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Synthesis, characterization, spectral studies and cytotoxic effects of mixed-ligand mono and binuclear copper(II) complexes and their amide ligands

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ABSTRACT

The amide ligands, N,N′-bis(2-pyrimidinyl)pyridine-2,6-dicarboxamide (**1**) and N,N′-bis(2-pyrimidinyl)4-chloropyridine-2,6-dicarboxamide (**2**) were prepared by the condensation reaction of pyridine-2,6-dicarbonylchloride and 4-chloropyridine-2,6-dicarbonylchloride (1:2) with 2-aminopyrimidine. The new mixed-ligand binuclear and mononuclear complexes $[Cu(pydc)(apym)]_2{\cdot}6H_2O$ (**3**) and $[Cu(4\text{-}Cl\text{-}pydc)(apym)(H_2O)_2]$ (**4**) (where pydc is pyridine-2,6-dicarboxylate and apym is 2-aminopyrimidine) were synthesized from the reaction of ligands (**1**) and (**2**) with $Cu(NO_3)_2{\cdot}9H_2O$. The structures of (**2**)–(**4**) were confirmed by X-ray crystallography. Also, all compounds were characterized by elemental and thermal analysis, FT-IR, UV–Vis and NMR spectroscopy. Possible mechanisms for amides hydrolysis of (**1**) and (**2**) were suggested as pH dependence. Cyclic voltammetry measurements on (**3**) revealed two redox couple corresponding to Cu(II)Cu(II)/Cu(I)Cu(II) and Cu(I)Cu(II)/Cu(I)Cu(I) at $E^{o\prime}$ of −0.290 to 0.195 V and on (**4**) displayed only one redox couple assigned to Cu(II)/Cu(I) at $E^{o\prime} = -0.14$ V, versus Ag/AgCl. The fluorescence properties of the compounds (**1**)–(**4**) in liquid state were investigated in solvents with different dipole moment. In this study, the cytotoxic potential of each of four compounds were evaluated, using oxaliplatin as a standard, under MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) method, against βTC (a mouse beta pancreatic), MCF7 (a human breast cancer) and HT29 (a human colon adenocarcinoma) cell lines. Complex (**3**) with IC_{50} values about 0.1–10 μM was more active than oxaliplatin and other synthetic compounds on all the three cell lines. The highest anti-proliferative properties for two complexes (**3**) and (**4**) were observed toward MCF7 cell line with IC_{50} values equal to 0.1 and 1 μM, respectively. Strong cytotoxic activity of complex (**3**) revealed that it can be further investigated for cancer treatment in the next set of experiments.

1. Introduction

Transition metal coordination complexes of amides, nucleic acid constituents, amino acids and other nitrogen containing ligands due to their diverse structural aspects and biological activities have been attracting considerable attention [1]. Multidentate ligands of pyridine dicarboxamide are synthesized from condensation reactions involving pyridyl-bearing amine or carboxylic acid precursors [2–6]. Amide bond is an important building unit in numerous biological, pharmaceutical and agrochemical molecules [7]. But another important aspect of amides is their variable bonding modes for complexation of the metal ions. These ligands often possess two binding modes [8], through amide–N atom by dissociation of the N–H proton for stabilizing metal ions in their high oxidation states and through the amide–O atom for stabilizing metal ions in their lower oxidation states [9]. The most important factors to control the topology of the obtained products in designing the metal–organic framework (MOF) are bonding properties of the ligands and the stereochemical preferences of the metals ions. Also, weak intra- and intermolecular interactions such as hydrogen bonding and π–π stacking interactions can be effective in regulating crystalline structure [10]. So far many complexes have been synthesized from amides and different metal ions with various coordination geometries [11–13]. For example the Cu(II) ion linked to the carboxamide [—C(O)NH—] group and arises geometries such as square-planar, square-pyramidal, trigonal bipyramidal and tetragonally elongated octahedral [14–15].

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Medicinal inorganic chemistry was developed after the discovery of cis-platin as anti-tumor and in continues copper and zinc complexes were used as anticancer drugs [16]. As well, amides were studied as therapeutic agents [17]. Surafenib(4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-N-methylpyridine-2-carboxamide), new cytostatic drug, is in fact the amide used for the treatment of renal cell and hepatocellular carcinoma [18]. Similarly, the potent small-molecule inhibitors of raf kinase are the amides used for hyperproliferactive disorders such as cancer [19]. While many researchers put their emphasis on the synthesis and characterization of amide ligands and their transition metal complexes [20–23], no more studies have been reported about the amide ligands hydrolyzing upon complexation and forming mixed-ligand complexes. In this regard present study describes the synthesis of amide ligands (**1**) and (**2**) by reacting pyridine-2,6-dicarbonylchloride and 4-chloropyridine-2,6-dicarbonylchloride with 2-aminopyrimidine, and two new mixed-ligand copper(II) complexes of hydrolysis (**1**) and (**2**) with Cu $(NO_3)_2{\cdot}9H_2O$ metal salt. Also, in this work characterization, crystal structures, mechanisms and some of effective factors in hydrolysis of amides, electrochemical and fluorescence properties of the compounds are fully discussed. More relevant to this study are recent reports that have shown copper complexes can also be used to treatment of many diseases including cancer [24–26]. These results, along with our interest in studying of treatment properties of new chemical compounds and with the aim of development of anticancer chemistry, the ability of synthetic compounds are examined against several cancerous cell lines *in vitro*.

2. Experimental

2.1. Materials and apparatus

Pyridine-2,6-dicarboxylic acid, pyridine-2,6-dicarbonylchloride, 4-hydroxy-pyridine-2,6-dicarboxylic acid and thionyl chloride were purchased from the commercial sources and used as received. The solvents were distilled for all synthetic works.

Melting points were obtained on an Electrothermal IA-9100 apparatus. The FT-IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer using KBr pellets. Electronic spectra were recorded on Specord 210, Analytik Jena spectrophotometer in the range of 200–900 nm at room temperature. The ^{1}H NMR spectra (400 MHz) were obtained from Bruker Ultrashield 400 spectrometer. Electrochemical experiments were performed using a μAUTOLAB modular electrochemical system (ECO Chemie, Ultrecht, The Netherlands) equipped with a PGSTAT type III module driven by GPES software in conjunction with a conventional three-electrode system an Ag/AgCl/3 M KCl and platinum wire as reference and counter electrode respectively and a GC as working electrode. All experiments were done under N_2 atmosphere and at 298 K. Microanalyses (C, H, N) were measured with a Perkin–Elmer 2004 (II) elemental analyzer. Thermal behavior was measured with a PL-1500 TGA apparatus with heating rate of 10 °C/min in N_2 atmosphere. The mass spectroscopy (MS) was determined using an Agilent (USA) spectrophotometer. Fluorescence properties were determined in a quartz cell, using Cary Eclipse winFLR apparatus at room temperature.

2.2. Syntheses

2.2.1. Synthesis of N,N′-bis(2-pyrimidinyl)pyridine-2,6-dicarboxamide (*1*)

Synthesis route of compounds are shown in Scheme 1. Compound (**1**) was synthesized with a modified method from the literature [27]. Anhydrous thionyl chloride (25 ml) was added to pyridine-2,6-dicarboxylic acid (1 mmol, 0.167 g) and refluxed at 80–90 °C under argon atmosphere for 3 h until a clear yellow solution was obtained. The excess thionyl chloride was removed under reduced pressure. The product was dried in vacuum, cooled and the obtained white precipitate was dissolved in dichloromethane, then 2-aminopyrimidine (2 mmol, 0.190 g) in dry pyridine (20 ml) was added to it, with occasional stirring, until the production of HCl was ceased. Dark green solution was stirred overnight at room temperature. During the time period white precipitate was formed slowly. The precipitate was filtered off, washed with 5% sodium bicarbonate solution and water, dried in the air and recrystallized in methanol. Despite the use of several crystallization techniques in this research, the suitable single crystals of (**1**) were not produced. Yield (83%). M.p.: 271 °C. Found (calc. for $C_{15}H_{11}N_7O_2$): C 56.21 (56.07), H 2.98 (3.43), N 28.69 (30.52)%. δ_H (400 MHz, DMSO-d^6, 295 K): 11.92 (s, 2H, NH), 8.81 (d, 4H, J = 5, $C_4H_3N_2$), 8.40 (d, 2H, J = 8, C_5H_3N), 8.29 (t, 1H, J = 8, C_5H_3N), 7.33 (t, 2H, J = 5 Hz, $C_4H_3N_2$). Selected IR bands (KBr pellet, cm^{-1}): 3326s (ν_{NH}), 1720s (ν_{CO}), UV–Vis: λ_{max} (CH_3OH, nm), 298. EI MS: m/z 321, M$^+$.

2.2.2. Synthesis of N,N′-bis(2-pyrimidinyl)4-chloropyridine-2,6-dicarboxamide (*2*)

The experimental procedure for preparation of ligand (**2**) was similar to ligand (**1**) with a replacement of pyridine-2,6-dicarboxylic acid by 4-hydroxy-pyridine-2,6-dicarboxylic acid (1 mmol, 0.183 g). After adding 2-aminopyrimidine (2 mmol, 0.190 g) in dry pyridine, dark brown solution was obtained, stirred in the room temperature for 15 h and the bright yellow precipitate was formed and filtered off. After several times of washing with 5% sodium bicarbonate solution and water, the yellow precipitate was dried in the air and recrystallized from methanol. Yield (76%). M.p.: 308 °C. Found (calc. for $C_{15}H_{10}N_7O_2Cl$): C 49.61 (50.70), H 2.11 (2.81), N 26.19 (27.60)%. δ_H (400 MHz, DMSO-d^6, 295 K): 12.03 (s, 2H, NH), 8.90 (d, 4H, J = 4.8, $C_4H_3N_2$), 8.45 (s, 2H, C_5H_2NCl), 7.43 (t, 2H, J = 4.8, $C_4H_3N_2$). Selected IR bands (KBr pellet, cm^{-1}): 3268s (ν_{NH}), 1714s (ν_{CO}), UV–Vis: λ_{max} (CH_3OH, nm), 236. EI MS: m/z 355, M$^+$.

2.2.3. Synthesis of [Cu(pydc)(apym)]$_2{\cdot}6H_2O$ (*3*)

Under aerobic conditions, to a stirring methanolic solution of ligand (**1**) (0.06 mmol, 0.019 g) at 50 °C was added NEt_3 (0.14 mmol, 0.02 ml) and a yellow solution was stirred for 10 min. Then a solution of $Cu(NO_3)_2{\cdot}9H_2O$ (0.06 mmol, 0.014 g) in methanol was added and the mixture was refluxed for 3 h. The dark blue precipitate was filtered off and recrystallized from water. Yield (71%). M.p.: >210 °C decomp. Found (calc. for $C_{22}H_{28}N_8O_{14}Cu_2$): C 34.91 (34.60), H 3.11 (2.90), N 15.34 (14.80)%. δ_H (400 MHz, DMSO-d^6, 295 K): 8.82 (m, 1H, $C_4H_3N_2$), 7.92 (m, 1H, $C_4H_3N_2$), 7.82 (m, 1H, C_5H_3N), 7.03 (m, 1H, C_5H_3N), 6.90 (m, 1H, $C_4H_3N_2$), 6.68 (m, 1H, J = 5.5 C_5H_3N), 3.19 (s, 2H, NH_2). Selected IR bands (KBr pellet, cm^{-1}): 3358, 3442 (ν_{NH2}), 1643s (ν_{CO}), UV–Vis: λ_{max} (CH_3OH, nm), 235. EI MS: m/z 755, M$^+$.

2.2.4. Synthesis of [Cu(4-Cl-pydc)(apym)(H_2O)$_2$] (*4*)

This complex was synthesized by a method identical to complex (**3**), but ligand (**2**) (0.06 mmol, 0.021 g) was used in place of ligand (**1**). After adding $Cu(NO_3)_2{\cdot}9H_2O$ and refluxing for 2 h, the produced green precipitate was filtered off and recrystallized from water. Yield (52%). M.p.: >230 °C decomp. Found (calc. for $C_{11}H_{11}N_4O_6ClCu$): C 32.85 (33.50), H 2.31 (2.79), N 13.62 (14.20)%. δ_H (400 MHz, DMSO-d^6, 295 K): 7.98 (w, 5H, C_5H_2NCl and $C_4H_3N_2$), 4.72 (s, 2H, NH_2). Selected IR bands (KBr pellet, cm^{-1}): 3335, 3177 (ν_{NH2}), 1656s (ν_{CO}), UV–Vis: λ_{max} (CH_3OH, nm), 274. EI MS: m/z 394, M$^+$.