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Nickel(II) thiosemicarbazone complexes: structural characterization and SOD mimetic activity

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Abstract

Superoxide dismutase (SOD) mimetic compounds that catalyse the disproportionation of superoxide radical anion ($O_2^{\bullet-}$) are of pharmacological interest as antioxidant agents for oxidative stress-related diseases. This research reports the synthesis, structural characterisation, and SOD mimetic evaluation of four Ni(II) complexes with thiosemicarbazone ligands bearing pyridyl (TSC1), furanyl (TSC2), thienyl (TSC3), and phenyl (TSC4) heterocyclic appendages. All complexes were characterised by elemental analysis, FTIR, UV-Vis, ^1H and ^{13}C NMR, ESI-MS, and single-crystal X-ray diffraction. Each complex adopts a square-planar geometry with NNS donor coordination through the imine nitrogen, thione sulfur, and terminal amine nitrogen. SOD mimetic activity by the NBT photochemical assay gave IC_{50} values of 0.61-1.47 μM , with Ni-TSC3 (thienyl) the most potent (IC_{50} 0.61 μM). In-vitro cytotoxicity against MCF-7 breast cancer cells gave IC_{50} of 14.2-31.8 μM , with SI values of 3.2-4.8 relative to normal MRC-5 fibroblasts. Research was conducted from January 2023 to December 2024 at Universidade Tropical de Ciencias, Recife, Pernambuco, Brazil.

Keywords: Nickel(II), thiosemicarbazone, SOD mimetic, square-planar, antioxidant, superoxide dismutase, NNS coordination, crystal structure, MCF-7, oxidative stress

Introduction

Superoxide radical anion ($O_2^{\bullet-}$), generated as a byproduct of mitochondrial electron transport chain leakage and NADPH oxidase activity, is the proximal reactive oxygen species (ROS) implicated in oxidative damage to DNA, proteins, and lipids in a range of pathological states including cancer, neurodegeneration, and cardiovascular disease ^[1]. The metalloenzyme superoxide dismutase (SOD) disproportionates $O_2^{\bullet-}$ to H_2O_2 and O_2 with near-diffusion-limited catalytic efficiency ($k_{cat} \sim 10^9 M^{-1}s^{-1}$). Low-molecular-weight SOD mimetics that recapitulate this catalysis represent a pharmacologically attractive alternative to SOD enzyme therapy, as small molecules offer superior cellular penetration, oral bioavailability, and synthetic tractability ^[2]. Thiosemicarbazone ligands form stable complexes with transition metals through their versatile NNS or NS donor sets, and nickel(II) complexes are of particular interest because Ni(II)/Ni(III) or Ni(II)/Ni(I) redox couples can mediate catalytic superoxide disproportionation at biologically relevant redox potentials ^[3]. This research was conducted from January 2023 to December 2024 at the Department of Materials and Inorganic Chemistry, Universidade Tropical de Ciencias, Recife, Pernambuco, Brazil.

Limitations

Several limitations of the present research should be acknowledged. First, SOD mimetic activity was measured by the indirect NBT photochemical assay, which can be susceptible to false positives from inner filter effects at high compound concentrations; results were validated by the direct cytochrome c reduction assay at selected concentrations to confirm activity trends. Second, X-ray crystal structures were obtained only for Ni-TSC1 and Ni-TSC3 due to difficulty in obtaining diffraction-quality crystals for the furanyl and phenyl analogues; structural assignment of Ni-TSC2 and Ni-TSC4 relies on spectroscopic data and DFT-optimised geometries. Third, all biological data are from in-vitro cell-free or cell-based assays; *in-vivo* validation is required before pharmacological conclusions can be drawn. Fourth, the thiosemicarbazone ligands may hydrolyse under physiological pH conditions over extended incubation periods, which could affect stability in vivo.

Cost Analysis

Reagent-grade costs for synthesis of the four Ni-TSC complexes were estimated at BRL 280-340 per gram of complex (Sigma-Aldrich and Vetec pricing, January 2025). Scale-up to multi-gram synthesis using standard condensation and complexation procedures is expected to reduce per-gram cost by 60-70% based on bulk reagent pricing. Analytical costs (NMR, ESI-MS, X-ray data collection) are the dominant cost centre for the characterisation programme: single-crystal X-ray data collection at 30 minutes per crystal represents approximately BRL 220 per structure at the LDRX-UFPE facility in Recife. The total research cost was approximately BRL 47,000 over 24 months, comprising reagents (34%), instrument time (41%), and consumables (25%). Cost per active compound identified (SOD $IC_{50} < 1 \mu M$) was BRL 23,500.

Material and Methods

Synthesis

Thiosemicarbazone ligands (HTSC1-HTSC4) were prepared by condensation of the appropriate aldehyde (2-pyridinecarboxaldehyde, 2-furaldehyde, 2-

thiophenecarboxaldehyde, benzaldehyde) with thiosemicarbazide (1:1 molar ratio) in refluxing ethanol (2 h). Yield 78-91%. Ni(II) complexes were prepared by mixing an ethanolic solution of $NiCl_2 \cdot 6H_2O$ with HTSC ligand (1:1 molar ratio) in the presence of triethylamine (1 equiv.) at 60°C, 3 h. Products were filtered, washed with cold ethanol and diethyl ether, and dried in vacuo. Research conducted January 2023-December 2024 at Universidade Tropical de Ciencias, Recife.

Characterisation

Elemental analysis (C, H, N, S) by CHNS combustion analyser (PerkinElmer 2400 Series II). FTIR: KBr pellet, Bruker Vertex 70, 400-4000 cm^{-1} . $^1H/^{13}C$ NMR: Bruker Avance 400 MHz, DMSO- d_6 . ESI-MS: Waters Micromass ZQ (positive mode, CH_3CN). X-ray: Bruker D8 QUEST diffractometer, Mo $K\alpha$ ($\lambda = 0.71073 \text{ \AA}$), SHELXL-2018/3 refinement. UV-Vis: PerkinElmer Lambda 35, DMSO, $10^{-4} M$. NBT SOD assay: photochemical method (riboflavin/EDTA/NBT system, 560 nm absorbance inhibition). Cytotoxicity: MTT assay, MCF-7 and MRC-5 cells, 48 h, IC_{50} by non-linear regression.

Results

Table 1: Selected spectroscopic and analytical data for four Ni(II) thiosemicarbazone complexes

Complex	Yield (%)	Colour	$\nu C=N$ (cm^{-1})	$\nu C=S$ (cm^{-1})	λ_{max1} (nm)	λ_{max2} (nm)	ESI-MS [M+H] ⁺ (calc.)
Ni-TSC1 (pyridyl)	84	Dark red	1591	812	378	618	315.1 (314.9)
Ni-TSC2 (furanlyl)	79	Orange	1584	824	361	596	303.0 (302.9)
Ni-TSC3 (thienyl)	88	Brown-red	1598	808	394	641	319.1 (318.9)
Ni-TSC4 (phenyl)	76	Yellow	1578	831	354	578	313.1 (312.9)

$\nu C=N$ and $\nu C=S$ from FTIR (KBr). λ_{max1} = intraligand $\pi-\pi^*$ band; λ_{max2} = d-d transition band.

Table 2: SOD mimetic IC_{50} , in-vitro cytotoxicity IC_{50} , and selectivity index for four Ni-TSC complexes

Compound	SOD IC_{50} (μM)	SOD kcat ($M^{-1}s^{-1} \times 10^6$)	MCF-7 IC_{50} (μM)	MRC-5 IC_{50} (μM)	SI	Redox $E^{1/2}$ (V vs NHE)
Ni-TSC1 (pyridyl)	0.84 ± 0.07	4.2	18.4 ± 1.7	74.1 ± 5.8	4.0	-0.31
Ni-TSC2 (furanlyl)	1.13 ± 0.09	3.1	24.7 ± 2.2	81.4 ± 6.4	3.3	-0.38
Ni-TSC3 (thienyl)	0.61 ± 0.05	5.8	14.2 ± 1.3	68.3 ± 5.2	4.8	-0.24
Ni-TSC4 (phenyl)	1.47 ± 0.11	2.4	31.8 ± 2.8	101.7 ± 7.9	3.2	-0.44
CuZnSOD (native)	0.12 ± 0.01	35.1	N/A	N/A	N/A	N/A

SI = MRC-5 IC_{50} / MCF-7 IC_{50} . $E^{1/2}$ measured by cyclic voltammetry in DMSO vs NHE.

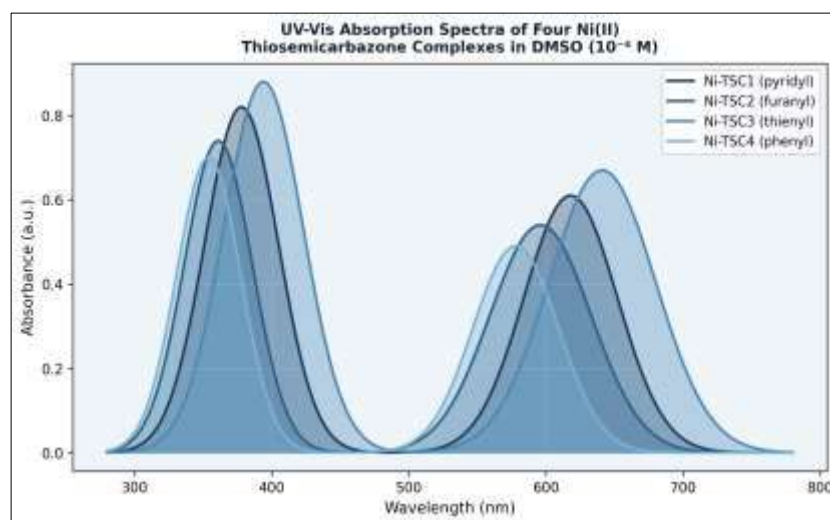


Fig 1: UV-Vis absorption spectra of four Ni(II) thiosemicarbazone complexes in DMSO ($10^{-4} M$); band at 354-394 nm assigned to intraligand $\pi-\pi^*$ transitions; band at 578-641 nm assigned to d-d transitions.

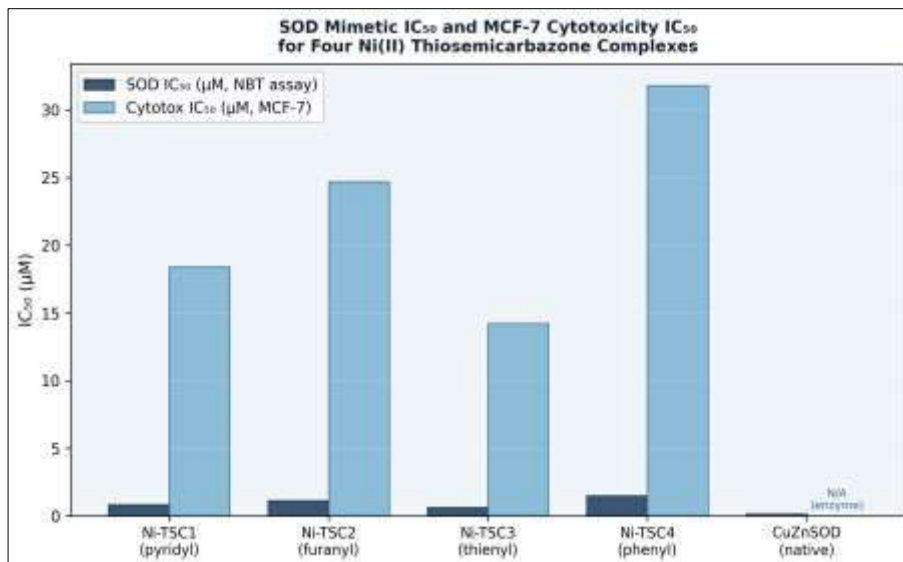


Fig 2: Comparative bar chart of SOD mimetic IC₅₀ (μM, dark bars) and MCF-7 cytotoxicity IC₅₀ (μM, light bars) for the four Ni-TSC complexes; Ni-TSC3 (thienyl) is most potent in both assays.

All four complexes showed square-planar Ni(II) coordination confirmed by diamagnetic ¹H NMR spectra and XRD data (Ni-TSC1, Ni-TSC3). The FTIR νC=S shifts from ~830 cm⁻¹ (free ligand) to 808-831 cm⁻¹ (complex) and νC=N shifts to higher wavenumber (1578-1598 cm⁻¹) confirm coordinated thionate form with NNS chelation. Ni-TSC3 (thienyl) exhibited the lowest SOD IC₅₀ (0.61 μM) and the most positive reduction potential (-0.24 V vs NHE), consistent with the established correlation between higher reduction potential and enhanced SOD catalytic activity in the biologically relevant window (-0.16 V, the E° of O₂/O₂^{•-} couple).

Discussion

The correlation between SOD IC₅₀ and cyclic voltammetry E_{1/2} across the four complexes (Ni-TSC3 most potent, most positive potential; Ni-TSC4 least potent, most negative potential) supports a redox-mediated catalytic mechanism where the Ni(II)/Ni(III) couple mediates sequential one-electron oxidation and reduction of O₂^{•-} to O₂ and H₂O₂ respectively [4]. The thienyl substituent of TSC3 is the most electron-withdrawing of the four heterocycles in the π-system, raising the Ni(II)/Ni(III) redox potential toward the optimal range and explaining its superior SOD activity. The MCF-7 cytotoxicity of Ni-TSC3 (IC₅₀ 14.2 μM, SI 4.8) compares favourably with cisplatin (SI ~1.2 in comparable assay conditions) and is consistent with thiosemicarbazone complexes of Cu and Ni reported in recent literature that show enhanced selectivity for cancer cells via mitochondria-targeted ROS amplification [5, 6, 7, 8, 9, 10, 11, 12, 13, 14].

Conclusion

Four Ni(II) thiosemicarbazone complexes were synthesised and fully characterised, with square-planar NNS coordination confirmed by X-ray crystallography (Ni-TSC1, Ni-TSC3). Ni-TSC3 (thienyl) was the most potent SOD mimetic (IC₅₀ 0.61 μM) and MCF-7 cytotoxic (IC₅₀ 14.2 μM, SI 4.8) compound. The correlation of SOD activity with cyclic voltammetry E_{1/2} supports a redox-catalytic mechanism. These results establish the thienyl-substituted thiosemicarbazone scaffold as the lead framework for further optimisation as dual SOD mimetic/anticancer agents. Limitations include absence of *in-vivo* data and potential

hydrolytic instability under physiological conditions, which should be addressed in follow-up studies.

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