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Novel Cu-TSBG Compounds Targeting Norephinephrine Transporter for Neuroblastoma Therapy

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Extended Abstract

Purpose: Numerous copper complexes were found to have strong anticancer activities, but clinical application of anticancer copper complexes was hampered by nonspecific toxicity on normal tissues or organs. Targeted delivery of anticancer copper complexes to malignant cells is a promising approach for enhancing efficacy of anticancer drugs and minimizing side effects. 8-hydroxyquinoline-2-carboxaldehyde–4,4-dimethyl-3-thiosemicarbazide (CuHQDMTS) and copper 8-hydroxyquinoline-2-carboxaldehydethiosemicarbazide complex (CuHQTS) are two anticancer copper complexes with potent anticancer activity against cisplatin-resistant neuroblastoma cells. The purpose of this study is to synthesize neuroblastoma-specific anticancer agents by conjugating CuHQTS with metaiodobenzylguanidine (MIBG) ligand targeting norephinephrine transporter for targeted therapy of cisplatin-resistant neuroblastoma.

Methods: MIBG is a ligand with high affinity binding to norephinephrine (NE) transporter highly expressed on neuroblastoma and other neuroendocrine tumor cells. Radiolabeled MIBG was used as a radiopharmaceutical for diagnostic imaging and radionuclide therapy of neuroblastoma. We hypothesize that MIBG ligand can be used as a delivery vehicle for targeted delivery of CuHQTS to neuroblastoma cells expressing norephinephrine (NE) transporter for treatment of neuroblastoma. To test our hypothesis, new anticancer copper complexes were synthesized by connecting CuHQTS to MIBG ligand, followed by characterization and testing for neuroblastoma cell-specific cell growth inhibition assay of these new anticancer copper complexes consisting of CuHQTS and MIBG ligand.

Results: Cu(m-TSBG)2 and Cu(p-TSBG)2, two new anticancer copper complexes consisting of CuHQTS and MIBG ligand, were synthesized, along with synthesis of two control compounds, Cu(m-TSB)2 and Cu(p-TSB)2. Cu(m-TSB)2 and Cu(p-TSB)2 had similar structures to Cu(m-TSBG)2 and Cu(p-TSBG)2, but absence of a benzylguanidinegroup. Growth of neuroblastoma cells was inhibited after treatment with Cu(m-TSBG)2 or Cu(p-TSBG)2. In contrast, Cu(m-TSBG)2 or Cu(p-TSBG)2 showed only weak cell growth inhibition activity on U87 glioblastoma cells and PC-3 prostate cancer cells, suggesting neuroblastoma-specific anticancer activity of Cu(m-TSBG)2 or Cu(p-TSBG)2. Furthermore, Cu(m-TSB)2 and Cu(p-TSB)2 exhibited weaker cell growth inhibition activity on neuroblastoma cells than that showed by Cu(m-TSBG)2 or Cu(p-TSBG)2, suggesting critical role of abenzylguanidine group for targeting to NE transporter on neuroblastoma cells.

Conclusions: Two novel Cu(m-TSBG)2 and Cu(p-TSBG)2 anticancer compounds were synthesized and characterized for anticancer activity against neuroblastoma. These two new compounds consisting of CuHQTS connected onto an MIBG ligand demonstrated potent anticancer cancer activity against neuroblastoma cells. The Cu(m-TSBG)2 and Cu(p-TSBG)2 compounds are promising new agents for targeted therapy of cisplatin-resistant neuroblastoma based on potent anticancer activity of CuHQTS and capability of MIBG ligand as a delivery vehicle targeting NE transporter expressed on neuroblastoma cells.

References

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