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Single crystal synthesis and structure of 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl) ethanone and antimalarial potential evaluation

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ABSTRACT

In the present investigation, 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl) ethanone was prepared and antimalarial activity was also evaluated. The reactions of phenylacetyl chloride and piperazine in trichloromethane at 60 ºC affording a dione, 2-Phenyl-1-(4-Phenylacetyl-piperazin-1-yl)ethanone (L) furnished a good yield. This compound was characterized by melting point determination, solubility, UV-Vis, FTIR and nuclear magnetic resonance spectroscopy. The crystal structure was confirmed and established by X-ray Crystallography. The afforded dione with molecular weight 322.40 crystallizes in monoclinic space group with lattice type p 21/n with a = 8.227(5), b = 11.689(6), c = 8.9954(5) A⁰, α = 90, β = 102.280(2), γ = 90⁰ and z = 2. Investigation of the antimalarial potential of this compound revealed the effects of sample on parasthemia count of mice infected with plasmodium berghie is dose dependent with 250 mg/kg showing 51.09% and 500 mg/kg having 65.91%. LD_{50} results of the compound show high effective dose since no mortality of mice was recorded even at high dose.

Capsule Summary: 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl) ethanone was prepared, characterized along with antimalarial activity evaluation and the prepared showed promising antimalarial activity.

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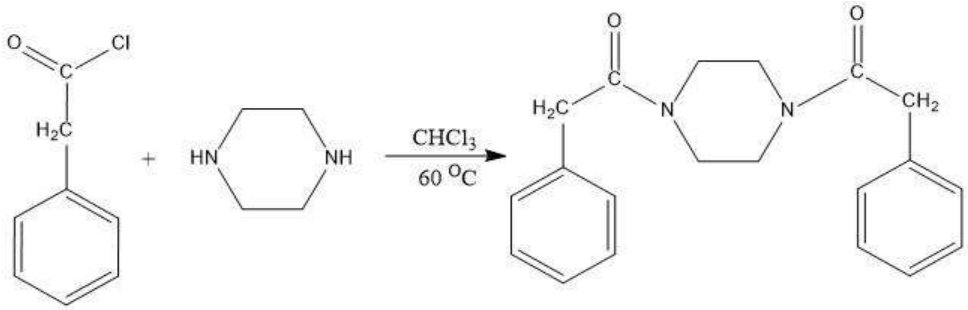
INTRODUCTION

Diones are versatile chemical compounds widely used as agro-chemicals, antidiabetic drugs, aldose reductase inhibitors, anticancer agents, anti-inflammatory drug, antimicrobial and core motifs for a large number of compounds of various applications. Diones derivatized from piperazine bearing phenylacetyl moiety have not been reported nor have their potentials been exploited even though piperazine are excellent reagents for designing bioactive molecules. Piperazine and pyrroline derivatives has been synthesized and evaluated for their capacity to inhibit the growth of *plasmodium falciparum* chloroquine resistant (FCR-3) strain in culture and 1-(4-fluoronaphtal)-3-[4-(4-nitro-2-trifluoromethylphenyl) piperazin-1-yl] propan-1-ol was discovered and reported to be potent on *P. falciparum* (Mendoza et al., 2011). They are wide range of anti-malaria drugs in circulation and the prevalent rate of the disease is on the increase due to multidrug resistance. There is need therefore, to synthesis new compounds which could have curative potency.



Scheme 1: Synthesis of 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl) ethanone (L)

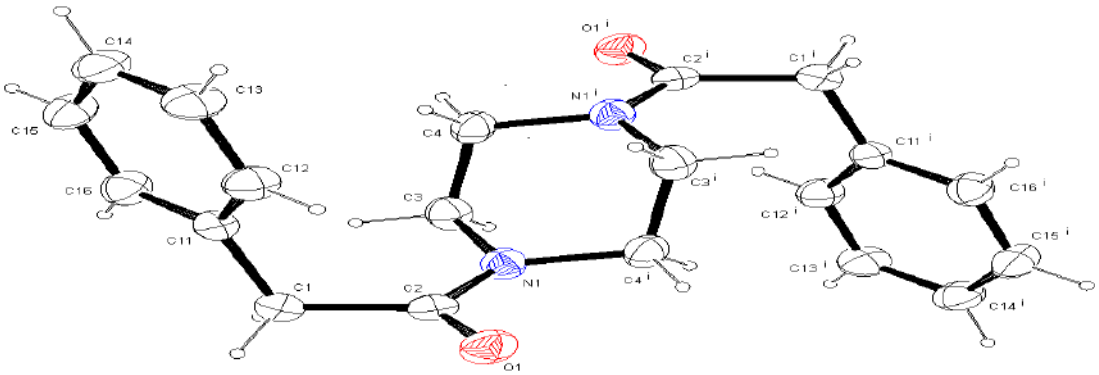


Fig. 1: Single Crystal Structure of 2-Phenyl-1-(4-Phenylacetyl-piperazin-1-yl)ethanone (L) (Deposition No. 2036863)

Based on aforementioned facts, in the present study, a single crystal synthesis and structure of 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl) ethanone and antimalarial potential evaluation.

MATERIAL AND METHODS

Preparation of dione

The study adopted the experimental design. A dione was prepared by coupling phenyl acetyl chloride with piperazine at 60 ^{o}C in chloroform. The compound was characterized by ^{1}H and ^{13}CNMR spectroscopy using Bruker AVIII-400 NMR spectrometer. UV-vis data were obtained in DMSO on Synergy Mx Biotex spectrometer. Infrared spectra were obtained in KBr discs on Perkin Elmer Spectrum ATR100 FT-IR spectrometer. Mass Spectra was generated by Electrospray ionization on Bruker MicroOTOF Mass Spectrometer. Single crystal X-ray diffraction data of L was obtained using Platon geometry (V-220719) diffractometer. The *in vitro* antimicrobial assay was done by Agar well diffusion method. The *in vivo* anti-malarial studies were performed by Peter's method (Peters, 1975). The results were analyzed using one way ANOVA (SPSS) version 20.

Preparation of ligands

The compound 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl) ethanone was synthesized following literature methods (EL-Gahami and Abdalla 2003; Atulkumar et al., 2012; Ming-Chihfang 2013). Phenylacetyl chloride (0.66 cm^3, 5 mmol) was reacted with 0.2 g (2.5 mmol) of piperazin in 50 cm^3 chloroform under reflux at 60 ^{0}C for 2 h. The solution was evaporated at room temperature to obtain the crystals which was purified by recrystallization with diethylether before further use (Scheme 1).

RESULTS AND DISCUSSION

Characterization

The percentage yield of L was 75.20, m.p 140-142, The UV-visible spectra of the compound absorbed at 303 nm, this could be attributed to π-π*transitions and n-π* transition of the lone pair of electrons of the oxygen atom in the ligand in agreement with literature (Eidaroti et al., 2013). FTIR show 3064-2918 cm^{-1} for C-H aromatic, 2726 cm^{-1} for aliphatic C-H and C= O stretch at 1693 cm^{-1} which are in agreement with piperazine substituted carbonyl compounds reported by (da Silva et al., 2010; Man and Sushma, 2012; Guskos et al., 2005). ^{1}H NMR spectra (ppm) revealed phenyl protons signal at 7.5 m, methylene protons at 2.5 (2H, s), piperazine moiety protons at 3.5-3.9 (2H, d). The result is in agreement with report on a novel synthesis of piperazine derivative by (da Silva et al., 2010). ^{13}CNMR spectra (ppm) revealed signals at 126-135 for phenyl carbons and C=O carbons at 175. Mass spectral data (m/z) showed peaks at 322.11 for

the parent molecular ion. The compound crystallized in monoclinic space group with lattice type p 21/n (Figs. 1-4).

Bioactivity potential

The inhibition zone (mm) of the bacteria and fungi strains by L ranges from 8-14 with minimum inhibitory concentration of 25 mg/ml. The effect of the compound on cell volume of the infected mice shows change (%) in PCV of 19.3 and 12.2 using 250 and 500 mg/kg respectively. The effect on HB shows 3.8 and 2.3% changes using the same concentration. These values are close to 4.61 % obtained for Artesunate used as standard drug. The changes (%) in RBC were 8.8 and 3.0 for 250 and 500 mg/kg.

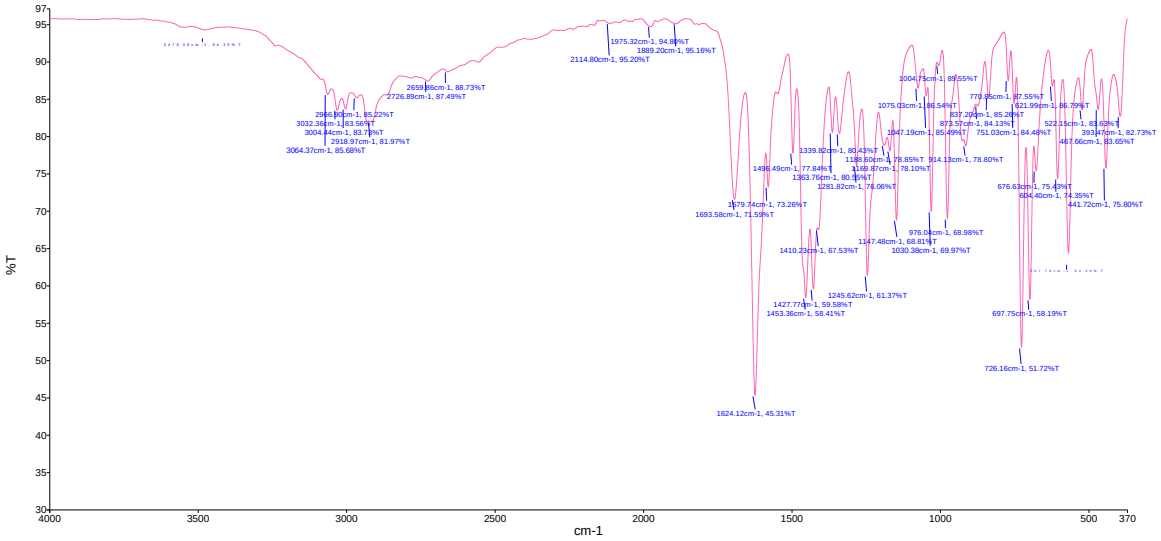


Fig. 1: FTIR spectrum of 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl)ethanone (L)

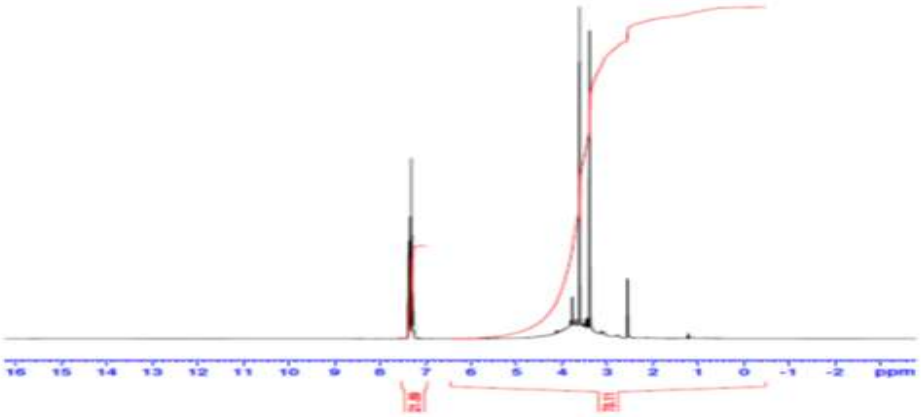
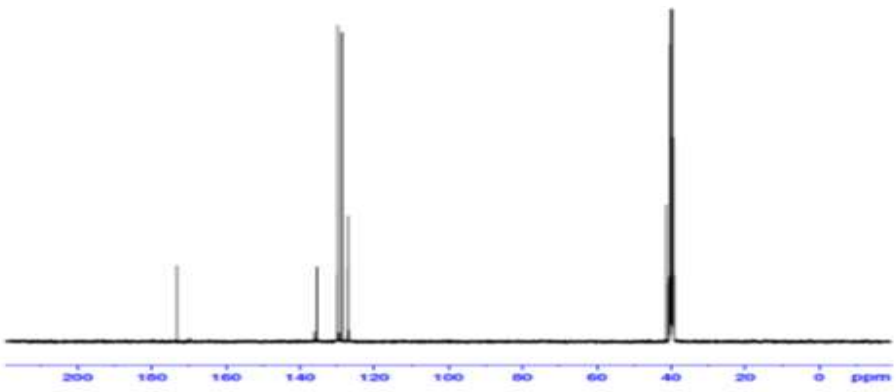


Fig. 2: [1]H NMR Spectra 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl)ethanone (L)



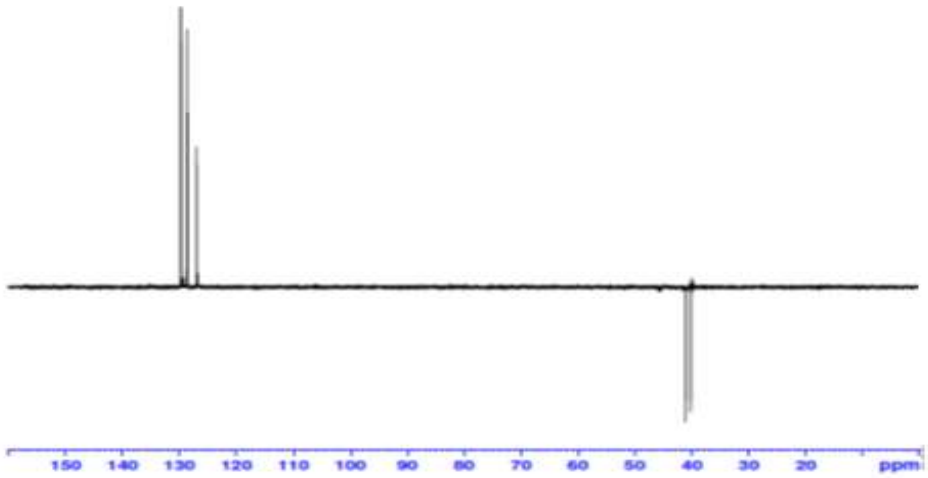


Fig. 4: ^{13}C DEPT NMR Spectra of 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl)ethanone (L)

The effect of sample on parasitemia count revealed 51.09 and 65.91 for 250 and 500 mg/kg with $p \leq 0.05$. Acute toxicity test shows the administration of this compound up to 5000 mg/kg could not cause any death in the animals. These findings reviled that 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl)ethanone is bioactive agent and could possible be used as a antibacterial and antimalarial agent (Ashton et al., 2021; Iyamu et al., 2022; Liz et al., 2019; Nguyen et al., 2021; Rathod et al., 2022; Svogie et al., 2016).

CONCLUSIONS

The synthesis and characterization of 2-phenyl-1-(4-phenylacetyl-piperazin-1-yl)ethanone (L) provide a new opportunity of developing a novel structural compound with potent antimalarial agent. The structure of this compound was elucidated using available spectroscopic techniques and confirmed by X-ray crystallography. The compound shows reasonable biological activities against the tested microbe as well as *plasmodium* parasite.

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