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Improving cytotoxicity by changing a linker from diphenylether to diphenylmethane and now to phenylene in binuclear dithiocarbamate complexes: synthesis and cytotoxicity study

Vinay K Sing[1], Vineeta Pillai[2], Shailyakumari K Patel[3], And Lipi Buch[4]

[1,2,3]Department of Chemistry, Faculty of Science, The M. S. University of Baroda, Vadodara, 390 002 India
[4]Department of Zoology, Faculty of Science, The M. S. University of Baroda, Vadodara, 390 002 India

Abstract

α-chloroamide 1,3-bis(2-chloroacetamido)phenylene (**L'**) is selected as a lead compound to derive 1,3-bis(2-(alkylamino)acetamido)phenylene (**L^1-L^3**). A programmed self-assembly involving L^1-L^3, CS_2 and Ni^{II}, Cu^{II} or Zn^{II} ions affords access to a new series of 32-membered binuclear macrocyclic dithiocarbamates [M^{II}_2-μ^2-bis-{(κ^2*S,S*-$S_2CN(R)CH_2CONH)_2C_6H_4$}]{R=*Cy*, M=$Ni^{II}$ **1 a**, Cu^{II} **1 b**, Zn^{II} **1 c**; R=^{i}*Pr*, M=Ni^{II} **2 a**, Cu^{II} **2 b**, Zn^{II} **2 c**; R=^{n}*Bu*, M=Ni^{II} **3 a**, Cu^{II} **3 b**, Zn^{II} **3 c**}. Compounds were characterized by spectroscopic (^{1}H, ^{13}C, DEPT 135, ^{1}H DOSY NMR, HRMS/ESI MS, UV-visible, Fluorescence, IR) and by the TGA. Evidently, L' forms a fascinating 2D infinite supramolecular molecular sheet. All the compounds were screened for their *in vitro* cytotoxic activity against malignant tumor Hep G2 (hepatoma) cell line by the MTT assay. A majority of compounds *ca* **L', L^1, 1 a, 1 b, 1 c, 2 a, 2 b, 2 c, L^3,3 a, 3 b, 3 c** display IC_{50} values lower than cisplatin and specificity for carcinoma Hep G2 over normal liver cell line (WRL-68). Evidently cytotoxic potentials of **L^1-L^3** improved tremendously upon formation of their corresponding bimetallic dithiocarbamate complexes. 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. Further, DFT level calculations have been performed on representative compounds to reinforce the experimental results.

Keywords: chloroacetamido; spectroscopic; hepatoma; dithiocarbamate; acridine; ethidium bromide