



Effect of cobalt(II) complexes with dipyriddyamine and salicylaldehydes on cultured tumor and non-tumor cells: Synthesis, crystal structure investigations and biological activity

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ABSTRACT

The synthesis of eight mixed-ligand cobalt(II) complexes with 2,2'-dipyriddyamine (dpamH) and substituted salicylaldehydes (X-saloH) was undertaken in an effort to discover new compounds with anticancer activity. The complexes with the general formula $[\text{Co}(\text{dpamH})_2(\text{X-salo})]\text{Y}$, (Y = Br or Cl) were characterized by elemental analyses, FT-IR and UV-visible spectroscopy, magnetic and conductivity measurements. The structures of two of them $[\text{Co}(\text{dpamH})_2(5\text{-CH}_3\text{-salo})]\text{Br}$ and $[\text{Co}(\text{dpamH})_2(3\text{-OCH}_3\text{-salo})]\text{Cl}$, as well as of the precursors $[\text{Co}(\text{dpamH})_3]\text{Br}_2$ and $[\text{Co}(\text{dpamH})_2\text{Cl}(\text{H}_2\text{O})]\text{Cl}$, were determined by X-ray crystallography revealing octahedral coordination of cobalt(II) and mononuclear complexes. The complexes were thermally stable up to 200 °C in nitrogen atmosphere, studied by simultaneous TG/DTG-DTA technique. The two precursor Co compounds, as well as four of the title compounds, were evaluated for their efficacy as anticancer agents against different cancer and normal human cell lines. The *in vitro* chemosensitivity of various human cell lines to these Co complexes was evaluated by measuring cell growth inhibition by employing the SRB colorimetric assay. A series of experiments showed a dose-dependent cytotoxic activity of the complexes against all cell lines used. These findings represent a prompting to search for possible interaction of these complexes with other cellular elements of fundamental importance in cell proliferation.

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1. Introduction

Since Rosenberg's initial discovery of *cis*-platin in 1962 [1] many more examples of metal-containing drugs have been reported in the literature. Gold containing complexes such as auranofin are used to treat rheumatoid arthritis and lung cancer [2], radiopharmaceuticals based on materials such as technetium and rhenium are used in imaging and radiotherapy and ruthenium complexes have had some success as anticancer drugs [3]. Complexes containing gadolinium, copper, zinc, aluminum and lutetium have all been used in medicine [4]. Complexes based on cobalt(III) were found to possess both antiviral and antibacterial activities [5]. Several cobalt complexes have been referred to exhibit anticancer activity [6–8].

Strong coordinating properties of 2-hydroxybenzaldehydes (salicylaldehyde, saloH) and their derivatives (X-saloH) with 3d transition metals have stimulated research on these compounds, leading

to their applications in both pure [9] and applied chemistry fields, including metallurgy [10] and tire industry [11]. These ligands, in their mono-anionic form, are known to bind transition metals adopting square-planar [12] or octahedral coordination geometry [13] in a bidentate chelating manner. It is also well known that cobalt cationic octahedral complexes with α -diimines have important biological properties [14]. Therefore one can expect that mixed-ligand coordination compounds of transition metal ions with salicylaldehyde derivatives and α -diimines should be suitable candidates to study diverse aspects of biological activity and to search for new industrial applications.

Recently, studies of the neutral addition compounds $[\text{Co}(\text{X-salo})_2(\alpha\text{-diimine})]$, where α -diimine = bipyridine (bipy), phenanthroline (phen) or neocuproine (neoc), have been reported by our research group [15–17]. As a continuation of this research, cationic cobalt(II) complexes with dipyriddyamine and salicylaldehydes of the general formula $[\text{Co}(\text{X-salo})(\text{dpamH})_2]\text{Y}$, where Y = Br, Cl and dpamH = 2,2'-dipyriddyamine, were synthesized and tested for their antiproliferative activity on cultured tumor and non-tumor cells

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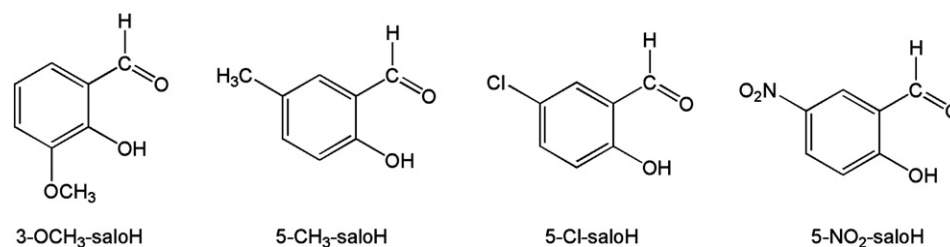


Fig. 1. Molecular structure of the salicylaldehyde ligands.

with the SRB method. In this series of experiments we have focused on the study of the possible anticancer activity of six Co complexes with dpamH, 3-OCH₃-salicylaldehyde and 5-NO₂-salicylaldehyde as ligands, with Br and Cl as counter anions, through *in vitro* experiments. Human cervical, breast, colon and kidney cancer cell lines (along with a non tumor human breast cell line) were selected for the purpose of preliminary anti-cancer screening of the tested compounds.

The salicylaldehyde ligands: 2-hydroxy-3-methoxybenzaldehyde (3-OCH₃-saloH), 2-hydroxy-5-methylbenzaldehyde (5-CH₃-saloH), 2-hydroxy-5-chlorobenzaldehyde (5-Cl-saloH), and 2-hydroxy-5-nitrobenzaldehyde (5-NO₂-saloH) are depicted in Fig. 1.

2. Experimental

2.1. Materials and physical measurements

The salicylaldehyde ligands, 2,2'-dipyridylamine (dpamH), and the metal salts CoCl₂·6H₂O, CoBr₂·xH₂O were obtained as reagent grade from Aldrich and used as received. Solvents for preparation and physical measurements of "extra pure" grade were obtained from Fluka and used without further purification.

Microanalyses were carried out using a Perkin-Elmer 240 B CHN microanalyzer and Perkin-Elmer 5100 PC Atomic Absorption Spectrophotometer for the metal content. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer in KBr discs at room temperature and are reported in cm⁻¹. Electronic absorption spectra in Nujoll and in MeOH solutions were obtained on a Shimadzu 160A spectrometer. Molar conductivities were measured in DMF solutions, employing a WTW conductivity bridge and a calibrated dip type cell. Magnetic susceptibility measurements on powdered samples were performed at 25 °C employing the Faraday method on a home-build balance calibrated against Hg[Co(SCN)₄]. The simultaneous TG/DTG-DTA curves were obtained on a SETARAM thermal analyzer model SETARAM SETSYS TG-DTA 16/18. The samples of about 8.0 mg were placed in platinum crucible and as a reference material was used an empty platinum crucible. The compounds were heated from ambient temperature to 1400 °C in a 50 mL/min flow of N₂, at a heating rate of 10 °C min⁻¹.

2.2. General procedure for synthesis of the complexes [Co(dpamH)₂(X-salo)]⁺ (1–8)

All the mixed-ligand complexes [Co(dpamH)₂(X-salo)]⁺ were prepared according to the following general procedure, under argon atmosphere, while well degassed solutions were used to avoid oxidation of the cobalt: to an ethanolic solution (20 mL) of 1 mmol cobalt(II) halogenide was added 2 mmol dpamH under stirring and drop-wise an ethanolic solution of 1 mmol substituted salicylaldehyde and 1 mmol CH₃ONa. The solution was refluxed for 2 h until a clear transparent solution appeared. An orange solid was formed after several days. The solid was filtered, washed with water, cold ethanol and diethylether and dried under vacuo. The compounds prepared are soluble in MeOH, DMF and DMSO and were found to have conductivity values in DMF solutions

between 65.0 and 83.0 μS/cm, denoting their ionic character as 1:1 electrolytes [18].

2.2.1. [Co(dpamH)₂(3-OCH₃-salo)]Br (1)

Orange microcrystalline solid, yield 62.0%. Stoichiometry calculated for C₂₈H₂₅N₆O₃CoBr: C, 53.16; H, 3.95; Co, 9.33; N, 13.29. Found: C, 52.99; H, 4.01; Co, 9.25; N, 13.05%. IR spectrum (KBr): selected peaks in cm⁻¹: 3295 m, 3202 m and 3130 m v(N–H), 2858 m v(C–H) of the OCH₃, 1618 s v(C=O), 1637 s δ(N–H), 1580 s v(C=N), 853 m and 725 s (pyridyl C–H), 548 m (Co–O), 424 m (Co–N). Conductivity in dimethyl formamide (DMF), Λ_M = 67.4 μS/cm and magnetic moment, μ_{eff} = 4.12 μ_B.

2.2.2. [Co(dpamH)₂(5-CH₃-salo)]Br·EtOH (2)

Orange microcrystalline solid, yield 60.0%. Stoichiometry calculated for C₂₈H₂₅N₆O₂CoBr·EtOH (or C₃₀H₃₁N₆O₃CoBr): C, 54.38; H, 4.68; Co, 8.91; N, 12.69. Found: C, 54.34; H, 4.61; Co, 9.19; N, 13.04%. IR spectrum (KBr): selected peaks in cm⁻¹: 3290 m, 3200 m and 3120 m v(N–H), 1391 m v(C–H) of the CH₃, 1637 s δ(N–H), 1625 s v(C=O), 1596 s v(C=N), 852 m and 723 s (pyridyl C–H), 543 m (Co–O), 417 m (Co–N). Conductivity in DMF, Λ_M = 66.0 μS/cm and magnetic moment, μ_{eff} = 4.10 μ_B.

2.2.3. [Co(dpamH)₂(5-Cl-salo)]Br (3)

Orange-brown microcrystalline solid, yield 61.0%. Stoichiometry calculated for C₂₇H₂₂N₆O₂CoBrCl: C, 50.90; H, 3.45; Co, 9.27; N, 13.19. Found: C, 50.27; H, 3.44; Co, 9.19; N, 12.85%. IR spectrum (KBr): selected peaks in cm⁻¹: 3280 m, 3180 m and 3100 m v(N–H), 769 m v(C–Cl), 1637 s δ(N–H), 1622 s v(C=O), 1598 s v(C=N), 853 m and 728 s (pyridyl C–H), 535 m (Co–O), 425 m (Co–N). Conductivity in DMF, Λ_M = 69.3 μS/cm and magnetic moment, μ_{eff} = 4.22 μ_B.

2.2.4. [Co(dpamH)₂(5-NO₂-salo)]Br (4)

Orange-brown microcrystalline solid, yield 61.0%. Stoichiometry calculated for C₂₇H₂₂N₇O₄CoBr: C, 50.08; H, 3.40; Co, 9.91; N, 15.14. Found: C, 50.25; H, 3.30; Co, 9.85; N, 15.14%. IR spectrum (KBr): selected peaks in cm⁻¹: 3292 m, 3190 m and 3110 m v(N–H), 1326 m v(C–NO₂), 1637 s δ(N–H), 1604 s v(C=O), 1598 v(C=N), 853 m and 728 s (pyridyl C–H), 529 m (Co–O), 414 m (Co–N). Conductivity in DMF, Λ_M = 72.5 μS/cm and magnetic moment, μ_{eff} = 4.19 μ_B.

2.2.5. [Co^{II}(dpamH)₂(3-OCH₃-salo)]Cl (5)

Orange microcrystalline solid, yield 65.0%. Stoichiometry calculated for C₂₈H₂₅N₆O₃CoCl: C, 57.19; H, 4.25; Co, 9.33; N, 14.30. Found: C, 56.75; H, 4.11; Co, 9.13; N, 14.30%. IR spectrum (KBr): selected peaks in cm⁻¹: 3297 m, 3186 m and 3130 m v(N–H), 2860 m v(C–H) of the OCH₃, 1614 s v(C=O), 1639 s δ(N–H), 1584 s v(C=N), 853 m and 728 s (pyridyl C–H), 551 m (Co–O), 426 m (Co–N). Conductivity in DMF, Λ_M = 67.6 μS/cm and magnetic moment, μ_{eff} = 4.13 μ_B.

2.2.6. [Co(dpamH)₂(5-CH₃-salo)]Cl (6)

Orange microcrystalline solid, yield 60.0%. Stoichiometry calculated for C₂₈H₂₅N₆O₂CoCl: C, 58.79; H, 4.37; Co, 10.32; N, 14.70. Found: C,

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