1. List of papers published

1. Pillai, V., Kadu, R., Buch, L. and Singh, V. K, Derivatives of Dapsone (dap): Synthesis and Study on In Vitro Anticancer Activity and DNA Laddering against Hep G2 and C6 Human Cancer Cell Lines. ChemistrySelect. 2 (2017) 4382-4391.
2. Kadu, R., Pillai, V., Amrit V. and Singh, V. K, Synthesis and spectral characterization of bimetallic metallomacrocyclic structures [MII^2-μ^2-bis-{(κ^2S,S-$S_2CN(R)C_6H_4)_2O$}] (M = Ni/Zn/Cd): density functional theory and host–guest reactivity studies. RSC Adv. **5** (2015) 106688-106699.

2. List of papers under communication

1. Pillai, V., Kadu, R., Buch, L. and Singh, V. K, Unusual fluorescence quenching of 4,4'bis(alkylamino)acetamido)diphenylmethane in Their Zn^{II}-dithiocarbamate Complexes: Synthesis, Characterization and *in vitro* Cytotoxicity of [M_2-μ^2-bis-{(κ^2*S*,*S*-$S_2CN(R)CH_2CONHC_6H_4)_2CH_2$}].
2. Pillai, V., Kadu, R., Buch, L. and Singh, V. K, Coordination driven self-assembly of 1,3-bis(2-(alkylamino)acetamido)phenylene, CS_2 and Ni^{II}, Cu^{II} or Zn^{II}:Synthesis, spectroscopic, DFT, crystallographic and cytotoxic study.
3. Pillai, V., Kadu, R., Buch, L. and Singh, V. K, A distinct *in vitro* cytotoxicity, ability to induce apoptosis and selectivity against Hep G2 cancer cells over normal cells of derivatives of 4, 4'- oxydianilne.
4. Pillai, V., Kadu, R., Buch, L. and Singh, V. K, Synthesis, spectral characterization, density functional theory and in vitro anticancer study of diphenyltin^{IV} dithiocarbamate macrocyclic complexes bearing varied linkers.

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Inorganic Chemistry

Derivatives of Dapsone (dap): Synthesis and Study on *In Vitro* Anticancer Activity and DNA Laddering Against Hep G2 and C6 Human Cancer Cell Lines

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Interesting biological profile of dapsone (dap) has encouraged us to derivatize it further into a novel series of diamines 4,4′-bis (2-(alkylamino) acetamido) diphenylsulfone L^1-L^3 and their ensuing metallomacrocyclic complexes of the type $[M_2\text{-}\mu^2\text{-bis-}\{(\kappa^2S,S\text{-}S_2CN(R)CH_2CONHC_6H_4)_2SO_2\}]$ {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**}. These compounds were characterized by standard spectroscopic methods. A DFT level calculation has been performed on selected compounds. *In vitro* anticancer activity against Hep G2 (hepatoma) and C6 (Glioblastoma) cell lines suggests specificity of these compounds for cancer cells over normal liver cells. Interestingly, complex **2c** holding zinc(II) and *N*-^{i}Pr substituents shows nearly 3 fold better cytotoxic activity against both Hep G2 (8.47 ± 0.016 μg/mL) and C6 (4.3 ± 0.019 μg/mL) cell lines, compared to the reference drug Cisplatin. The morphological changes and moderate to heavy DNA laddering clearly demonstrate the induction of apoptotic cell death, required for major chemical therapeutic implications.

Introduction

The interest in dap has been continued since its inception in clinical practice[1] as antibiotic in the late 1940s. Reports suggest that it is active against various species of Pneumocystis, Plasmodia, Toxoplasma, and Mycobacteria and used in both cancer and human immunodeficiency virus (HIV) patients.[2] A combination of dap and chlorproguanil which is commercially known as Lapdap act synergistically against malaria[3] however, this drug reportedly causes haemolysis in patients with G6PD deficiency.[4] It is slowly absorbed after oral administration with a mean absorption half-life of 1.1 hours that reaches peak serum or plasma concentrations in about 2–6 hours with considerable variations[5] Absolute oral bioavailability is calculated to exceed 85%[6] where 70–90% of dap is bound to plasma protein and distributed throughout the tissues, crosses the placenta and is excreted in breast milk, saliva, feces and urine as 4,4′-diaminodiphenyl sulfone hydroxylamine.[7] It can also be bio-transformed to a nontoxic metabolite, the mono-acetyl dapsone (MADDS) by arylamine NAT.[8,9]

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The success of a wide range of natural product bearing a macrocyclic motif in clinical use with a high degree of potency as well as selectivity[10] has inspired synthetic chemists to explore a broader use of macrocyclic scaffolds in medicinal chemistry. The past two decades have witnessed that the combination of metal with di-or-oligofunctional ligands allows the creation of a large number of metallosupramolecular architectures having either macrocyclic, cage-like or polymeric structures.[11] A series of different applications such as selective molecular and ion recognition, separation, storage, transport and catalysis are envisioned for these systems.[12] A variety of guest substrates have been encapsulated and stabilized by metallomacrocyclic structures as well as chemical reactions being catalyzed, within these "micro reactor" cores.[13] Recently our group has successfully utilized 4,4′-diaminodiphenyl ether to derive a number of bisimines, diamines, bimetallic metallomacrocyclic structures and systematically investigated these derivatives from medicinal perspectives.[14a-c]

In the light of these observations, it was pertinent to select dap as a lead compound to derive 4,4′-bis(2-(cyclohexylamino) acetamido)diphenylsulfone (L^1), 4,4′-bis(2-(isopropylamino) acetamido)diphenylsulfone (L^2), 4,4′-bis(2-(n-butylamino) acetamido)-diphenylsulfone (L^3) and their ensuing metallomacrocyclic dithiocarbamate complexes to explore their possible anticancer abilities against human cancer cell lines viz. Hep G2 (Hepatoma) and C6 (Glioblastoma). Hepatocytes have the ability to metabolize, detoxify and inactivate exogenous compounds such as drugs and also endogenous compounds like steroids and thus liver is a major site of synthesis and metabolism of major biomolecules like proteins and carbohydrates. In particular, Hep G2 (hepatoblastoma) cell line is commonly used for xenobiotic metabolic studies as it maintains many specialized functions of liver cells. Moreover, neuronal

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Synthesis and spectral characterization of bimetallic metallomacrocyclic structures [M^{II}_2-μ^2-bis-{(κ^2S,S-$S_2CN(R)C_6H_4)_2O$}] (M = Ni/Zn/Cd): density functional theory and host–guest reactivity studies†

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A series of bimetallic dithiocarbamate metallomacrocyclic complexes [M^{II}_2-μ^2-bis-{(κ^2S,S-$S_2CN(R)C_6H_4)_2O$}]·L {R = benzyl; M = Ni^{II} **1**, Zn^{II} **2**, Cd^{II} **3**; R = 1-naphthylmethyl; M = Ni^{II} **4**, Zn^{II} **5**, Cd^{II} **6** and L = Et_3N for **1**, **4** only} were efficiently synthesized through a self-assembly process involving 4,4′-bis(arylmethylamino)diphenyl ethers L^1, L^2, CS_2 and $M(OAc)_2$. The compounds were characterized by micro-, relevant spectroscopic (ESI-MS, FT-IR, ^1H, ^{13}C and ^1H DOSY NMR, UV-visible absorption, fluorescence) and TGA/DTA analyses. The geometry of all the complexes has been optimized by a DFT method with B3LYP/LanL2DZ basis sets. Notably, the fluorescence properties of L^1 and L^2 were enhanced upon complexation with Ni, Zn or Cd metal ions in the binuclear complexes **1–6**. Ni^{II} complexes **1** and **4** gave stable residual masses of 20.1% and 29.5% in their thermogravimetric analyses which correspond to NiS (calc. 14.18% for **1** and 12.26% for **4**) plus char, respectively. A Job plot experiment reveals the ability of macrocycles **1–4** to form host–guest complexes in 1 : 1, 1 : 2 and 2 : 1 stoichiometry, depending on the relative sizes of the hosts and guests and their electronic nature.

Introduction

Coordination-driven self-assembly provides a robust tool for the preparation of a broad range of supramolecular structures that includes macrocyclic cages or polymers with fascinating physicochemical properties.[1–7] Among these structures, metallomacrocyclic structures with varied cavity sizes are of particular interest due to their potential applications in catalysis,[4] host–guest chemistry,[2,5] molecular and ion sensing,[6] separation, transport, and storage.[7] The insights of changes induced by external perturbations on self-assembly can facilitate the design and development of macrocyclic compounds with potential applicability in drug delivery, two-phase transport and biosensing.[8] In this connection, the ability of dithiocarbamate ligands to display varied binding modes while stabilizing various transition/non-transition metal ions present in different oxidation states, makes them highly promising for the development of diversified self-assembled molecular structures.[2,4e,5a,b,9,10]

Besides, transition metal complexes with sulphur rich ligands exhibit a wide range of applications in the area of electrical conductivity, molecular magnetism, electrochemical, optoelectronic properties and biological processes.[11,12] Their potential uses in medicine reportedly arise due to the existence of the dithiocarbamate moiety in a variety of biologically active molecules.[13] These complexes have also been used as a single source precursor for the synthesis of high-quality semiconductor nanoparticles.[14] Their widespread industrial applications such as foam rubber, fungicides, effective heat stabilizers, antioxidant action, reprocessing of polymers have been advocated by thermogravimetric study[15] which indeed suggests the suitability of the complexes to be used as single source precursors for the synthesis of metal sulphide nanoparticles and thin films.[16] The size and shape of the metal sulphide nanoparticles greatly depends on the nature of the ligand framework of the complexes which in turn affects the fundamental properties such as optical, electrical and mechanical.[17]

Recently our group has utilized 4,4′-diaminodiphenyl ether to derive a number of bimetallic metallomacrocyclic structures and systematically investigated these derivatives from medicinal perspectives.[18] Earlier Professor N. Yoshida *et al.*[19] had demonstrated the use of bis-*N*,*O*-bidentate Schiff-base ligands derived from 4,4′-diaminodiphenyl methane/4,4′-diaminodiphenyl sulfone to bind two separate metal ions owing to the fact that the bridging group (–$C_6H_4CH_2C_6H_4$–/–

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Papers presented at National /State Level Seminars / Conferences –Poster Presentation.

1. National Seminar on Structures and Chemistry of Materials [SCM],15th October 2016, The Maharaja Sayajirao University of Baroda,Vadodara-390023.
2. National Seminar on Frontier Areas in Chemical Sciences, March19-2016, UGC-CAS II Program, Department of Chemistry, The Maharaja Sayajirao University of Baroda,Vadodara-390002.
3. National Conference on Material Characterization, NCMC-16, March 18-19, 2016.Department of Physics, The Maharaja Sayajirao University of Baroda-390002
4. 17th CRSI National Symposium in Chemistry, 6-8 February, 2015.CSIR-National Chemical Laboratory, Pune. India
5. National Workshop on X-Ray Crystallography, 19-25 Jan 2015.Department of Chemistry, The M. S. University of Baroda, Vadodara-390002.
6. Indian Society of Analytical Scientists, Baroda Chapter. Department of Chemistry. , The M. S. University of Baroda, Vadodara-390002.