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GROUP 10 THIOSEMICARBAZONE METAL COMPLEXES AS AN ANTIPROLIFERATIVE PLATFORM FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Introduction

Head and neck squamous cell carcinomas (HNSCC) remain associated with a high clinical burden and limited therapeutic options in advanced and recurrent disease, largely due to toxicity and resistance to conventional chemotherapy. In this context, metallopharmaceuticals with tunable coordination chemistry may offer a strategy to improve antitumor potency and tumor selectivity. Square-planar Group 10 complexes of nickel(II), palladium(II), and platinum(II) coordinated to thiosemicarbazones provide a chemically controlled platform to investigate metal-dependent antiproliferative responses in HNSCC models.

Objectives

To synthesize and characterize a series of Group 10 thiosemicarbazone metal complexes and evaluate their antiproliferative activity and tumor selectivity in HNSCC cellular models.

Materials and Methods

The thiosemicarbazone ligand H2bmt was synthesized and used to prepare square-planar complexes of the type [M(bmt)(PPh3)] (M = NiII, PdII, and PtII), along with chemical controls (free ligand, PPh3, and metal precursors). Compounds were characterized by FTIR, HRMS, and multinuclear NMR ($^{1}H/^{13}C/^{31}P$), including solution-stability assessment. Antiproliferative activity was investigated in SCC-25 and SCC-9 (tongue squamous cell carcinoma) and FaDu (hypopharyngeal squamous cell carcinoma), using HaCaT keratinocytes as a non-tumoral model. MTT assays were performed using serial dilutions across the micromolar range. In parallel, SRB assays (48h) were conducted using selected concentrations within the same micromolar window, enabling consistent comparison between methods. In SRB, growth was determined using T0 and T1 measurements, and GI50 values were obtained by sigmoidal regression. Cisplatin and 5-fluorouracil were used as positive controls.

Results

The complexes displayed clear metal-dependent antiproliferative profiles and cell line–specific sensitivity. Overall, HaCaT keratinocytes were largely preserved, with GI50 > 100 µM for most tested complexes, supporting a favorable selectivity window relative to tumor models. Among the candidates, C5 was the most potent compound, showing GI50 = 0.3 µM in FaDu, while remaining non-cytotoxic to HaCaT within the tested range (GI50 > 100 µM). In SCC-9, two compounds stood out: C4 (GI50 = 1.7 µM) and C7 (GI50 = 2.0 µM), both with GI50 > 100 µM in HaCaT, indicating tumor-directed activity. C6 showed the most consistent tumor activity across models (GI50 = 23.6 µM in SCC-25; 7.8 µM in SCC-9; 7.3 µM in FaDu) while also maintaining GI50 > 100 µM in HaCaT, suggesting an improved safety margin. In contrast, C2 and C3 were inactive (GI50 > 100 µM) across the evaluated tumor lines. Reference drugs behaved as expected, with cisplatin showing high activity but measurable impact in HaCaT (GI50 = 7.4 µM) and 5-fluorouracil exhibiting moderate broad activity including HaCaT.

Conclusion

Group 10 thiosemicarbazone complexes constitute a promising antiproliferative platform for HNSCC with a selectivity pattern supported by limited effects on HaCaT (GI50 > 100 µM) for the most active candidates. Based on GI50 profiling, C5 is prioritized as the lead compound (highest potency in FaDu with preserved HaCaT), while C4 and C7 are highlighted for SCC-9 sensitivity, and C6 for consistent multi-line activity combined with a favorable non-tumoral profile. These candidates warrant downstream mechanistic investigation and expanded validation.

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Keywords

HNSCC; Thiosemicarbazone; Group 10 metal complexes; Nickel; Palladium; Platinum; SRB; GI50; Tumor selectivity

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