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Research Article

## Synthesis, Characterisation and Analgesic Activity of Diethylenediamine Copper Complex

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### ABSTRACT

A new Copper-based compound was synthesized from coordination reaction of diethylenetriamine and copper ions, using copper chloride dehydrate in ethanol. This synthesized compound was characterized by a number of spectroscopic methods including UV, IR, and by elemental analysis. IR calculated vibration was carried out HyperChem 08 software, whereas analgesic activity was evaluated *in vivo* against acetic acid induced pain in mice model. Results obtained from theoretical and experimental investigations demonstrate the high analgesic effect of copper complex towards acetic acid with percentages of 85.39 and 89.68% respectively, which is comparable with that of aspirin and tramadol (18.9 and 79.78 % respectively).

**Keywords:** Copper complex, Synthesis, Analgesic, Prediction.

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### INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue injury. Painful transmission is a complex phenomenon involving electrophysiological and neurochemical mechanisms [1]. Traumatic, inflammatory or ischemic lesions cause the release of damaged chemicals. These substances can either directly activate the nociceptors (bradykinins, potassium ions, hydrogen, nitric oxide, histamine and serotonin) or sensitize the nociceptors to other stimuli. In addition, Prostaglandins and leukotrienes, play a role of sensitizers of nociceptors acting on other substances such as the peptides involved in the transmission of the pain message. Substance P is best known as a neuropeptide (neurotransmitter) and plays a primordial role in nociception and has a vasodilatory action at the origin of algogenic inflammation [2]. An analgesic is a drug used in the fight against pain. Generally, analgesic drugs are associated with various undesirable gastrointestinal effects [3]. From these reasons, there is the need for the search of new safe analgesics.

In this study, Copper-based compound was predicted for their analgesic activity using the web tool PASS online, then synthesized, characterized and investigated *in vivo* for their

analgesic effect using acetic acid intraperitoneal injection in mice model. This complex was synthesized from the coordination reaction of copper (II) chloride dehydrate and diethylenetriamine in ethanolic solution.

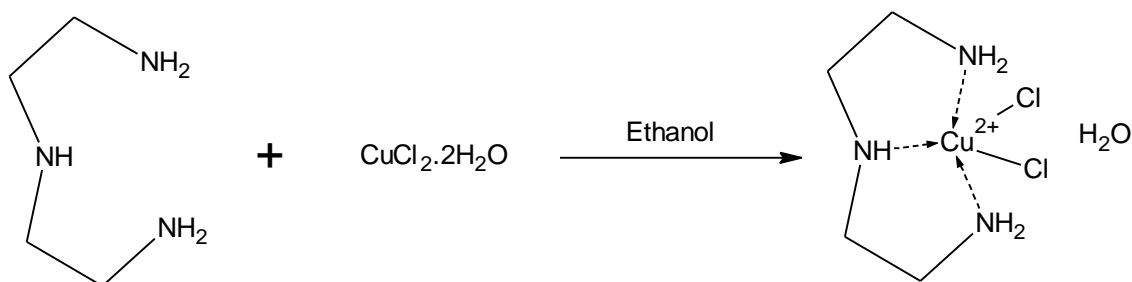
### MATERIALS AND METHODS

#### MATERIALS

The chemicals was purchased and used without further purification: diethylenetriamine, copper chloride dehydrate (Sigma-Aldrich), Acetic acid (Merck). Infrared spectra (IR) were obtained, as KBr disks, on a Shimadzu FTIR-8400S spectrophotometer. The electronic absorption spectra in the 200–900 nm range were recorded on a UV-1800 Shimadzu UV-visible spectrophotometer. Elemental analysis (C, H, and N) was carried out with a EuroVector EA3000 instrument.

#### Synthesis of diethylenediamine copper complex

Ethanolic solution of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (0.01 mol, 1.0748 g) was added to diethylenetriamine (0.01 mol, 1.0317 g), the mixture was refluxed for 1h at 78 °C. After cooling, the precipitate solid was filtered, isolated and washed several time with ethanol (**Scheme 1**).



**Scheme 1.** Synthesis of copper complex

Yield 86%. UV-Vis (H<sub>2</sub>O)  $\lambda_{\max}$  (nm) 247. IR (KBr, cm<sup>-1</sup>):  $\nu_{\max}$ : 3276-3243 (br, NH<sub>2</sub>), Anal. Calcd for C<sub>4</sub>H<sub>15</sub>Cl<sub>2</sub>CuN<sub>3</sub>O: C, 18.79; H, 5.91; N, 16.44. Found: C, 19.52; H, 5.59; N, 16.83%.

### Theoretical vibration data prediction

Calculated vibration was carried out HyperChem 08 software, with molecular mechanic force field (MM+) and semi-empirical AM1, PM3 methods [4].

### In silico analgesic activity prediction

The web tool PASS online was employed for analgesic activity predictions, in which the obtained values are the results of the difference between the probability of molecular activity and inactivity values [5].

### In vivo analgesic activity evaluation

In this assay, female mice were employed, divided into five groups of five animals each (n = 5). These mice were subjected to fasting for 12 h before the experiment but allowed free access to water except during the experiment. Mice were intra-peritoneally injected with 0.1% (v/v) acetic acid to induce writhes after 60 minutes of oral treatment with water as a vehicle, Copper complex (5 and 10 mg/kg) or

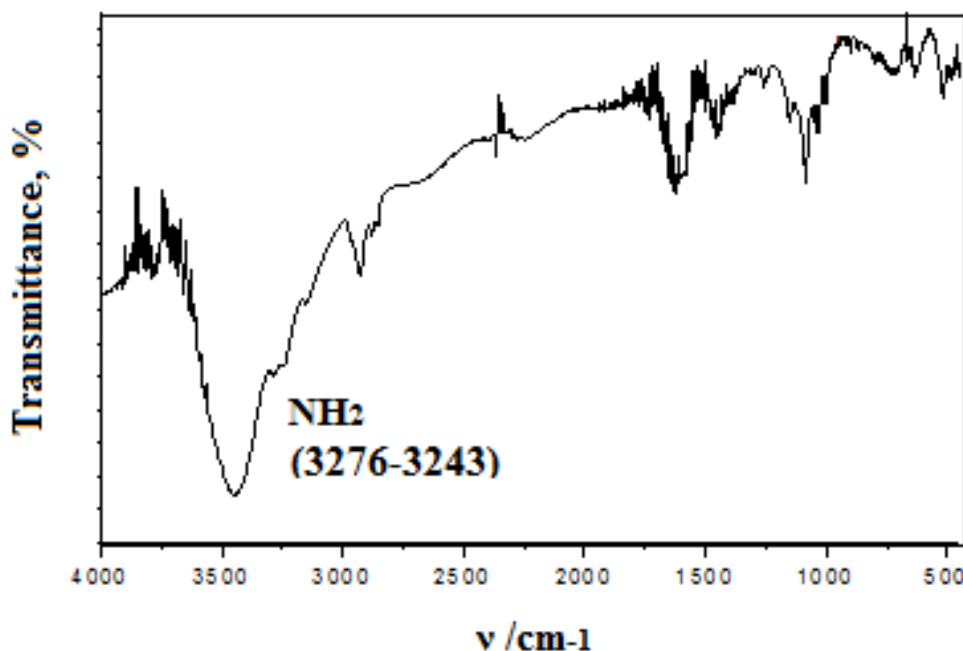
aspirin (100 mg/kg) as a positive control. Number of abdominal constrictions was counted over a period of 30 minutes by an observer unaware of the treatment after 5 minutes of injection. The percentage inhibition of writhing reflex was calculated using the formula: % inhibition (protection) = 100 x (Nc-Nt)/Nc, where Nc = mean number of writhes in control Nt = mean number of writhes in test [6].

## RESULTS AND DISCUSSION

### Chemistry

Copper complex was prepared from the reaction between copper chloride dehydrate and diethylenetriamine.

The infrared spectra of the synthesized complex indicate the presence of the amine group (NH<sub>2</sub>) at 3276-3243 cm<sup>-1</sup>. Also, the appearance of new bands between 500 and 600 cm<sup>-1</sup> is due to the coordination of copper ions with nitrogen of the amine. This confirms that the synthesis of the complex has taken place (Fig 1).

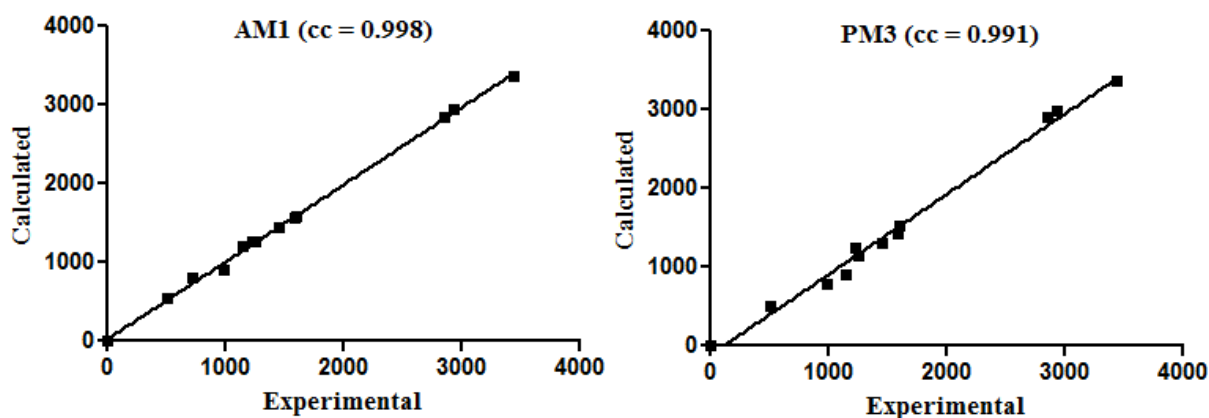


**Fig 1:** FT-IR spectrum of Copper complex

In addition, experimental analysis data are in perfect agreement with the theoretical data of this compound.

Furthermore, an excellent correlation was obtained between experimental and calculated IR vibration in the both

methods, AM1 and PM3, with correlation coefficient values of 0.998 and 0.991 for the synthesized complex (Fig 2).



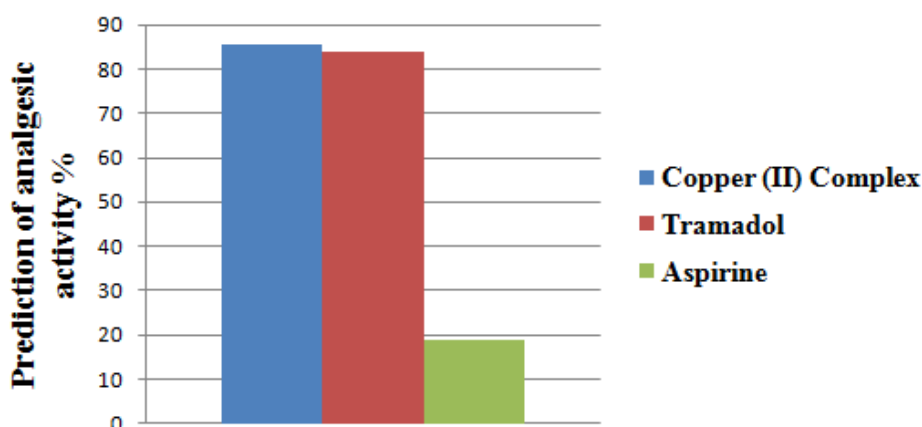
**Fig 2:** Graphical correlations between the experimental and calculated IR vibration of Complex obtained by AM1 and PM3 semi-empirical methods (cc = correlation coefficient).

### *In silico* analgesic activity prediction

Pain is one of the most important health problems because of its prevalence and the disability it can cause. Chronic pain may be the result of inflammatory diseases or tissue damage such as nerve damage in the case of neuropathic pain. In Europe, chronic pain affects about 17 to 45% of the population [7]. In addition, chronic pain is often resistant to existing therapy; for this reason, there is a great need for new drug research [8]. In recent years, computational methods were used as a first step for drug discovery and development. This approaches, have an exclusive advantage

of being able to evaluate the biological effect of drug-candidate substances before they are synthesized. According to these efficient approaches, the synthesized copper complex was investigated *in silico* for their analgesic activity. The predicted results (Fig 3) demonstrate that the synthesized copper complex exhibit an excellent analgesic effect with probability of 85.39%, followed with the opioid drug; Tramadol with 83.83% and no-opioid drug; aspirin with 18.9%. From these results, the synthesized copper complex has a similar effect of the opioid drug; Tramadol which exhibit their spinal analgesic effect via  $\mu_2$ ,  $\kappa_1$ ,  $\delta_2$  receptors [9].

### Analgesic activity Prediction



**Fig 3:** *In silico* prediction of analgesic potential of Copper complex, Tramadol and Aspirin

### *In vivo* analgesic activity evaluation

The intraperitoneal injection of acetic acid in mice causes a pain syndrome that results in characteristic writhing type of stretching movement of the hind legs and the dorso-ventral musculature. These events are strongly related to the sensitization of the nociceptive receptors that will induce the synthesis of PGE<sub>2</sub>, PGF<sub>2</sub> $\alpha$ , serotonin and histamine [10]. This assay has the great interest in analgesic drugs screening [11]. The analgesic substances cause the decrease in these contortions. In this study, the obtained results presented in Fig 4 show that the administration of 10 and 5 mg/kg of the synthesized copper complex and 100 mg/kg of aspirin exerted a protective effect against the pain caused by the

acetic acid. The potent inhibitory effect of abdominal contractions is recorded at the doses of 10 and 5 mg/kg, which exhibited an inhibitory effect of 89.68 and 76.07 % respectively. These effects are better than that of 100 mg/kg aspirin (79.78%). In literature, several studies demonstrate that copper represents an oligoelement with high analgesic activities [12]. Also, demonstrate that copper complexes of anti-inflammatory enhanced analgesic effect of these drugs. In conclusion, the experimental results are in good correlation with theoretical results. From these results, the synthesized copper complex could be an analgesic candidate drug, which proposed act on the peripheral and central nervous systems.

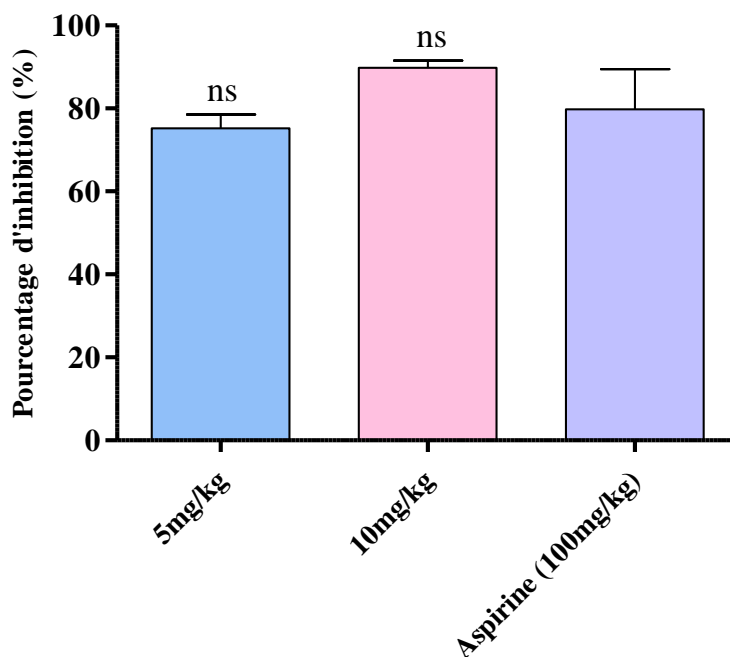


Fig 4: Analgesic activity of Copper complex (5 and 10 mg/kg) and aspirin (100 mg/kg)

## CONCLUSIONS

We conclude that the synthesized copper complex could be an analgesic candidate drug, which proposed act on the peripheral and central nervous systems.

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