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Short Communication

Synthesis and Analgesic Activity of 5,6-difluoro-2-Methyl-4H-benzo(d) (1,3)-Oxazin-4-one and 3-Amino-5,6-difluoro-2-Mehtyl-quinzolin 4(3H)-One

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Abstract

The current study is aimed at the synthesis and Antibacterial evaluation of quinazolinone derivatives. The condensation of Methyl-2-amino-5,6-diflorobenzoate with acetic anhydride yielded the cyclic compound 2-methyl 5,6-diflorobenzo [d] [1,3]-oxazine-4-one which further produce 3-Amino-2-Methyl 5,6-difloro quinazolin-4(3H)-ones via the reaction with hydrazine hydrate. The compounds synthesized were unequivocally confirmed by means of Infrared, Nuclear Magnetic Resonance (^{1}H and ^{13}C), *Gas Chromatography Mass Spectrophotometry* and Elemental analysis. The synthesized compounds were screened against various strains of *microorganism, Staphylococcus aureus, Bacillus species, Escherichia coli, Klebsiella pneumonia, Serratia Marcensces,* and *Candida albicans.* The compounds 1and 2 showed significant activity as an Anagesic agent.

Keywords: 5,6-difloro-2-methyl-4H-benzo [d] [1,3]-oxazine-4-one; 3-amino-5,6-difloro-2-methyl-quinazolin-4(3H)-one; Nucleophile; Quinazoline-4(3H)-one; Analgesic

Introduction

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Among a wide variety of nitrogen heterocycles that have been explored for developing role in medicinal chemistry and subsequently have emerged as a pharmacophore [1].

Quinazolinone derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceutical and agrochemicals. Several reports have been published on the biological activities of quinazolinone derivatives, including their anti-inflammatory [1-7], antimalarial [8-16], anticonvulsant [17-20], and antitumor [21,22], activities.

Quinazolinone peptides were reported for their anti-inflammatory, antioxidant, anthelminthic, antibacterial and antifugal activities [23].

Materials and methods

General Experimental Procedure

All reagents and solvents were purchased from sigma-Aldrich, in Germany. Melting points were determined on a kofler hot stage apparatus and were uncorrected. IR spectra were recorded on a Buck scientific IR M500 instrument. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d6 at 400 MH_z with HAZ VOLATILE V2. M Chemical shifts Sare reported in ppm relative to tetramethylsilane. Gas chromatography mass spectra were obtained on a Finingan MAT 44S mass spectrophotometer operating at 70eV. Elemental analysis agreed favourably with the calculated values. Analytical thin layer chromatography (TLC) was used to monitor the reactions.

Elemental Analysis

Table 1: Characterization and Physical data of Synthesized Compounds.

Compound No	Solvent	Formula M. wt	Analysis% Calc/ Found	
			C	H
1	Ethanol	$C_9H_6F_2N0_2$	55.22	3.08
		(240.053)	55.21	3.07
2	Ethanol	$C_9H_8F_2N_3O$	51. 53	3.83
		(254.083)	51. 52	3.82

The compositions of the compounds are summarized in (Table 1). The C and H contents (both theoretically calculated values and actual values) are indicated.

General procedure for the synthesis of 5,6-difloro-2-methyl-4H-benzo [d] [1,3]-oxazine-4-one, (1)

This involved the condensation of 0.76g (0.005mol) Methyl 2-amino-5,6-diflorobenzoate with 10ml, 1.02g, (0.01mol) acetic anhydride in 30ml ethanol medium. The reaction was heated under reflux with stirring using a magnetic stirrer until the reaction mixture showed no trace of starting material when the TLC was developed (2 hours). Yield was 2.01g (96%), mp: 149-151°C [24].

General procedure for the synthesis of 3-amino-5,6-difloro-2-methyl-quinazoline-4(3h)-one (2)

Equimolar amounts (1.61g, 0.01mol) of 5,6-diflöro-2-methyl-4H-benzo [d] [1,3]-oxazine-4-one, and (0.51g, 0.01mol) hydrazine hydrate were heated under reflux in 30ml ethanol with stirring using a magnetic stirrer until the reaction mixture showed no trace of starting material when the TLC was developed (3 hours). At the end of the reaction, the reaction mixture was concentrated in vacuum under reduced pressure using rotary evaporator. The white precipitate formed was then filtered, washed three times with 20ml of distilled water [20ml x 3]. The white crystals were dried and recrystallized from dimethylformamide (DMF) to give pure 3-amino-5,6-difloro-2-methyl-quinazolin-4(3H)–one. Yield was 1.50g(95%) mp : 138-140°C [25].

Chemistry

Table 2: ^{13}C-NMR of Synthesized Compounds.

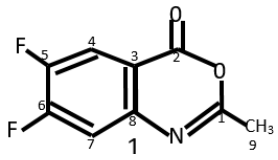
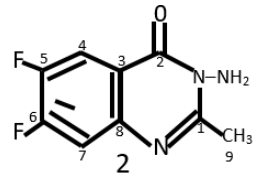
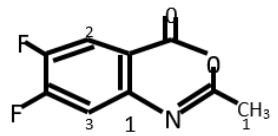
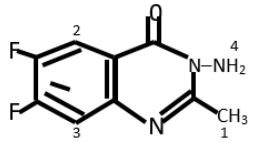
Compound No	δ (ppm) Carbon atom number
	155.15(C-1), 160.48(C-2), 120.14(C-3), 128.09(C-4), 112.71(C-5), 112.61(C-6), 122.15 (C-7), 148.10 (C-8), 24.10 (C-9)
	154.51(C-1), 160.14 (C-2), 120.28(C-3), 128.21 (C-4), 112.41 (C-5), 112.14 (C-6), 122.20 (C-7), 148.05(C – 8), 24.15 (C- 9).

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

Compound No	δ (ppm) Carbon atom number
	7.21 – 7.96 (m, 3H, ArH), 2.52 (s, 3H CH§)
	7.51 – 7.14 (m, 3H, Ar-H), 5.03 (s, 2H), 2.53 (s, 3H, CH_3)

The introduction of 2-amino substituent is a successful strategy to improve the chemical stability of benzoxazinone. Due to the pharmacological activities of 4(3H)-quinazolinone derivatives, 2,3-disubstituted derivative of quinazoline-4-one were synthesized via the interaction of the benzoxazinone derivative with nitrogen nucleophile with the aim of obtaining more pricise information about the course of the reaction and some interesting pharmaceutical compounds. The reaction of 4, 5-disubstituted derivatives of methylanthranilate and acetic anhydride yielded the cyclic compound 5,6-diforo-2-methyl-4H-benzo[d] [1,3]-oxazin-4-one. The reaction of this compound with hydrazine hydrate yielded 3-amino-5,6-difloro-2-methyl-quinazoline-4(3H)-one (Table 1-3).

Characterization of 5,6-difloro 2-methyl-4H-benzo [d] [1,3] -oxazin-4-one.(1)

^{1}H NMR (400MHz, DMSO) δ 7.21 – 7.96 (m, 3H, ArH), 2.52 (s, 3H $CH_§$), ^{13}CNMR (400MHz, DMSO) δ 160.48, 155.15,148.10, 128.09, 120.14, 122.15, 112.71, 112.61, 24.10,. IR (KBr,cm^1) 3135, (NH2), 3018 (CH aromatic), 2951, 2871, 2718 (CH aliphatic),1730(C=0),1150 (C-0).Anal. Cal for $C_9H_6BrN0_2$; C 55.21; H 3.07. Found: C 55.22, H 3.08. Yield was 2.01g (96%), mp: 149-151°C.

Characterization of 3-amino- 5,6-difloro 2-methyl-quinazoline-4(3H)-one. (2).

^{1}H NMR (400 MHz, DMSO) δ 7.51 – 7.14 ($_m$, 3H, Ar-H), 5.03 (s, 2H), 2.53 (s, 3H, CH_3), ^{13}C NMR (400MHz, DMSO) δ 160.14, 154.51, 148.08, 128.21, 122.20, 120.28, 112.41, 112.14, 24.15, IR (KBr,cm^1)3350(NH_2),1685 (C=0),1620 (C=N), Anal. Cal. for $C_9H_8BrN_30$; C 51. 52, H 3.82; Found, C 51.53, H 3.83.Yield was 1.00g (95%) mp: 98-100°C.

Discussion

The present study reported the synthesis of two derivatives of quinazolinone, 5,6-difluoro-2-methyl-4H-benzo [d] [1,3]-oxazin-4-one,(1) and 3-amino-6,7-difluoro-2-methyl quinazolin-4(3H)-one(2).The compounds were investigated for their Antimicrobial activity.

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 1 displayed a singlet at δ 3.68 which was due to methyl group. Other singlets appeared at δ7.16 and 6.41 attributed to aromatic protons. Also, ^{1}H NMR spectrum of compound 2 showed a characteristic signal at δ 2.58 (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 1 were characterized by absence of υ NH2and presence of υ C-O stretch in 1102cm^{-1} region of the compound. Compound 2 was characterized by absence of υ C-0 and presence of υNH2 in 3301cm^{-1} region of the compound.

The ^{13}C NMR spectrum of compound 1, revealed signals at δ16.95, attributed to methyl group, while the aromatic carbon at-

oms 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, attributed to methyl group, 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 compounds synthesized exhibited promising antimicrobial activities against Staphylococcus aureus, *Bacillus species, Pseudomonas Aeroginosa, Escherichia coli, Klebsiella pneumonia,* and *candida albicans* stock cultures.

Conclusion

The present study has showed that the quinazolinone derivatives 1 and 2 have antibacterial activity. Compound 2 has a higher activity against Serratia Marcescens compared to Compound 1.

Conflict of interest

The author declares no conflict of interest.

Funding

No fund was obtained during the research.

Author 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.

Ethics Approval and Consent to Participate

Ethic approval, consent to participate and the procedure used was approved by the Ethic approval committee of Ondo State University of Science and Technology, Okitipupa, Ondo State, Nigeria.

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Declaration Statement

The author declares there is no conflict of interest.

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