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Analgesic activity of newly synthesized 7-chloro–2–methyl-4H–benzo[d] [1,3]–oxazin–4–one and 3–amino-7-chloro-2–methyl-quinazolin-4(3H)–one

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Abstract. The current study is aimed at the analgesic evaluation of quinazolinone derivatives. The quinazolinone derivatives 7-chloro-2-methyl-4H-benzo[d][1,3]-oxazin-4-one and 3-amino-7-chloro-2-methyl-quinazolin-4(3H)-one were evaluated pharmacologically for their *in vivo* analgesic activities by acetic acid induced writhing in mice. The compounds exhibited significant analgesic activity in the range of 74.67 - 83.80% in comparison to control.

Keywords: 3-amino-7-chloro-2-methyl-quinazolin-4(3H)-one, 7-chloro-2-methyl-4H-benzo[d][1,3]-oxazine-4-one, quinazolin-4(3H)-one, analgesic activity.

1. Introduction

Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities [1].

Researchers have already determined many of the therapeutic activities of quainazoline derivatives, including anti-cancer [2-4], anti-bacterial [5-8], anti-cytotoxin [9], anti-spasm [10], anti-tuberculosis [11], anti-oxidation [12], anti-obesity [13], anti-psychotic [14]. 2, 3–Disubstituted quinazolin-4(3H) – ones have been discovered with favorable analgesic and anti-inflammatory function [15, 16].

Alagarsamy *et al.* reported several 2, 3-disubstituted quinazoline analogues with potent analgesic and anti-inflammatory activity, such as 2 – phenyl-3-substitued quinazolines [17], 2-methyl-3-substituted quinazolines [18], 2-methyl-thio-3-substituted quinazoline [19], and 2, 3-disubstituted quinazolines [18].

The aim of this work was to determine the analgesic activity of 7-chloro-2-methyl-4H-benzo[d] [1,3]-oxazin-4-one and 3-amino-7-chloro-2-methyl-quinazolin-4(3H)-one.

2. Experimental

2.1. Materials and methods

All reagents and solvents were purchased from Sigma-Aldrich chemical supplier in Germany.

2.2. Synthesis

The synthesis of 7-chloro-2-methyl-4H-benzo[d] [1,3]-oxazin-4-one (1) and 3-amino-7-chloro-2-methyl-quinazolin-4(3H)-one (2) have been describe in our previous study [20]. This involves the condensation of 0.76 g (0.005 mol) of 4-chloroanthranilate with 1.02 g (10 mL, 0.01 mol) acetic anhydride in 30 mL ethanol medium to yield 7-chloro-2-methyl-4H-benzo[d][1,3]-oxazin-4-one (1), and equimolar amounts of 7-chloro-2-methyl-4H-benzo[d][1,3]-oxazin-4-one (1.61 g, 0.01 mol), and hydrazine hydrate (0.51 g, 0.01 mol) were heated under reflux in 30 mL ethanol to give pure 3-amino-7-chloro-2-methyl-quinazolin-4(3H)-one (2).

2.3. 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 ($p < 0.05$) at 400 mg/kg compare to control.

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 % acetic acid (10 mL/kg body weight) interaperitoneally. The

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number of writhing movements was counted for 30 minutes [22].

2.4. Statistical analysis

All data were expressed as the mean ± S.E.M. (standard error of mean), the student *t*-test was applied to determine the significance of the difference between the control group and the test compounds.

3. Results and discussion

The *in vivo* analgesic activity of 7-chloro-2-methyl-4[H]-benzo[d][1,3]-oxazin-4-one (1) and 3-amino-7-chloro-2-methyl-quinazolin-4(3H)-one (2) was determined using mouse writhing assay and the results obtained are summarized in Table 1.

Table 1. Effect of the test compounds on acetic acid induced writhing in mice.

Compound No.	Doses mg/kg (P.O.)	Numbers of writhing (per 20 min)	% Inhibition
1	20 40	36.11 ± 0.18 20.42 ± 2.45	74.67 77.41
2	20 40	27.56 ± 1.16 16.01 ± 0.22	79.06 83.80
TWEEN 80	0.2 mL	69.00 ± 0.12	-
Acetylsalicylic acid	-	22.50 ± 3.07	67.39
Indomethacin	10	14.80 ± 4.95	78.55

Where: values are mean ± S.E.M;
$p < 0.001$, significantly different from control, paired *t*-test ($n = 5$);
P.O = per oral.

Compound 2 showed the highest activity at 40 mg/kg compared to the other compound 1, acetylsalicylic acid and indomethacin. It may be that the substitution of amino group at position three increase the activity. These compounds synthesized have a higher activity than acetylsalicyclic acid, which is a standard analgesic drug.

The acetic acid induced abdominal constriction method is widely used for the evaluation of peripheral antinociceptive activity [23]. 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 [23, 24]. Local peritoneal receptors are postulated to be partly involved in the abdominal constriction response [25]. The method has been associated with prostanoids in general, *e.g*. increased levels of PGE_2 and PGE_{2a} inter peritoneal fluids [26], as well as lipoxygenase products by some researchers [27, 28]. Indomethacin (10 mg/kg) was administered orally as reference drug while 10% olive oil was used as negative.

4. Conclusion

Compound 1 has analgesic activity of 74.67% and 77.41% at 20 mg/kg and 40 mg/kg dose levels, while compound 2 has analgesic activity of 79.06% and 83.80% at 20 mg/kg and 40 mg/kg dose levels.

The compounds have high analgesic activity. Compound 2 has a higher analgesic activity compared to compound 1 and also has a higher analgesic activity compared to Indomethacin, a standard analgesic drug. It is therefore concluded that compound 2 could be a potential analgesic and a tool in pharmaceutical drug delivery.

Conflict of interest

The author declare no conflict of interest.

Author's declaration

The author 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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