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Synthesis, characterization and biological activity of new mixed ligand complexes of Zn(II) naproxen with nitrogen based ligands

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ABSTRACT

A series of novel Zn(II) complexes $[Zn_2(nap)_4]$ **(1)**, $[Zn(nap)_2$1,10-phen**]** **(2)**, $[Zn(nap)_2$2,9-dmphen**]** **(3)**, $[Zn(nap)_2(2\text{-ampy})_2]$ **(4)**, $[Zn(nap)_2(imid)_2]$ **(5)**, $[Zn(nap)_2(1,2\text{-dmimid})_2]$ **(6)** (nap = naproxen, 1,10-phen = 1,10-phenanthroline, 2,9-dmphen = 2,9-dimethyl-1,10-phenanthroline, 2-ampy = 2-aminopyridine, imid = imidazole, 1,2-dmimid = 1,2-dimethyl imidazole) were synthesized and characterized using IR, UV–Vis, ^{1}H NMR, $^{13}C\{^1H\}$ NMR spectroscopy. The crystal structure of complex **3** was determined using single-crystal X-ray diffraction. In order to assess the effect of the metal ions on the anti-bacterial activity, complexes **1**–**6** have been screened *in vitro*, against (G^+) bacteria (*Staphylococcus aureus* and *Micrococcus luteus*) and (G^-) bacteria (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Escherichia coli*) using the agar well diffusion method. Complex **2** was the only complex that showed antibacterial activity against *P. aeruginosa*, where the complexation of the parent ligand 1,10-phenathroline enhanced significantly the activity. All the complexes showed different activity against the different bacteria, and were compared with activity of the parent ligands. The complexes were tested also for their anti-malarial activity using two methods: a semi-quantitative micro-assay and a previously self-developed quantitative *in-vitro* method. Both were used to study the efficiency of these complexes in inhibiting the formation of the Malaria pigment. This is considered an important target of many known anti-malarial drugs such as Chloroquine and Amodaquine. Results showed that the efficiency of complex **3** in preventing the formation of β-hematin was 75%. The efficiency of Amodiaquine as a standard drug was reported to give 92.5.

1. Introduction

Zinc is one of the most important trace elements in the body and it is considered an essential element for many processes in living organisms [1–3]. Zinc ions exist primarily in the form of complexes with proteins and nucleic acids and participate in all aspects of intermediary metabolism, transmission and regulation of the expression of genetic information, storage, synthesis and action of peptide hormones and structural maintenance of chromatin, biomembranes and extracellular matrices [4]. Zinc ions possess some anti-bacterial effects, good thermal and color stability with low cost and little toxicity [5]. The growth of *Escherichia coli* is inhibited at high concentrations of zinc(II). However, low concentrations of zinc(II) have a promoting action on the growth of *E. coli* [6]. Zinc also can inhibit the growth of *Streptococcus faecalis*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and some soil bacteria [7]. Many anti-bacterial drugs when chelated to the metal, show altered bioability and sometimes the chelated drug is more effective than the free ligand [8]. This is due to the chelation of a bulky ligand to a metal cation which reduces the polarity of the ion and increases the lipophilicity of the metal complex, which can result in increased damage to bacterial cell walls and prohibit the transfer of zinc into the cell [9].

Malaria is one of the most prevalent parasitic diseases in the world. It is caused by different species of *Plasmodium*, *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae* and *Plasmodium ovale* of which *P. flaciparum* is the most virulent human malaria parasite. The parasite lives within human red blood cells and consumes over two thirds of the hemoglobin of the host cell.

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Digestion of hemoglobin by malaria parasite leads to the continuous liberation of free heme (Iron protoporphyrin IX) along with oxygen, causing formation of a ferric form of heme called ferriprotoporphyrin IX. This heme can lead to the killing of the parasite which has evolved a unique detoxification method of free heme through its conversion into a non-toxic, inert, insoluble, crystalline and black-brown pigment called homozoin [10–14]. β-Hematin crystals (Hemazoin) are made of dimer of hematin molecules that are oxygen coordinate bond links the central iron of one hematin to the oxygen of the carboxylate side-chain of the adjacent hematin [15]. Many clinically used antimalarial drugs such as chloroquine, amodaquine; mefloquine and 4-aminoquinoline are thought to act by inhibiting the formation of hemozoin in the food vacuole. This prevents the detoxification of the heme released in this compartment, and kills the parasite [16]. Chloroquine, a quinoline-ring drug, is widely used for malaria treatment. However, resistance to chloroquine has increased owing to extensive and uncontrolled use [17,18]. Chloroquine resistance is considered as major universal challenging problem and the need of new effective anti-malarial drugs is an urge. In this research both a semi-quantitative [19] and a quantitative screening methods for a new potential antimalarial drugs were used [20,21]. Naproxen [(+)-6-methoxy-α-methyl-2-naphthalene acetic acid], Fig. 1 is a non-steroidal drug with antipyretic, anti-inflammatory and analgesic properties [22–24]. In addition, naproxen is used to relieve fever, pain and symptoms of arthritis, gout, bursitis and menstrual cramping. It acts as cyclooxygenase inhibitor that interferes with the COX-1 and COX-2 forms of that enzyme [25]. Some anti-inflammatory drugs are sodium salts of carboxylic acids; the Na metal can be replaced by transition metals to improve some of these drugs characteristics. Metal ion complexation with naproxen increases the transport of naproxen into the cells as supported by the fact that the transport of organic ligands into cells can be facilitated by the formation of metal complexes [24,26].

Zinc complexes of aliphatic carboxylates such as formate, acetate, propionate and butyrate and aromatic carboxylates such as benzoate, 2-bromobenzoate 5-chlorosalicylate, 4-chlorosalicylate and salicylate with nitrogen based ligands have been synthesized and screened as bio-active compounds [1,6,27–38]. Zn(naproxen)$_2$ complex have been synthesized and characterized by IR, NMR and their anti-inflammatory studies were performed [24]. The interactions of this drug have been studied widely for copper with biologically active N-donor ligands such as 2,2-bipyridine, 1,10-phenanthroline and pyridine [22]. Other metal complexes of naproxen such as; the cobalt(II) complexes with naproxen in the presence of nitrogen–donor heterocyclic ligands (1,10-phenanthroline, 2,2-bipyridine and pyridine) have been synthesized and characterized with physiochemical and spectroscopic techniques [39]. The ligands 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, 2-aminopyridine, imidazole and their derivatives, as well as many of their complexes, are exhibiting antibacterial [40–46], anti-viral [47,48], and anti-malarial [49,50], anti-fungal [51] and anti-tumor activities [49,52,53] depending on the nature of the ligand and the type of the metal ion. In this work, synthesis, characterization, antibacterial and antimalarial activity of novel mixed ligand complexes of Zn(II) naproxen with nitrogen based ligands i.e, 2,9-dimethyl-1,10-phenanthroline, 1,10-phenanthroline, 2-aminopyridine, imidazole and 1,2-dimethyl imidazole are reported. The crystal structure of complex **3** which showed a promised antimalarial activity was also determined.

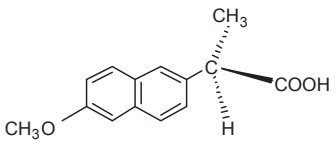

Fig. 1. Structural formula of D-naproxen.

2. Results and discussion

2.1. Synthesis of zinc complexes

[Zinc naproxen complex] **(1)** was prepared by reacting 1 eq of zinc chloride with 2 eq of sodium naproxen in water Scheme 1. The desired product was obtained as a white solid. Five mixed ligand zinc naproxen compounds have been prepared by the reaction of 1:2 molar ratio of complex **(1)** with the nitrogen donor ligands in acetone with stirring at ambient conditions Scheme 2. The physical properties of **1**–**6** are summarized in Table S1 (Appendix A. Supplementary Materials).

2.2. X-ray crystallographic study of complex 3

Suitable crystals for complex **3** were obtained by recrystallization from 1:1 mixture acetonitrile/chloroform and X-ray crystallographic analysis was determined. The crystal structure of complex **3** with the atomic labeling is illustrated in Fig. 2 and a summary of selected bond lengths and bond angles are given in Table S2.

Complex **3** crystallized in the monoclinic space group P2(1) with four molecules in the unit cell and one acetonitrile molecule per each complex molecule. Two crystallographically inequivalent molecules of [Zn(nap)$_2$2,9-dmphen] exist in the asymmetrical unit, these two units are contacted by π···π interaction between the aromatic group of naproxen in one molecule and the 2,9-dmphen of the other Fig. 3.

In the first asymmetrical molecule, zinc has a distorted tetrahedral ZnO2N2 chromophore; the Zn1 atom is coordinated to two monodentate oxygen atoms from naproxen ligands with Zn1–O1 and Zn1–O4 distances equal to 1.960 and 1.927 Å, respectively, this is in agreement with Zn–O bond distances in reported monodentate zinc benzoate complexes, zinc nitro benzoate complexes and 4-hydroxy benzoate complexes (1.96–2.20 Å) [54–56]. On the other hand, Zn1–O2 and Zn1–O5 non-bonded contacts are 2.927 and 2.792 Å, respectively. Bond angles around zinc are in agreement with tetrahedral angles (Table S2) with slight deviation that arises from the rigidity of the five-member ring that form with 2,9-dmphen.

In the second asymmetrical molecule of [Zn(nap)$_2$2,9-dmphen] with ZnO3N2 chromophore, using the geometrical parameter τ ($\tau = (\beta - \alpha)/60$, where β and α are the largest angles around the central atom) defined by Addison et al. [57]; the analysis of this complex gives a value of 0.11 which suggest a distorted square pyramidal arrangement around Zn(II) atom. Here one of the naproxen coordinated in asymmetrical chelating bidentate coordination with Zn2–O7 and Zn2–O8 distances equal to 2.241 and 2.141 Å, respectively. The other naproxen is coordinated in monodentate mode, Zn2–O10 = 1.921 Å, and Zn2–O11 non-bonded contacts = 2.997 Å. The distorted tetragonal base plane is defined by the atoms O8, N4, N3 and O7. Deviation from regular tetragonal geometry is apparent from the observed binding angles, {N(3)–Zn(2)–O(8) = 91.39, N(3)–Zn(2)–O(7) = 137.59, N(4)–Zn(2)–O(7) = 97.05, N(4)–Zn(2)–O(8) = 130.98, O(7)–Zn(2)–O(8) = 58.24} and the axial position are occupied by the O10. However, bond distances and angles within 2,9-dmphen and naproxen gave the expected values for such complexes.

2.3. Infrared and UV–Vis spectra

Infrared spectral data of zinc naproxen complexes **1**–**6** in the 400–4000 cm^{-1} range as KBr disk are summarized in Tables S3–S6