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Synthesis, Spectroscopic Studies and Antifungal Activity of 7 -amino-4-methyl-quinolin-2(1H)-one

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ABSTRACT
The synthesis of 7-amino-4-methyl-quinolin-2(1H)-one has been successfully carried out, and its structural characterization was perfumed using Fourier Transformed Infrared (FT-IR) and Nuclear magnetic resonance (^{1}H and ^{13}C-NMR) spectroscopic techniques. The compound obtained was off white in colour with percentage yield of 47 and Melting point of 269-272^{o}C. It shows poor solubility in polar and non polar solvents at room temperature but soluble in hot DMSO and DMF. Antifungal evaluation of the compound against a clinical isolate of the fungal strain *Candida albican* with a standard antifungal drug Terbinafine as a positive control demonstrate moderate inhibition of the growth of the organisms with a range of 18.0mm - 20.1mm.

Keywords: Antifungal activity, Characterization, Quinolin-2(1H)-one, Spectroscopy

INTRODUCTION
Quinoline alkaloid family is an important class of heterocyclic compounds which are known for their different biological activity (Kulakarni *et al*., 2006).Quinolin-2(1H)-one derivatives have particularly demonstrated various therapeutic abilities as basis of many medicinal drugs used in the treatment of cancer, heart failure and inflammatory disease (Fujioka *et al*., 1992).

Candida albicans is one of the human pathogenic fungi in most clinical setting (Pappas *et al.*, 2018) that cause both mucosal and deep tissue infections (Sardi *et al.,* 2013; Kovalishyn *et al*., 2014). It is the most virulent specie among *Candida* species and other yeast and the sixth cause of most common nosocomial infection (Sheevani and Aggarwal., 2013). Nosocomial Candida infections have become an increasingly serious problem (Pfaller and Diekema 2007., Pfaller and Diekema 2010) due to the increase in antimicrobial resistance and the restricted number of antifungal drugs (Sardi *et al*, .2013).Ordinarily *Candida albican* can live as harmless commensal in many different body locations precisely the mucous membranes, and in almost half of the population. However, in response to a change in the host environment i.e. weakened immune system due to HIV infections, cancer chemotherapy or neonates, *Candida albicans* can convert from a benign commensal into a disease-causing pathogen, causing infections in the oral, gastrointestinal and genital tracts (ref). For instance *Candida albican* is responsible for painful mucosal infections such as virginities in women and oral pharyngeal thrush in AIDS patients. In certain group of vulnerable patients, it causes severe, life-threatening blood stream infections (Candidemia) and subsequent infections in the internal organs (Joon and Peter, 2011).Women are more susceptible to infections with *Candida albican* when they undergo stress as a result of poor diet, lack of sleep or due to other illness (Nwosu and Djieyep., 2007). Candida infection also causes food intolerance, gall blader infection, emotional symptoms and frequent urination during the day (John, 2010).The use of detergents or douches ,hormonal or physiological can affect the normal viginal flora, consisting of lactic acid bacteria , such as lactobacilli cells causing symptoms of infection such as inflammation (Mardhet *et al*,.2003). In this work synthesis, characterization and evaluation of antifungal activity of 7-amino-4-methyl-quinolin-2(1H)-one has been reported. Although the synthesis of the compound has been reported previously, It was however noted that the structural characterization was partially carried out (Zhang *et al*., 2003), while the antifungal activity has never been reported.

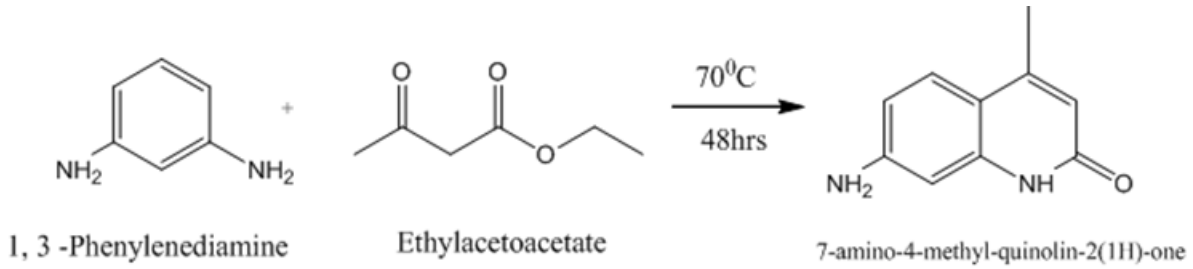
MATERIALS
All chemical used were of analytical grade and purchase from Sigma and Aldrich. FT- IR spectral analysis was recorded on Agilent technology model carry 630 FTIR in the range 4000 – 650Cm^{-1}, ^{1}H-NMR and ^{13}C-NMR were carried out using Agilent Spectrophotometer at 400MHz and 100MHz respectively. Melting point was determined using Stuart automatic melting

point /SMT40/apparatus. *Candida albican* isolates were obtained from Ahmadu Bello University Teaching hospital (ABUTH) and *Candida albican* ATCC 2876 from NIPRD (National Institute for Pharmaceutical Research and Development, Abuja, Nigeria) .Sabouraud Dextrose Agar (SDA) was used as media.

METHODS

Synthesis

1,3-phenylenediamine (2.00 g, 18.49 mmol) and ethyl acetoacetate (2.36 mL, 18.51 mmol) were refluxed for 48h.The solidified mixture was treated methanol (5mL) and filtered to produce an off-white solid product (Scheme 1). The compound was further recrystallized using methanol in accordance with procedure adapted from Zhang *et al.* (2003).



Scheme 1: Synthesis of 7-amino 4-methyl- quinolin-2(1H)-one

Antifungal Assay

The compound was evaluated for activity against *Candida albican* by diffusion method on Sabouraud dextrose agar as medium. It was prepared according to the manufactures instructions, sterilized at 121^0C for 15minutes, poured into sterile Petri dishes and was allowed to cool and solidified. 0.002 mg of the compound was weighed and dissolved in 10 cm^3 of DMSO to obtain a concentration of 200µg/cm^3. This was the initial concentration of the compound used to determine the antifungal activity. The sterilized medium was seeded with 0.1cm^3 of the standard inoculums of the test microbes, the inoculums were spread evenly over the surface of the medium by the use of a sterile swab. Using a standard cork borer of (6mm in diameter), a well was cut at the centre of each inoculated medium. Then 0.1 cm^3 of the solution of the compound of (200µg/cm^3) was then introduced into the inoculated medium. Incubation was made at 37^0C for 72hours, after which the plates of the medium were observed for the zone of inhibition. Subsequently the zone was measured with a transparent ruler and the result recorded in millimeter (mm). The standard drug used as reference was Terbinafine.

RESULTS AND DISCUSSIONS

7 – Amino – 4 – methylquinolin - 2(1H) – one, was obtained as an off-white crystalline solid with a yield of 47% and a relatively high melting point of 273^OC.Furthermore the compound was found to be insoluble in water ,methanol, ethanol, acetone, diethyl ether, Acetonitrile and benzene. But it was found to be soluble in DMSO and DMF.

The Infrared spectral analysis revealed two absorption bands at 3290 and 3310cm^{-1} which are assigned to $-NH_2$ while the peak at 3200cm^{-1} assignable to NH of the amide group. The amide carbonyl stretching vibration ν(C=O) was observed at 1640cm^{-1}. (Figure 1)

The ^{1}H-NMR spectrum (Table1, Figure 2) of 7 – Amino – 4 – methylquinolin - 2(1H) – one in deuterated DMSO-d^6 showed the presence of signals due to aromatic protons at 7.45ppm, 6.55ppm and 6.52ppm suggesting the presence of tri-substituted aromatic ring. Protons associated with the amide, conjugated double bond, amino and methyl groups were observed as singlet at 11.28ppm, 6.03ppm, 5.86ppm, and 2.36ppm respectively.

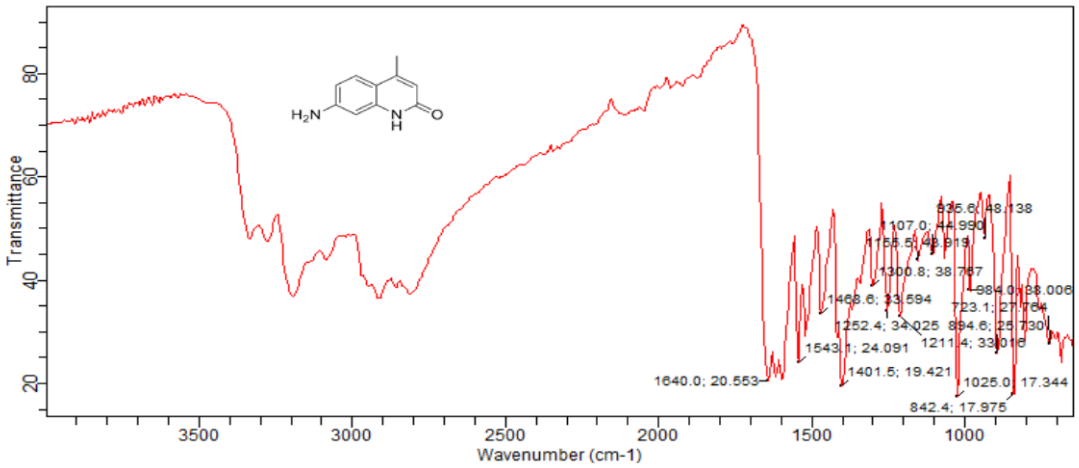


Figure 1: IR spectrum of 7-Amino-4-methylquinolin-2(1H)-one

Table 1: ^{1}H- NMR spectrum of 7-Amino-4-methylquinolin-2(1H)-one

Proton Type	δ(ppm)
NHC=O	11.28
CH	6.03
CH	6.55
CH	7.45
CH	6.52
CH_3	2.36
NH_2	5.86

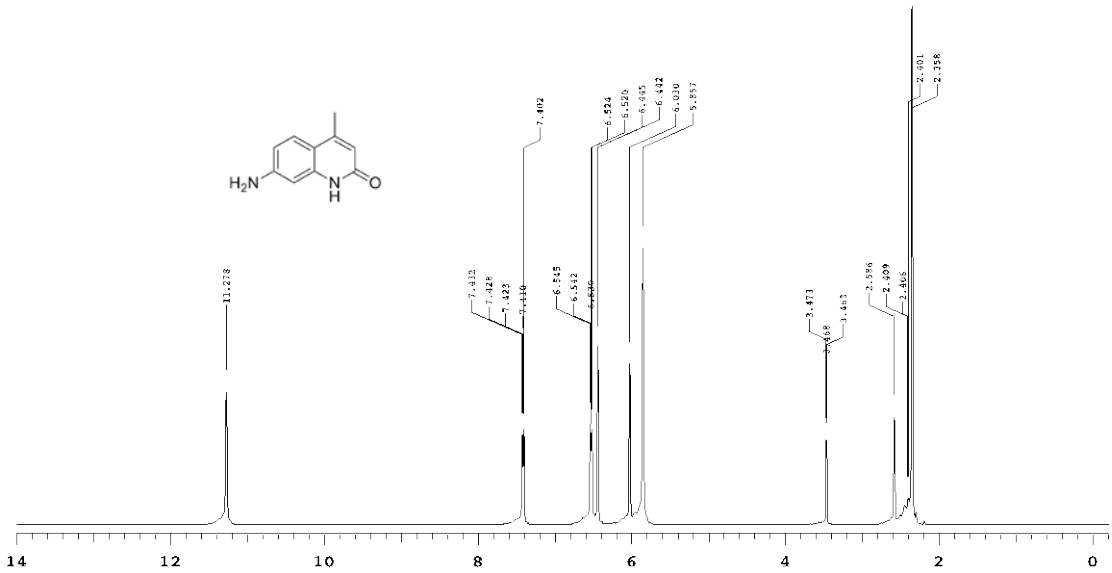


Figure 2: ^{1}H-NMR Spectrum 7-Amino-4-methylquinolin-2(1H)-one

The ^{13}C-NMR data (Table 2, Figure 3) corroborate with the H-NMR spectrum in the confirmation of the presence of aromatic carbon atoms and conjugated double bond carbons (97.3ppm - 151.7ppm range). A prominent signal was observed at 163.0ppm assignable to amide carbonyl carbon while the signal at 19.1ppm was assigned to the methyl group. The antifungal activity of the synthesized compound as zone of inhibition (Table 3) against the isolates demonstrated moderate inhibitory activity when compared with the standard drug, Terbinafine.

Table 2: ^{13}C-NMR spectroscopic data 7-Amino-4-methylquinolin-2(1H)-one

Carbon Type	δ(ppm)
C=O	163.0
CH	115.3
Quaternary C	151.7
CH	126.2
CH	110.9
Quaternary C	148.6
CH	97.3
Quaternary C	111.0
Quaternary C	141.3
CH_3	19.1

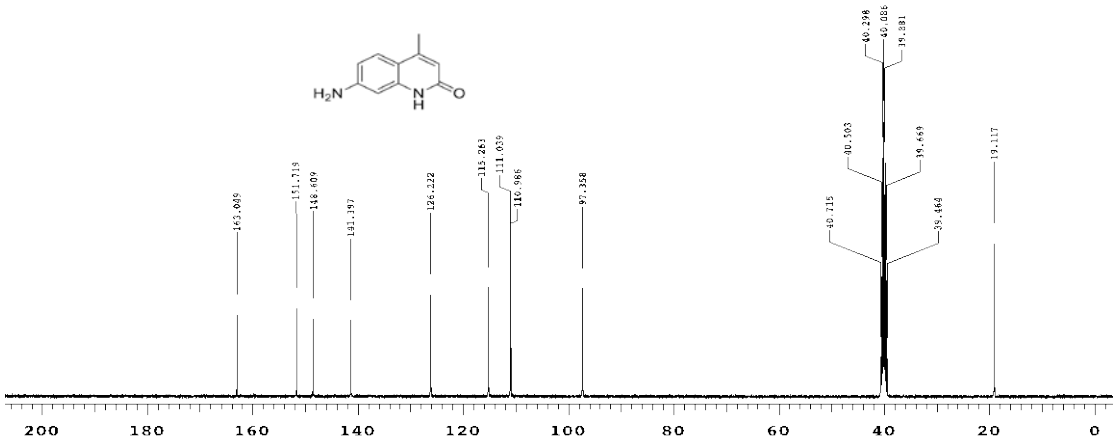


Figure 3: ^{13}C-NMR Spectrum 7-Amino-4-methylquinolin-2(1H)-one

Table 3: Zone of inhibition of 7-amino-4-methylquinolin-2(1H)-one and Terbinafine against test microbes (mm)

Type of organisms	7-amino-4-methylQuinolin-2(1H)-one	Terbinafine
Candida albican (1)	18.0	27.5
Candida albican (2)	17.9	26.0
Candida albican (3)	18.2	26.4
Candida albican (4)	18.3	26.1
Candida albican ATCC 2876	20.1	29.0

CONCLUSION

The synthesis, ^{1}H-NMR and ^{13}C-NMR spectroscopic characterization, and antifungal activity of 7-amino-4-methylquinolin-2(1H)-one has been carried out successfully. It was found for the first time that compound demonstrated some moderate antifungal activity against different *Candida albican* strains.

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