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New binuclear dithiocarbamate complexes [M_2-μ^2-bis-{(κ^2S,S-$S_2CN(R)CH_2CONHC_6H_4)_2CH_2$}] (M=$Ni^{II}$, Cu^{II}, and Zn^{II}): synthesis, characterization, DFT, and *in vitro* cytotoxic study

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Abstract

A new series of binuclear dithiocarbamate macrocyclic complexes [M_2-μ^2-bis-{(κ^2*S*,*S*-$S_2CN(R)CH_2CONHC_6H_4)_2CH_2$}] {R=*Cy*, M = Ni^{II} **1a**, Cu^{II} **1b**, Zn^{II} **1c**; R=^{i}*Pr*, M = Ni^{II} **2a**, Cu^{II} **2b**, Zn^{II} **2c**; R=^{n}*Bu*, M = Ni^{II} **3a**, Cu^{II} **3b**, Zn^{II} **3c**} have been efficiently synthesized by using a self-assembly process involving diamino precursor 4,4'-bis(2-(alkylamino)acetamido) diphenylmethane (L^1, L^2, or L^3), CS_2 and Ni^{II}, Cu^{II}, or Zn^{II} ion. Compounds are suitably characterized by ^{1}H, ^{13}C, DEPT135, ^{1}H DOSY NMR, HRMS, ESI MS, UV–Visible absorption, IR, and TGA/DTA methods. The experimental results are further supported by DFT level calculations. Compounds have been screened for their *in vitro* cytotoxicity against HepG2 (hepatoma) cell line by the MTT assay. The results showed much better activity of all the newly synthesized derivatives than clinically used drug cisplatin and specificity (except L') for cancer cells over normal liver cells. Exceptionally, macrocyclic dithiocarbamate complexes **1b** (IC_{50}: 6.91 µM ± 0.22 µM) and **1c** (IC_{50}: 5 µM ± 0.16 µM) holding N–Cy substituents showed nearly 10–15 fold better cytotoxic activity against HepG2 cell lines compared to the reference drug cisplatin (IC_{50}: 75.67 µM ± 0.25 µM). The shrinking of cells can be clearly visualized by acridine orange/ethidium bromide (AO/EB) staining, indicating the induction of apoptosis as part of the mechanism of action of these compounds.

Keywords: Dithiocarbamate; Binuclear Macrocyclic; Electrochemistr; Density Functional Theory; Cytotoxic; Cell Staining; Apoptosis