reported the antibacterial activity of quinazolinone derivatives.

Quinazolinone and its derivatives are a 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 shown antitumor, anticonvulsant, antitubercular activities, anti-inflammatory, analgesic, antimicrobial and anticoagulant activities.

Quinazolinones have been frequently used in medicine, such as quinethazone and metolazone and are used in medicine as diuretics while prazosin is a vasodilator, which is also used as an antihypertension drug. Quinazolinones are also a class of drugs which function as hypnotic/sedatives that contain a 4-quinazolinone core. Their use has also been proposed in the treatment of cancer.

The synthesized compounds were screened for their analgesic activity using the acetic acid induced abdominal constriction method which is widely used for the evaluation of peripheral antinociceptive activity. The compounds synthesized display analgesic activity. Compounds 1, 2, and 3 showed significant analgesic activity.

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Synthesis Of 4-(3H)-Quinazolinone (1)

Anthranilamide (0.68g (0.005mol) and triethyl orthoacetate (0.81g (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 under 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°C.

Synthesis Of 2-Methyl-4-(3H)-Quinazolinone (2)

Anthranilamide (0.68g (0.005mol) and triethyl orthoacetate (0.81g (0.005mol) were refluxed following the procedure for 1 above. Yield was 0.64g (94%), mp: 231-233°C.

Synthesis Of 2-Phenyl-4-(3H)-Quinazolinone (3)

Anthranilamide (0.68g (0.005mol) and triethyl orthobenzoate (1.12g (0.005mol) were refluxed following the procedure for 1 above. Yield was 0.57g (83%), mp: 198-200°C.

Pharmacological Evaluation

Swiss mice (18-23g) of both sexes were used. The animals were maintained under standard diet and water. Test compounds were administered orally at dose levels. Ethics committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Analgesic activity

The acetic acid induced abdominal constriction method is widely used for the evaluation of peripheral antinociceptive activity (Gene et al., 1998). It is very sensitive and able to detect antinociceptive effects of compounds at dose levels that may appear inactive in other methods like the tail-flick test (collier et al., 1968; Bentley et al., 1981).

Local peritoneal receptors are postulated to be partly involved in the abdominal constriction response (Bentley et al., 1983).

The method has been associated with prostanoids in general, e.g. increased levels of PGE2 and PGE2a in peritoneal fluids (Derardt et al., 1980) as well as lipooxygenase products by some researchers (Levini et al., 1984; Dhara et al., 2000). Indomethaun (10mg/kg) was administered orally as reference drug while 10% olive oil was used as negative.

Statistical analysis

All data were expressed as the mean ± SEM, the student ' 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}N_{04} (221.209) | 62.20 5.18 |
| 2           | Ethanol | C_{11}H_{13}N_{03} (235.239) | 56.11 5.53 |
| 3           | Ethanol | C_{11}H_{13}N_{03} (235.239) | 56.11 5.53 |

Table 2: $^{13}$C-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: $^1$H-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 |

Characterization of 4-(3H)-Quinazolinoine (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=O), Anal Cal. for C$_{8}$H$_{6}$N$_{2}$O: C 66.12, H 4.13, Found: C 67.42 H 4.99.

Characterization of 2-Methyl-4(3H)-Quinazolinoine (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 172.18, 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=O), 3015 (CH aromatic), 1693 (C=O), Anal Cal. for C$_{9}$H$_{8}$N$_{2}$O: C 67.42, H 4.99, Found: C 68.96 H 4.77.

Characterization of 2-Phenyl-4(3H)-Quinazolinoine (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=O), Anal Cal. for C$_{14}$H$_{10}$N$_{2}$O: C 75.61, H 4.50, Found: C 75.10 H 4.11.
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 methyl group which was absent in compound 1. Other signals 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 1H NMR 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, 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.

Also, 1H NMR spectrum of compound 2 showed a characteristic signal at δ 2.56 (singlet) corresponding to methyl group. Two singlets appeared at 67.41 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 the NH and presence of νC=H 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.
Conflict of interest

The authors declare no conflict of interest.

Authors’ declarations

The authors hereby declare 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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