Cobalt(III) Bis(thiosemicarbazones) as Therapeutic Agents in Hypoxic Environments

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Tumor Hypoxia

- Tumors outgrow blood supply resulting in oxygen deficiency
- Alters tumor cell biology
- Characteristically reductive environment with low pH

Copper Bis(Thiosemicarbazone) complexes

- Some Cu(II) complexes target hypoxia selectively
- Also being developed as diagnostic agent for PET imaging
Cobalt(III) Bis(Thiosemicarbazone) Prodrugs

- Kinetically Inert
- Octahedral Coordination
- Reduces to kinetically labile Co(II) to release ligands into cells

\[
\begin{aligned}
R &= H \\
R' &= H \text{ or } CH_3 \\
L &= \text{Various Axial Ligands}
\end{aligned}
\]
Bis(Thiosemicarbazones) or btsc

- The R,R’ backbone of the btsc modifies complex reduction potentials.
- Methyl groups (CH$_3$) donates more electrons, decreasing the reduction potential.
- Tetradentate ligand.
- Known anti cancer agent.
Bis(Thiosemicarbazones)

PTS

GTS

ATS
Axial Ligands

- Want to modulate reduction potential using ligands
- Ammonia is best sigma donor
- Water solubility for ligands decreases from left to right
- Nitrobenzylamine is hypoxia activated
Cobalt(III) GTS Benzylamine
Cytotoxicity of Co(III) complexes

• Believed to act by thymidine and uridine inhibition

• Also believed to inhibit ATP production

• Complex Cytotoxicity is equatorial ligand dependent (GTS>PTS>ATS)

• Cytotoxicity determined by mtt assay
CoGTS(Im)$_2$ and CoGTS(NH$_3$)$_2$ Exhibit Modest Hypoxia Selectivity

![Bar graph showing EC$_{50}$ (Normoxia)/EC$_{50}$ (Hypoxia) for various compounds. Cisplatin, Tirapazamine, GTS, CoGTS(NH$_3$)$_2$, and CoGTS(Im)$_2$ are compared. The graph indicates that Tirapazamine and CoGTS(Im)$_2$ have selectivity in hypoxia.]
[CoGTS(Im)$_2$]$^+$ Shows Selective Toxicity Toward Cancer Cells

Cytotoxicity of [CoGTS(Im)$_2$]$^+$ in MRC-5 cells

Cytotoxicity of [CoGTS(Im)$_2$]$^+$ in HeLa cells
Conclusions and Future Directions

• Nine Co\textsuperscript{III}btsc(L)\textsubscript{2} complexes have been synthesized

• Complexes exhibit cancer selectivity and some hypoxia selectivity

• These complexes will be tested for imaging

• Electrochemical studies will be performed

• Therapeutic mechanisms require further study
Thank you!

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