ScienceDirect

Journal of Trace Elements in Medicine and Biology

Volume 79, September 2023, 127211

In vitro anti-proliferative, and *in silico* ribonucleotide reductase and pharmacokinetics studies of heteroleptic silver(I), nickel(II) and copper(II) complexes of 4-methyl-3-thiosemicarbazones and ibuprofen

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Received 13 April 2022, Revised 10 November 2022, Accepted 17 May 2023, Available online 18 May 2023, Version of Record 30 May 2023.

https://doi.org/10.1016/j.jtemb.2023.127211

Highlights

- Heteroleptic complexes of TSCs and ibuprofen were synthesized and characterized.
- *In vitro* anti-proliferative, apoptotic and cellular uptake activity were studied.
- *In silico* interaction with ribonucleotide reductase (RNRs) was analysed.
- *In silico* pharmacokinetics studies predicted the drug-likeness of the complexes.
- Copper(II) complexes with hydrophobic substituents showed enhanced activity.

Abstract

Objectives

The present research focuses on the *in vitro* anti-proliferative, and *in silico* ribonucleotide reductase and pharmacokinetics studies of twelve heteroleptic metal complexes of the general formulae [Ag(L^{1-4})(ibu)] (**1**–**4**) and [M(L^{1-4})$(ibu)_2$] (**5**–**12**), where L^{1-4} =2-(1-(4-substitutedphenyl)ethylidene)-*N*-methylhydrazinecarbothioamide, ibu =non-steroidal anti-inflammatory drug (ibuprofen), and M =Cu(II) and Ni(II).

Methods

Various spectroscopic techniques were used to authenticate the structure of the synthesized complexes. UV-Vis and cyclic voltammetry techniques were used to analyse the stability and the reducing ability of the complexes. *In vitro* anti-proliferative studies by MTT assay, apoptotic behaviour and cellular uptake studies were investigated followed by the *in silico* interaction with ribonucleotide reductase (RNR) enzyme.

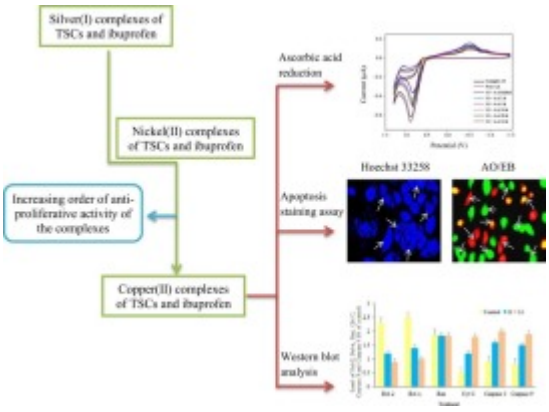
Results

The spectral studies predicted distorted tetrahedral geometry around silver(I) ion and distorted octahedral geometry around nickel(II) and copper(II) ions. The reducing ability of the copper(II) complexes was analysed using ascorbic acid by UV-Vis and cyclic voltammetry techniques, which authenticate the reducing ability of the complexes and the possible interactions within the cells. The *in vitro* anti-proliferative activity of the synthesized complexes against three cancerous (estrogen positive (MCF-7), estrogen negative (MDA-MB-231) and pancreatic (PANC-1)) and one normal (MCF-10a) cell lines by MTT assay showed enhanced activity for copper(II) complexes **11** and **12** containing the hydrophobic substituents. The apoptotic and cellular uptake studies showed that the complex **12** is readily taken up by PANC-1 cell lines and induces ROS-mediated mitochondrial and caspase-dependent apoptosis. The *in silico* studies indicated hydrogen bonding, hydrophobic and π-pair (π–π, π–σ and π–cation) interactions between the complexes and the ribonucleotide reductase (RNR) enzyme. The *in silico* pharmacokinetics studies of the complexes predicted the drug-likeness characteristics of the complexes.

Conclusion

The synthesized complexes are found to be less toxic to normal cells and inhibit the growth of cancerous cells by inducing mitochondrial-mediated and caspase dependent apoptotic pathway in PANC-1 cells.

Graphical Abstract



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Twelve heteroleptic metal (Ag(I), Ni(II) and Cu(II)) complexes were designed, which showed enhanced cytotoxicity activity for copper(II) complexes against MCF-7, MDA-MB-231 and

PANC-1 cell lines and found to induce ROS-mediated mitochondrial and caspase-dependent apoptotic behaviour, and interact with RNR enzyme.

Introduction

Over the past few decades multifunctional donor ligands such as thiosemicarbazones (TSCs) have gained pervasive success, in particular, for their biological applications because of their π-delocalization, configurational flexibility and versatility of donor atoms [1]. The biological activities of TSCs improve significantly on complex formation with various metal ions. The wide range of biological applications of TSCs and their metal complexes include antibacterial, antifungal, antiviral, antileukemic, anti-HIV and antitumor activities [2], [3]. Triapine (3-aminopyridine-2-carbaldehydethiosemicarbazone) is a well-known antitumor compound, which crossed many clinical trials but failed due to severe side effects [4]. It is presumed that the inhibition of DNA topoisomerase-II enzyme, which regulates DNA topology leads to the cytotoxicity activity of thiosemicarbazone-based metal complexes [5]. The platinum-based drugs such as cisplatin, carboplatin and oxaliplatin are ushered success models for healing various types of cancers, and paved way towards the interest in developing metallodrugs to fight cancer. However, their usage is in a narrow spectrum due to unusual side effects such as ototoxicity, nephrotoxicity and neurotoxicity [6], [7]. This forces the researches to develop a far-reaching search in designing nonplatinum-based metallodrugs with ameliorated pharmacological properties.

Many nonplatinum-based metal complexes have been designed with various metals and ligand combination, and evaluated for both *in vitro* and *in vivo* antitumor activities [8]. Silver, nickel and copper complexes exhibit promising activities because of their known biological roles. Silver is already in use for many medical applications such as antibacterial, antiseptic and anti-inflammatory agents, and as antibiotic coating in medical devices and in wound dressing [9], [10]. Many nickel bearing enzymes catalyze various reactions in living organisms, and play an important role in biosystems [11], [12]. Copper is a trace dietary mineral of living organisms, and plays key role as catalytic and structural centre of various enzymes involved in biological process [13]. Several classes of thiosemicarbazone-based silver, nickel and copper complexes have been designed and successfully evaluated for their anti-proliferative activity against cancerous and normal cell lines [14], [15], [16], [17].

The non-steroidal anti-inflammatory drugs (NSAIDs) are used in the treatment of various diseases such as inflammation, pain and fever, and non-selectively inhibit cyclooxygenase (COX-1 and COX-2) metabolism, which further inhibits cancer growth. Ibuprofen (α-methyl-4-(isobutyl)phenylacetic acid), a member of phenylalkanoic acids, is a non-steroidal anti-

inflammatory drug, used as analgesic, antipyretic and anti-inflammatory agent [18]. It is the first member of propionic acid derivatives to replace aspirin in 1969, due to which ibuprofen gained importance in research. In order to reduce the side effects associated with the NSAIDs, a successful strategy is the usage of d-block metal complexes of NSAIDs as a therapeutic agent. For example, nickel complexes of NSAID, ibuprofen, showed promising anti-proliferative activity against lung fibroblast (WI-26VA4) cells [19]. Thus, the interest towards NSAIDs coordinated to metal ions have been increased with designing more efficient metallodrugs, which showed significant results such as the improved pharmaceutical activity with reduced toxicity of NSAIDs, and exhibiting additional efficacy such as antitumor activity [20], [21], [22], [23].

An in-depth literature survey revealed that the long-standing reports has not been appeared till date on the heteroleptic metal complexes of NSAIDs with thiosemicarbazone, and their anti-proliferative and molecular docking studies. In accordance of these observations and in continuation of our recent report on heteroleptic metal complexes with terpyridines and NSAIDs, naproxen [24], [25], the current research has been converged in developing new heteroleptic metal complexes of thiosemicarbazones and ibuprofen, as the anti-proliferative activity of ibuprofen complexes was found to be inadequate in literature. The *in vitro* anti-proliferative activity of the complexes was tested against one normal cell line (MCF-10a) and three cancerous (estrogen positive (MCF-7), estrogen negative (MDA-MB-231) and pancreatic (PANC-1)) cell lines by MTT reduction assay. Interest is extended in exploring the mode of interaction of metal complexes with ribonucleotide reductase enzyme (RNR), and to screen the complexes for drug-likeness and ADMET properties by *in silico* molecular docking and pharmacokinetics studies, respectively.

Section snippets

Chemicals

4-Methyl-3-thiosemicarbazone, silver(I) nitrate ($AgNO_3$), nickel(II) chloride ($NiCl_2.6H_2O$), copper(II) chloride ($CuCl_2.2H_2O$) and Ibuprofen were purchased from Sigma Aldrich. The

solvents such as methanol, DMF and DMSO were purchased as analytical grade from E. Merck and used as such without any further purification. The supporting electrolyte, tetra(*n*-butyl)ammonium perchlorate (TBAP), used in the electrochemical measurements, was purchased from Fluka (Switzerland).…

Physical measurements

Elemental analysis (CHN) of…

Design and synthesis of heteroleptic silver(I), nickel(II) and copper(II) complexes of 4-methyl-3-thiosemicarbazones and ibuprofen

A series of heteroleptic silver(I), nickel(II) and copper(II) complexes with general formulae $[AgL^{1-4}(ibu)]$ (**1–4**) and $[ML^{1-4}(ibu)_2]$ (**5–12**) were synthesized with good yield by the reaction of 2-(1-(4-substitutedphenyl)ethylidene)-*N*-methylhydrazinecarbothioamide with ibuprofen/KOH in the presence of $AgNO_3$/$NiCl_2.6H_2O$/$CuCl_2.2H_2O$ in methanol (Scheme 1, Scheme 2). Trials to obtain good quality crystals under various conditions and solvents went unsuccessful. All the complexes were found to be…

Conclusion

In this work, twelve heteroleptic silver(I), nickel(II) and copper(II) complexes (**1**–**12**) containing 2-(1-(4-substitutedphenyl)ethylidene)-*N*-methylhydrazinecarbothioamide as the main ligand and ibuprofen as an auxiliary ligand are reported. The spectral and magnetic studies suggested distorted tetrahedral geometry around silver(I) ion, and distorted octahedral geometry around nickel(II) and copper(II) ions. The reduction ability of the copper(II) complexes in the presence of reducing agent,…

Ethical approval

This work does not contain any studies regarding to human or animal participants performed by any of the authors.…

CRediT authorship contribution statement

Sundaram Bharathi: Conceptualization, Methodology, Investigation, Software, Writing – original draft. **Dharmasivam Mahendiran:** Resources, Visualization, Data curation. **Sumeer**

Ahmed: Software, Visualization, Data curation. **Aziz Kalilur Rahiman:** Conceptualization, Validation, Supervision, Writing – review & editing. All authors have given approval to the final version of the manuscript.…

Declaration of Competing Interest

All the authors declare no conflict of interest.…

Acknowledgements

The authors thank Department of Chemistry, IIT Madras, Chennai - 600 036, for ESI-mass data, and SIF, Chemistry Division, VIT, Vellore - 632 014, for ^{1}H NMR data.…

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