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Letter to the Editor

### Letter to the Editor: Expanding the Polypharmacological Landscape of Dimethyltin(IV)–Edaravone Hybrids Beyond SET/HAT Mechanisms

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#### Letter to the Editor

The recent publication on *Dimethyltin(IV) formulations derived from 4-acylated edaravone* represents a valuable contribution to the growing field of hybrid antioxidant pharmacophores. While the study elegantly delineates the single-electron transfer (SET) and hydrogen-atom transfer (HAT) pathways underlying the antioxidant behavior of these complexes, I wish to highlight an important and underexplored dimension: their broader polypharmacological and multitarget potential, particularly on non-canonical redox-responsive pathways and toxicological interfaces that extend beyond classical radical-quenching mechanisms <sup>[1]</sup>.

Edaravone itself is a paradigmatic multitarget agent, exerting effects on lipid peroxidation, mitochondrial stabilization, microglial activation, and NLRP3 inflammasome signaling. When conjugated with dimethyltin(IV), the resulting hybrid scaffolds acquire additional coordination-driven reactivity, altered lipophilicity, and enhanced membrane permeability—features that collectively expand their biological reach. The presence of Sn–O chelate rings, as demonstrated in the reported complexes, suggests the potential for metal-mediated interactions with nucleophilic biomolecules, including thiol-rich proteins, transcription factors, and redox-sensitive enzymes <sup>[1, 2]</sup>.

#### 1. Polypharmacology Beyond Radical Scavenging

Dimethyltin(IV) complexes are known to modulate multiple intracellular pathways through mechanisms such as <sup>[1, 3]</sup>:

- Inhibition of thioredoxin reductase (TrxR), a master regulator of redox homeostasis. Organotin compounds have been shown to bind the selenocysteine active site, leading to downstream effects on apoptosis and oxidative signaling.
- Interference with mitochondrial permeability transition pores (mPTP), influencing calcium flux and apoptotic cascades.
- Modulation of MAPK and NF-κB pathways, which are central to inflammation and cell survival.

Given that edaravone derivatives already influence oxidative and inflammatory circuits, their conjugation with dimethyltin(IV) may produce synergistic multitarget effects, positioning these hybrids as promising candidates for diseases characterized by network-level dysregulation, such as neurodegeneration, ischemia-reperfusion injury, and metabolic inflammation <sup>[1, 3]</sup>.

#### 2. Potential for Metal-Mediated Enzyme Interactions

The distorted octahedral geometry and electrophilic tin center in these complexes raise the possibility of direct interactions with metalloproteins, including:

- Zinc-dependent dehydrogenases
- Metalloproteases
- Iron–sulfur cluster proteins

Such interactions could modulate enzymatic activity in ways that are therapeutically beneficial—or toxicologically concerning—depending on dose and exposure duration <sup>[4, 5]</sup>.

#### 3. Toxicological Considerations

While the antioxidant potential of these complexes is compelling, organotin compounds are historically associated with cytotoxicity, endocrine disruption, and mitochondrial injury. Therefore, any therapeutic development must integrate a rigorous toxicological framework.

Key considerations include:

- Sn–C bond stability: cleavage may release reactive tin species capable of binding DNA or proteins.
- Bioaccumulation potential: lipophilic complexes may persist in membranes and adipose tissue.
- Mitochondrial toxicity: organotins can uncouple oxidative phosphorylation, leading to ATP depletion.
- Immunotoxicity: modulation of T-cell signaling and cytokine production has been reported for related compounds.

Interestingly, the hybridization with edaravone may mitigate some toxic effects by enhancing antioxidant buffering capacity, but this hypothesis requires empirical validation through *in vitro* hepatotoxicity assays, mitochondrial respiration profiling, and *in vivo* pharmacokinetic–toxicokinetic studies <sup>[1, 6]</sup>.

#### 4. Future Directions

To fully harness the therapeutic potential of dimethyltin(IV)–edaravone hybrids, I propose the following research priorities <sup>[1, 6]</sup>:

1. Network pharmacology modeling to map predicted multitarget interactions.
2. Proteomic profiling to identify off-target protein binding signatures.
3. Assessment of SPLET and RA (radical addition) pathways, which may operate alongside SET/HAT mechanisms.
4. Comparative toxicology between mono-acylated and di-acylated complexes to determine structure–toxicity relationships.
5. Evaluation in disease-relevant models, such as neuronal oxidative injury and endothelial inflammation.

These steps will clarify whether the observed antioxidant activity represents only one facet of a broader polypharmacological profile <sup>[1, 3]</sup>.

#### Conclusion

Dimethyltin(IV)–edaravone hybrids represent a promising class of multitarget agents whose biological effects extend beyond classical SET and HAT pathways. Their potential to modulate redox enzymes, inflammatory signaling, and mitochondrial function warrants deeper investigation, particularly with respect to toxicological safety. A polypharmacology-informed approach will be essential to advance these complexes toward translational relevance <sup>[1, 2, 6]</sup>.

Sincerely,

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