

Article

Synthesis and Antitumor Activity of Metallates Incorporating Functionalized Azolium Salts

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Abstract

Azolium-derived metallates are well-established intermediates in metal–*N*-heterocyclic carbene chemistry; however, their potential as standalone therapeutic agents remains largely unexplored. Herein, we report the first systematic biological investigation of a diverse family of Au(I), Cu(I), Pt(II), Pd(II), and Ru(II) metallates paired with functionalized azolium cations. The complexes were synthesized quantitatively through a simple, atom-economical, and purification-free protocol under aerobic conditions in technical-grade green solvents. Structural characterization by multinuclear NMR spectroscopy and single-crystal X-ray diffraction confirmed metallate formation and enabled the first isolation and crystallographic characterization of unprecedented azolium-derived ruthenates. The antiproliferative activity of the complexes was evaluated against cisplatin-sensitive (A2780) and cisplatin-resistant (A2780*cis*) ovarian cancer cell lines, alongside non-cancerous MRC-5 fibroblasts. Backbone-functionalized derivatives emerged as the most potent compounds, displaying activities comparable or superior to cisplatin in A2780 cells and up to 1000-fold higher potency in the resistant A2780*cis* model. Notably, unlike cisplatin, the metallates retained nearly unchanged IC₅₀ values across both ovarian cancer lines, strongly suggesting resistance-evasive mechanisms of action. While benzylazido- and methyl guanosine-derived complexes generally exhibited lower overall potency, several members retained significant activity in resistant cells while showing markedly reduced toxicity toward normal fibroblasts, highlighting promising selectivity profiles. Ethoxide-functionalized derivatives and platinum-based metallates combined pronounced anticancer activity with favourable therapeutic windows. Overall, this work establishes azolium-derived metallates as a previously overlooked class of metal-based anticancer agents combining exceptional synthetic accessibility, broad structural tunability, and remarkable activity against platinum-resistant ovarian cancer.



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1. Introduction

Platinum-based chemotherapeutics, such as cisplatin, carboplatin, and oxaliplatin, remain the cornerstone of clinical regimens for a wide variety of solid malignancies [1,2]. However, their long-term efficacy is severely compromised in aggressive diseases like ovarian cancer, which remains one of the most lethal gynecological malignancies worldwide, with high-grade serous ovarian carcinoma (HGSOC) accounting for most related deaths [3,4]. The strikingly poor prognosis of this disease is largely attributable to an insidious lack of early symptoms, meaning that diagnosis frequently occurs only after extensive peritoneal dissemination. Standard first-line therapy typically consists of cytoreductive surgery followed by platinum-based chemotherapy—most commonly cisplatin or carboplatin in combination with paclitaxel [5]. While initial clinical responses are often favourable, disease relapse is exceedingly frequent, and many patients eventually develop platinum-resistant or refractory disease. At this advanced stage, therapeutic options are severely limited. Furthermore, the clinical utility of classic platinum drugs is dose-limited by several systemic sideeffects, including nephrotoxicity, neurotoxicity, and ototoxicity [6]. This grim clinical scenario underscores the urgent need for novel chemotherapeutic strategies that exploit mechanisms of action fundamentally distinct from those of classical platinum drugs, drawing attention to alternative, biologically relevant late transition metals such as gold, copper, palladium, and ruthenium [7–31].

To address this critical need, our attention has focused on a highly promising yet biologically underexplored class of coordination compounds: metallates of late transition metals formed by the direct interaction of an azolium salt with a suitable metal precursor. Historically, this specific subset of metallates has been investigated almost exclusively from a mechanistic perspective. Pioneering studies, particularly the investigation of various “ate” complexes (aurates, cuprates, platinates, and palladates) by Nolan and coworkers, identified these species as the key transient intermediates in the synthesis of metal-*N*-heterocyclic carbene (NHC) complexes via the “weak base route” [32–36]. In this synthetic pathway, the metallate structural arrangement precisely positions the metal center in immediate proximity to the azolium proton. Upon the introduction of a mild, inexpensive inorganic base (e.g., potassium carbonate, sodium acetate, or aqueous ammonia), a transient carbene is generated and instantaneously trapped by the adjacent metal, entirely circumventing undesired decomposition pathways such as Wanzlick dimerization [32,37].

Beyond their mechanistic role, these azolium-derived metallates possess an exceptional, inherently translational pharmaceutical appeal. Modern drug discovery heavily prioritizes synthetic efficiency, favouring potential drug candidates that require a minimal number of synthetic steps, exhibit high yields, and circumvent complex or costly purification procedures. The metallates investigated herein perfectly satisfy these stringent demands: they can be synthesized with remarkable ease, either mechanochemically or in solution of technical-grade green solvents (acetone or ethanol) under aerobic conditions [32–36]. These reactions are characterized by reduced reaction times and quantitative yields, high to 100% atom economy with absolutely no byproduct formation. Consequently, these robust species have also emerged as highly valuable starting materials for the generation of metal-NHC complexes in continuous flow setups, enabling high-throughput synthesis, short residence times, and the eco-friendly recycling of both solvents and reactors.

Despite such elegant, atom-economical synthesis and intriguing structural properties, the exploration of these specific azolium-derived metallates as therapeutic agents remains remarkably scarce. To date, biological evaluations have been confined to simple aurates, which were identified as potent *in vitro* inhibitors of platelet-activating factor (PAF) with promising anti-atherogenic and anti-inflammatory properties [38,39], and allyl palladates [40,41]. We recently discovered that these organopalladium species trigger immunogenic cell death (ICD) and inhibit thioredoxin reductase (TrxR), exhibiting high cytotoxicity against ovarian cancer models [42]. However, while highly active, these palladates showed comparable, albeit slightly diminished, toxicity toward non-cancerous cells, highlighting a pressing need to widen their therapeutic window.

To bridge this fundamental gap and significantly expand the therapeutic scope of these compounds, this work presents the first comprehensive and comparative biological study of a broad class of functionalized metallates. By systematically varying the metal center (Pt(II), Au(I), Cu(I), Pd(II), and Ru(II)), we aimed to dissect its specific role when paired with three distinct categories of highly tailored azolium cations. Initially, we focused on backbone-functionalized azolium salts. These were selected due to the exceptionally promising biological and anticancer activities recently reported for metal-NHC complexes derived from analogous ligands [43], making them prime structural candidates for metallate formation.

Building upon this structural diversity, a second category features benzylazido-functionalized azolium salts. We recently utilized this versatile moiety to perform selective photobioconjugation on proteins and monoclonal antibodies [44]. Beyond its utility as a bio-orthogonal handle, organic azides are prominent pharmacophores embedded in numerous bioactive molecules and serve as precursors to nitrogen-containing heterocycles, with several azido-containing compounds displaying extensively documented antimicrobial, antiviral, and anticancer properties [45]. Crucially, we previously observed that complexes bearing this benzylazido function exhibit high propensity to crystallize [44]. In the present work, this physical property proved vital for the structural elucidation of our target metallates. Most notably, it enabled us to isolate and crystallographically characterize novel ruthenate species—an unprecedented milestone, as there are no prior reports in the literature detailing their existence.

Finally, with the aim of enhancing the selectivity and systemic tolerance of these novel metal-based drugs, we investigated a third class of cations consisting of guanosine-derived azolium salts. The incorporation of biologically active molecules is a highly effective strategy to improve pharmacological profiles; indeed, *in vivo* studies have repeatedly demonstrated that functionalizing metal complexes with endogenous biomolecules can facilitate cellular uptake by hijacking natural transport mechanisms, thereby increasing targeted accumulation in cancer cells [46]. To this end, the employed methylated guanosine salt mimics the 5' mRNA cap-0 structure—an essential biological feature responsible for mRNA stability, efficient translation, and immune system evasion—thus offering a strategic and biomimetic vector for selective cellular engagement [47].

Given the urgent clinical landscape described above, we selected robust ovarian cancer models to rigorously evaluate the antitumor activity of our synthesized metallates. By dissecting the synergistic roles of the metal center and the functionalized azolium salt, we aim to demonstrate that repurposing these synthetically pristine intermediates as primary active drugs can yield potent and innovative alternatives to classical cisplatin-based chemotherapy.

2. Results

2.1. Synthesis of Azolium-Derived Metallates

A defining advantage of metallates obtained from azolium salts lies in the remarkable simplicity and efficiency of their synthetic protocol. Utilizing azolium chlorides **1a–f**—which include backbone-functionalized derivatives (**1a–d**) [43], a benzylazido-functionalized salt (**1e**) [44], and a methylated guanosine derivative (**1f**) [48]—the corresponding metallates were readily accessed. The synthesis was performed by treating the salts with the appropriate metal precursors, namely [Au(dms)Cl] (dms = dimethyl sulfide), CuCl, [Pt(dms)₂Cl₂], [PdCl(allyl)]₂ (0.5 equiv.), and [Ru(*p*-cymene)Cl₂]₂ (0.5 equiv.). Notably, the reactions were carried out in technical-grade (“green”) acetone as a benign solvent, heating the mixture at 60 °C in air for 30 min (Scheme 1). The progress of the reaction is marked by a distinct color change within minutes and can be straightforwardly monitored via ¹H NMR spectroscopy. Furthermore, the workup procedure is exceptionally straightforward: the isolation of the desired products consists solely of solvent removal under reduced pressure, completely circumventing the need for any subsequent purification steps such as crystallization or column chromatography.

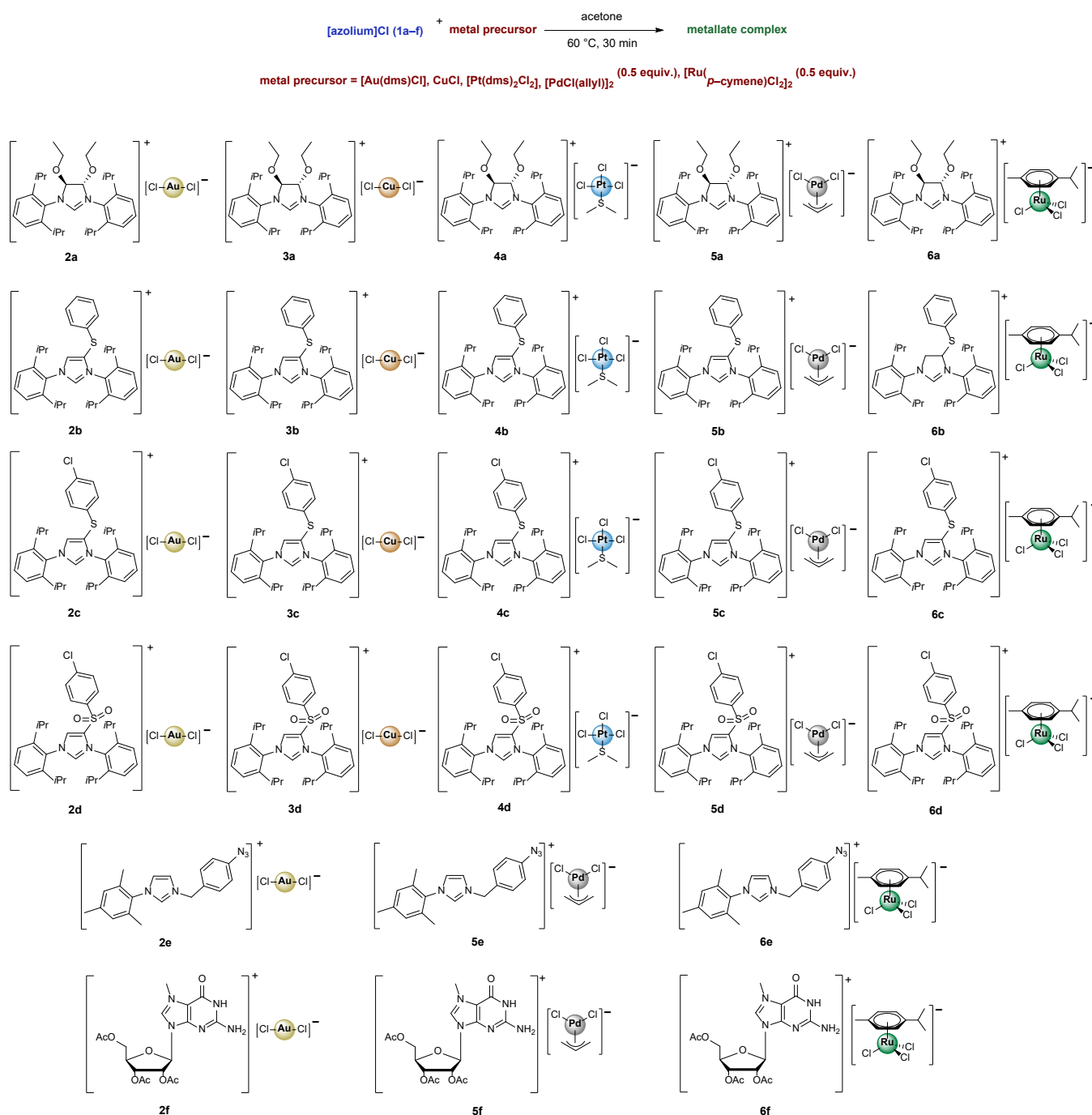
The ¹H NMR spectra of the resulting metallates retain the characteristic signals of the parent azolium salts, albeit with significant diagnostic shifts (Figures S1–S53), accompanied by signals arising from the ancillary ligands of the metal precursors (e.g., the allyl moiety for palladates, coordinated dms for platinates, and *p*-cymene for ruthenates). In the case of aurates **2a–f** and platinates **4a–f**, the spectra confirm the displacement of a dms ligand from the coordination sphere (one for gold and one of the two originally present in the platinum precursor). Remarkably, ruthenate species have hitherto remained unobserved and unisolated in the literature.

Taking the imidazolium salt **1a** as an example of common precursor, the corresponding metallate derivatives display a series of characteristic ¹H NMR signals. In all complexes, the methylene protons of the ethoxy substituents appear as quartets in the 3.0–4.0 ppm region, while the corresponding methyl groups resonate as triplets between 1.1 and 1.3 ppm. Likewise, the two diisopropylphenyl substituents consistently exhibit the expected septets for the methine protons at 3.5–3.8 ppm and doublets for the methyl groups at 1.3–1.4 ppm.

All compounds also display the characteristic acidic azolium NCHN proton at markedly downfield chemical shifts, although significant variations are observed depending on the metallate anion. In particular, the signal appears at 8.8 ppm for the aurate derivative, 9.0 ppm for the cuprate, 10.0 ppm for the platinate, 10.8 ppm for the palladate, and 9.1 ppm for the ruthenate complex.

Additional diagnostic resonances are observed for specific metallates. The platinated complex **4a** exhibits a singlet at 2.4 ppm, attributable to the protons of the dimethyl sulfide ligand coordinated to platinum. In the palladate derivative **5a**, the central allyl proton resonates at 5.2 ppm, whereas the *anti* and *syn* allyl protons appear at approximately 2.7 ppm and underneath the ethoxy signals, respectively. Finally, the ruthenate complex **9a** displays the characteristic aromatic resonances of the coordinated *para*-cymene ligand at around 5 ppm.

For the sake of clarity, although non-negligible interactions often exist between the acidic NCHN proton of the azolium moiety and the anionic metallate fragment, all synthesized species are herein described as separated ion pairs, as depicted in Scheme 1.



Scheme 1. Synthetic route to targeted metallate complexes.

The formation of the target metallate complexes was unequivocally confirmed by single-crystal X-ray diffraction analysis of six representative complexes (Figure 1). Crystals suitable for XRD were obtained by slow evaporation of diethyl ether into chloroform solutions at 5 °C. While the architectures of the palladates and aurates are consistent with related metallates recently reported by our group, we highlight the structural characterization of ruthenate **6e**. This result confirms the existence and stoichiometry of a species that had remained elusive until now. In **6e**, the ruthenium center adopts a distorted octahedral geometry, with three coordination sites occupied by the *para*-cymene ligand and the remaining three by chloride ligands (Ru–Cl distances ~ 2.4 Å), one of which is derived from the starting azolium salt. Interestingly, two of these chlorides engage in hydrogen bonding with the acidic NCHN proton (H–Cl distances ~ 2.85 Å), a motif reminiscent of

most literature-reported palladates [40]. Detailed crystallographic parameters and further structural considerations are provided in Table 1 and in the Supporting Information (see Tables S1–S7).

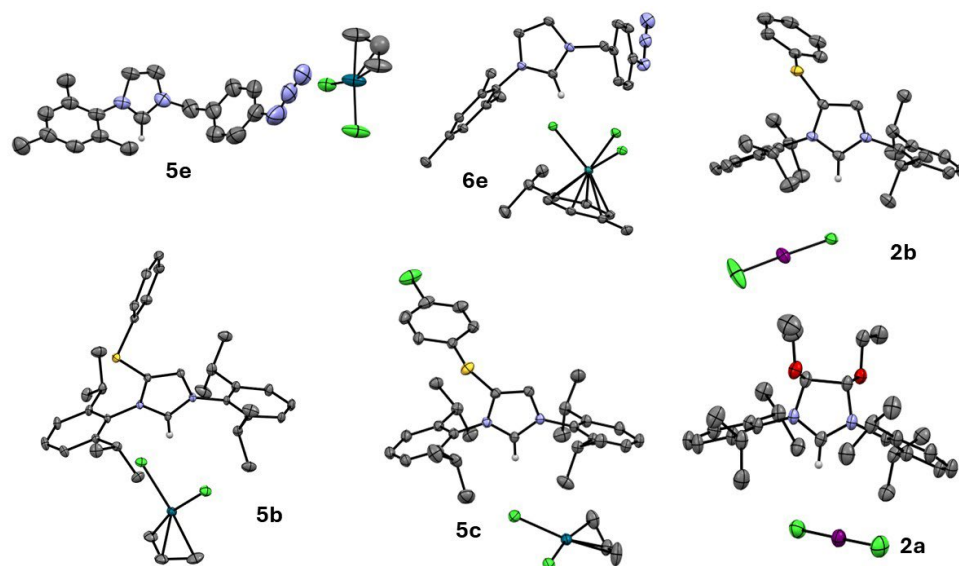


Figure 1. X-ray molecular structures of 2a, 2b, 5b, 5c, 5e and 6e are presented, showing thermal displacement ellipsoids at the 50% probability level with non-relevant hydrogen atoms, counterions and solvent molecules omitted for clarity (black = C, grey = azolium H, green = Cl, purple = Au, violet = N, blue = Pd or Ru, red = O, yellow = S).

Table 1. Crystallographic data at 100 K.

Compound	5b—100 K	5c—100 K	5e—100 K
Formula	$\text{PdCl}_2\text{C}_3\text{H}_5[\text{C}_{33}\text{H}_{41}\text{N}_2\text{S}]$	$\text{PdCl}_2\text{C}_3\text{H}_5[\text{C}_{33}\text{H}_{40}\text{ClN}_2\text{S}]$	$\text{PdCl}_2\text{C}_3\text{H}_5[\text{C}_{19}\text{H}_{20}\text{N}_5] \cdot \frac{1}{2}\text{CHCl}_3$
M/g·mol ^{−1}	716.11	750.55	596.45
Space group	<i>P</i> -1	<i>P</i> <i>ca</i> 2 ₁	<i>C</i> 2/ <i>c</i>
Crystal system	Triclinic	Orthorhombic	Monoclinic
<i>a</i> /Å	10.864 (2)	17.244 (3)	27.851 (6)
<i>b</i> /Å	11.595 (2)	8.805 (2)	14.294 (3)
<i>c</i> /Å	16.208 (3)	23.600 (5)	14.157 (3)
α /°	83.19 (3)	90	90
β /°	71.52 (3)	90	111.11 (3)
γ /°	64.80 (3)	90	90
<i>V</i> /Å ³	1752.0 (8)	3583.3 (12)	5258 (2)
<i>Z</i>	2	4	8
T/K	100 (2)	100 (2)	100 (2)
<i>D_c</i> /g·cm ^{−3}	1.357	1.391	1.507
<i>F</i> (000)	744	1552	2408
μ /mm ^{−1}	0.525	0.564	0.735
Measured Reflections	85,924	73,308	45,641
Unique Reflections	14,556	15,800	10,911
<i>R</i> _{int}	0.1049	0.0623	0.0539
Obs. Refl.ns [<i>I</i> ≥ 2σ(<i>I</i>)]	13,994	15,236	7251
$\theta_{\text{min}}-\theta_{\text{max}}$ /°	1.16–31.17	1.51–31.10	1.37–31.11
<i>hkl</i> ranges	−17,16; −19,19; −26,27	−27,27; −13,13; −39,39	−43,44; −22,22; −19,20
<i>R</i> (<i>F</i> ²) (Obs.Refl.ns)	0.0432	0.0348	0.0759
<i>wR</i> (<i>F</i> ²) (All Refl.ns)	0.1195	0.0950	0.2783
No. Variables	401	406	304
Goodness of fit	1.034	1.047	1.108
$\Delta\rho_{\text{max}}; \Delta\rho_{\text{min}}$ /e·Å ^{−3}	2.26; −1.30	1.24; −0.86	1.25; −2.01
CCDC Deposition N.	2518446	2518448	2518450

Table 1. Cont.

Compound	6e—100 K	2a—100 K	2b—100 K
Formula	$\text{RuCl}_3\text{C}_{10}\text{H}_{14}[\text{C}_{19}\text{H}_{20}\text{N}_5]$ $\cdot\text{C}_4\text{H}_{10}\text{O}$	$\text{AuCl}_2[\text{C}_{31}\text{H}_{47}\text{N}_2\text{O}_2]$ $\cdot\frac{1}{2}\text{C}_4\text{H}_{10}\text{O}$	$\text{AuCl}_2[\text{C}_{33}\text{H}_{41}\text{N}_2\text{S}]$
M/g·mol ^{−1}	734.15	784.63	765.60
Space group	<i>P</i> -1	<i>P</i> -1	<i>P</i> 2 ₁ / <i>n</i>
Crystal system	Triclinic	Triclinic	Monoclinic
<i>a</i> /Å	9.417 (2)	10.666 (2)	8.417 (2)
<i>b</i> /Å	13.215 (3)	17.452 (3)	19.079 (4)
<i>c</i> /Å	14.980 (3)	19.530 (4)	20.529 (4)
α /°	78.04 (3)	83.16 (3)	90
β /°	75.41 (3)	85.78 (3)	94.56 (3)
γ /°	72.50 (3)	75.15 (3)	90
<i>V</i> /Å ³	1703.0 (7)	3485.4 (13)	3286.3 (11)
<i>Z</i>	2	4	4
T/K	100 (2)	100 (2)	100 (2)
<i>D</i> _c /g·cm ^{−3}	1.432	1.495	1.547
<i>F</i> (000)	760	1588	1528
μ /mm ^{−1}	0.499	3.082	3.304
Measured Reflections	70,002	46,248	43,301
Unique Reflections	14,657	13,168	14,411
<i>R</i> _{int}	0.0994	0.0603	0.1144
Obs. Refl.ns [<i>I</i> ≥ 2σ(<i>I</i>)]	13,624	11,995	11,214
$\theta_{\text{min}}-\theta_{\text{max}}/^\circ$	1.24–31.17	1.06–22.21	1.27–31.12
<i>hkl</i> ranges	−15,15; −21,21; −23,23	−13,13; −21,21; −23,23	−13,13; −31,31; −34,34
<i>R</i> (<i>F</i> ²) (Obs.Refl.ns)	0.0412	0.0356	0.0547
<i>wR</i> (<i>F</i> ²) (All Refl.ns)	0.1135	0.1002	0.1364
No. Variables	397	755	379
Goodness of fit	1.055	1.018	0.957
$\Delta\rho_{\text{max}}; \Delta\rho_{\text{min}}/\text{e} \cdot \text{\AA}^{-3}$	1.40; −1.72	2.17; −1.69	1.14; −2.42
CCDC Deposition N.	2518453	2518455	2518456

2.2. Antiproliferative Activity of Metallate Complexes Towards Ovarian Cancer and Normal Cells

With the aim of exploring the potential anticancer effects of these azolium-derived metallate complexes, we evaluated their activity against two human ovarian cancer cell lines: A2780, a cisplatin-sensitive model, and its resistant counterpart A2780*cis*, which is widely used to investigate mechanisms of acquired resistance to platinum-based drugs. Cells were exposed to the synthesized compounds and cisplatin (positive control) for 96 h. In parallel, antiproliferative activity was also assessed on MRC-5 normal cells (human lung fibroblasts) to evaluate the degree of in vitro selectivity towards cancer cells.

Before proceeding with biological assays, we assessed the stability of the metallate complexes in a 1:1 D₂O/DMSO-*d*₆ solution by ¹H NMR spectroscopy. Over a 24-h period, negligible changes were observed in the spectra, indicating that the complexes retain their original structure under these conditions.

The results of the antiproliferative activity assays, expressed as half maximal inhibitory concentration (IC₅₀) values, are summarized in Table 2.

The in vitro cytotoxic profiles of the synthesized complexes reveal several structure–activity relationships. A primary observation is that the nature of the azolium salt functionalization significantly dictates the antiproliferative potency of the resulting complexes. Specifically, derivatives featuring functionalized backbones on the azolium moiety consistently exhibit superior activity—often by an order of magnitude—compared to those bearing benzylazido or methyl guanosine groups. In the latter category, the ruthenium-based complex **6f** stands out as notably inactive, failing to reach the IC₅₀ threshold even at concentrations exceeding 100 μM across all tested cell lines.

Table 2. Antiproliferative activity on A2780, A2780cis, MRC-5 cell lines and selectivity index (IC₅₀ on normal cells/average IC₅₀ on cancer ones).

Compound	IC ₅₀ (μM)			Selectivity Index (S.I.)
	A2780	A2780cis	MRC-5	
Cisplatin	0.23 ± 0.02	80 ± 20	3 ± 1	0.075
2a	0.24 ± 0.05	0.15 ± 0.08	4.0 ± 0.3	21
2b	0.24 ± 0.07	0.2 ± 0.1	0.27 ± 0.05	1
2c	0.21 ± 0.05	0.2 ± 0.1	0.24 ± 0.05	1
2d	0.7 ± 0.1	1.4 ± 0.4	4.0 ± 0.5	4
2e	3.0 ± 0.8	17 ± 2	80 ± 20	8
2f	13 ± 4	3 ± 2	90 ± 10	11
3a	0.18 ± 0.03	0.20 ± 0.08	5.3 ± 0.7	28
3b	0.11 ± 0.04	0.21 ± 0.07	0.25 ± 0.05	1.6
3c	0.06 ± 0.01	0.2 ± 0.1	0.26 ± 0.05	2
3d	0.10 ± 0.07	0.13 ± 0.07	0.5 ± 0.2	4
4a	0.4 ± 0.1	0.20 ± 0.03	4.3 ± 0.1	14
4b	0.23 ± 0.04	0.2 ± 0.1	2.4 ± 0.4	11
4c	0.26 ± 0.03	0.27 ± 0.09	4.1 ± 0.2	15
4d	0.10 ± 0.02	0.2 ± 0.1	5.4 ± 0.2	36
5a	0.26 ± 0.03	0.3 ± 0.2	5 ± 2	18
5b	0.25 ± 0.05	0.2 ± 0.1	0.33 ± 0.05	1.5
5c	0.31 ± 0.06	0.3 ± 0.1	9 ± 1	30
5d	0.14 ± 0.07	0.2 ± 0.1	0.43 ± 0.09	2.5
5e	1.6 ± 0.1	1.73 ± 0.06	80 ± 20	48
5f	4.0 ± 0.2	5.3 ± 0.6	>100	>22
6a	0.26 ± 0.07	0.14 ± 0.09	5.8 ± 0.6	29
6b	0.24 ± 0.03	0.2 ± 0.1	0.25 ± 0.02	1
6c	0.20 ± 0.04	0.2 ± 0.1	0.29 ± 0.05	1
6d	0.19 ± 0.05	0.2 ± 0.1	0.26 ± 0.03	1
6e	5.9 ± 0.1	10 ± 2	80 ± 10	10
6f	>100	>100	>100	N.A.

The backbone-functionalized azolium complexes emerged as the most potent agents against the investigated tumour cell lines. Interestingly, their cytotoxicity appears to be largely independent of the specific metal center or the exact type of functionalization employed. These compounds demonstrated efficacy comparable or superior to cisplatin in the A2780 ovarian cancer line, but their performance was most striking in the cisplatin-resistant A2780cis line. In this resistant model, the complexes were between 100 and 1000-fold more potent than the reference drug. It is also noteworthy that even the less active benzylazido and methylated guanosine derivatives (**2e–f**, **5e–f** and **6e**) maintained a degree of efficacy in the resistant line, outperforming cisplatin by up to tenfold.

The mechanistic implications of these findings are significant. While cisplatin undergoes a dramatic 400-fold reduction in cytotoxicity when transitioning from the A2780 to the A2780cis line, the IC₅₀ values for our metallate complexes remain remarkably con-

sistent across both models, independently of the nature of the azolium cation and the metallate anion employed. This absence of cross-resistance suggests that these compounds operate through a mechanism of action distinct from that of classical platinum-based chemotherapeutics, potentially bypassing established resistance pathways.

Notably, the palladate derivatives investigated in this work (**5a–f**) display cytotoxic activity against ovarian cancer cell lines that is comparable to that of the most effective palladate systems reported to date in the literature. In particular, their biological performance is in line with that previously observed for palladates featuring 12-membered cyclic alkyl substituents [41] and azolium salts bearing two chlorine atoms on the backbone [40].

A deeper analysis of the structure–selectivity relationship highlights the pivotal role of the azolium backbone in modulating off-target toxicity. Notably, while backbone modifications exert a negligible impact on tumour cell inhibition, they profoundly influence activity against the non-tumorigenic MRC-5 cell line, underscoring their role in tuning the therapeutic window. Complexes incorporating two ethoxide groups (**2a**, **3a**, **4a**, **5a** and **6a**) in the backbone demonstrated a favourable selectivity profile, being approximately ten-fold less active toward normal cells than against cancer cells. Conversely, derivatives containing thioether or sulfone groups exhibited similar toxicity across both normal and malignant cell types, indicating a lack of preferential targeting.

The identity of the metal center further influences the therapeutic window. When comparing identical azolium moieties, the platinum-based complexes (platينات, **4a–d**) proved more selective than their counterparts, maintaining a tenfold lower activity in normal cells compared to tumour cell lines. In parallel, the benzylazido and methyl guanosine derivatives (**2e–f**, **5e–f** and **6e**), despite their lower overall potency, were characterized by minimal toxicity toward non-tumour cells, delineating an interesting trend for in vitro selectivity.

In conclusion, several candidates, specifically **2a**, **2e**, **2f**, **3a**, **4a–d**, **5a**, **5c**, **5e**, **5f**, **6a**, and **6e**, warrant prioritized investigation. These derivatives strike an optimal balance between remarkable cytotoxicity against ovarian cancer lines and reduced toxicity toward non-tumorigenic cells. Future efforts will focus on elucidating their precise molecular mechanisms and evaluating their performance in advanced biological models, moving from 2D cultures to 3D organoids and animal models. A dedicated screening utilizing patient-derived ex vivo 3D organoids will be essential to refine this selection and identify the most promising leads for further preclinical development.

3. Materials and Methods

3.1. Reagents

Metal precursors were commercially sourced (Umicore, Hanau, Germany, and Sigma-Aldrich, Darmstadt, Germany) and utilized without further purification. All azolium salts (**1a–f**), in the form of chloride salts, were synthesized according to the published procedures [43,44,48]. Notably, in the case of compound **1f**, an ion exchange on DOWEX 21KCl resin was performed to replace iodide with chloride. The A2780, A2780cis, and MRC-5 cell lines were obtained from Sigma-Aldrich (Darmstadt, Germany) and used according to the appropriate protocols.

3.2. Instruments

1D-NMR and 2D-NMR spectra were acquired using Bruker 300 (Bruker, Rheinstetten, Germany) and 400 MHz Advance spectrometers (Bruker, Rheinstetten, Germany). Chemical shift values (ppm) were referenced to TMS for ^1H and ^{13}C . Elemental analyses were carried out using an Elemental CHN “CUBO Micro Vario” analyzer (Elementar Analysensysteme GmbH, Langenselbold, Germany).

3.3. Synthesis of Metallates Derived from Azolium Salts

Complex 2a. In a 5 mL vial equipped with a magnetic stir bar, 70.4 mg of **1a** (0.136 mmol) and 40.6 mg of [Au(dms)Cl] (0.136 mmol) were dissolved in 2 mL of acetone. The resulting solution was stirred at 60 °C for 30 min. Subsequently, the solvent was removed under reduced pressure to afford the product, as an off-white solid, in quantitative yield.

¹H NMR (300 MHz, CDCl₃, T = 298 K, ppm): δ 8.84 (s, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.29–7.35 (m, 4H), 5.43 (s, 2H), 3.77 (dq, *J* = 9.4, 7.0 Hz, 2H), 3.62 (dq, *J* = 9.4, 7.0 Hz, 2H), 3.16 (m, 2H), 2.89 (m, 2H), 1.41 (d, *J* = 6.8 Hz, 6H), 1.34 (d, *J* = 6.7 Hz, 6H), 1.29 (d, *J* = 6.8 Hz, 6H), 1.26–1.18 (m, 12H).

¹³C NMR (CDCl₃, T = 298 K, ppm): δ 159.10, 147.30, 145.71, 132.27, 127.67, 125.41, 125.24, 99.42, 69.09, 29.04, 28.91, 26.02, 25.25, 23.70, 23.40, 15.05.

Elemental analysis calcd (%) for C₃₁H₄₇AuCl₂N₂O₂: C, 49.81; H, 6.34; N, 3.75. Found: C, 50.05; H, 6.23; N, 3.61.

Complex 2b. Complex **2b** was prepared in an analogous manner to that described for **2a** starting from 71.2 mg of **1b** (0.133 mmol) and 38.6 mg of [Au(dms)Cl] (0.133 mmol). The product was obtained in quantitative yield as an off-white solid.

¹H NMR (300 MHz, CDCl₃, T = 298 K, ppm): δ 9.78 (s, 1H), 7.63 (dt, *J* = 19.1, 7.8 Hz, 2H), 7.39 (m, 10H), 2.42 (m, 2H), 2.28 (m, 2H), 1.25 (m, 24H).

¹³C NMR (CDCl₃, T = 298 K, ppm): δ 145.3, 144.5, 139, 134.5, 132.9, 132.8, 132.7, 130.5, 130.4, 129.4, 127.9, 127.1, 125.4, 125.1, 125.1, 77.4, 77, 76.6, 29.6, 29.3, 25.4, 24.6, 24, 22.7.

Elemental analysis calcd (%) for C₃₃H₄₁AuCl₂N₂S: C, 51.77; H, 5.40; N, 3.66. Found: C, 51.90; H, 5.29; N, 3.54.

Complex 2c. Complex **2c** was prepared in an analogous manner to that described for **2a** starting from 70.4 mg of **1c** (0.124 mmol) and 36.3 mg of [Au(dms)Cl] (0.124 mmol). The product was obtained in quantitative yield as an off-white solid.

¹H NMR (300 MHz, CDCl₃, T = 298 K, ppm): δ 9.78 (m, 1H), 7.62 (dt, *J* = 19.4, 7.8 Hz, 2H), 7.39 (m, 9H), 2.41 (m, 2H), 2.27 (m, 2H), 1.34–1.15 (m, 24H).

¹³C NMR (CDCl₃, T = 298 K, ppm): δ 145.39, 144.58, 139.05, 132.98, 132.76, 132.70, 130.57, 130.44, 125.44, 125.08, 125.03, 29.60, 29.33, 25.44, 24.62, 24.06, 22.74.

Elemental analysis calcd (%) for C₃₃H₄₀AuCl₃N₂S: C, 49.54; H, 5.04; N, 3.50. Found: C, 49.80; H, 4.92; N, 3.39.

Complex 2d. Complex **2d** was prepared in an analogous manner to that described for **2a** starting from 70.0 mg of **1d** (0.116 mmol) and 36.3 mg of [Au(dms)Cl] (0.116 mmol). The product was obtained in quantitative yield as an off-white solid.

¹H NMR (300 MHz, CDCl₃, T = 298 K, ppm): δ 9.77 (s, 1H), 7.62 (dt, *J* = 19.4, 7.8 Hz, 4H), 7.43–7.33 (m, 15H), 2.41 (m, 4H), 2.27 (m, 3H), 1.32–1.17 (m, 42H).

¹³C NMR (CDCl₃, T = 298 K, ppm): δ 145.4, 144.6, 139.1, 134.5, 132.9, 132.8, 132.7, 130.6, 130.4, 129.5, 127.9, 127.1, 125.5, 125.1, 125.1, 77.5, 77.3, 77.1, 76.6, 29.6, 29.3, 25.4, 24.6, 24.1, 22.7, 22.4, 14.1.

Elemental analysis calcd (%) for C₃₃H₄₀AuCl₃N₂O₂S: C, 47.64; H, 4.85; N, 3.37. Found: C, 47.40; H, 4.96; N, 3.44.

Complex 2e. Complex **2e** was prepared in an analogous manner to that described for **2a** starting from 40.4 mg of **1e** (0.114 mmol) and 33.6 mg of [Au(dms)Cl] (0.114 mmol). The product was obtained in quantitative yield as an off-white solid.

¹H NMR (400 MHz, CDCl₃, T = 298 K, ppm): δ 9.42 (s, 1H), 7.63 (s, 1H), 7.61 (d, *J* = 8 Hz, 2H), 7.19 (s, 1H), 7.08 (d, *J* = 8 Hz, 2H), 7.00 (s, 2H), 5.80 (s, 2H), 2.34 (s, 3H), 2.07 (s, 6H).

¹³C NMR (CDCl₃, T = 298 K, ppm): δ 141.8, 141.6, 136.4, 134.2, 130.9, 130.4, 130.0, 129.0, 123.8, 123.0, 120.2, 53.45, 21.1, 17.8.

Elemental analysis calcd (%) for $C_{19}H_{20}AuCl_2N_5$: C, 38.93; H, 3.44; N, 11.95. Found: C, 39.20; H, 3.29; N, 12.10.

Complex 2f. Complex **2f** was prepared in an analogous manner to that described for **2a** starting from 56.0 mg of **1f** (0.122 mmol) and 35.9 mg of $[Au(dms)Cl]$ (0.122 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (400 MHz, CD_3CN , T = 298 K, ppm): δ 10.22 (s, 1H), 8.61 (s, 1H), 6.25 (s, 2H), 6.10 (d, J = 4 Hz, 1H), 5.79 (dd, J = 4 Hz, 1.40 Hz, 1H), 5.58 (t, J = 5.83 Hz, 1H), 4.52 (dd, J = 5.5 Hz, 3.3 Hz, 1H), 4.44 (dd, J = 3.7 Hz, 9.1 Hz, 1H), 4.36 (dd, J = 5.24 Hz, 7.2 Hz, 1H), 4.05 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (CD_3CN , T = 298 K, ppm): δ 171.4, 170.6, 170.4, 156.7, 154.0, 150.0, 136.7, 110.1, 89.6, 82.1, 74.2, 70.8, 63.7, 36.8, 21.0, 20.7, 20.6.

Elemental analysis calcd (%) for $C_{17}H_{22}AuCl_2N_5O_8$: C, 29.50; H, 3.20; N, 10.12. Found: C, 29.61; H, 3.12; N, 10.23.

Complex 3a. Complex **3a** was prepared in an analogous manner to that described for **2a** starting from 70.6 mg of **1a** (0.137 mmol) and 13.7 mg of $CuCl$ (0.137 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm): δ 1.23 (t, J = 6.5 Hz, 6H), 1.36 (m, 24H), 2.89 (m, 2H), 3.17 (m, 2H), 3.69 (m, 4H), 5.42 (s, 2H), 7.34 (m, 4H), 7.55 (m, 2H), 9.00 (s, 1H).

^{13}C NMR ($CDCl_3$, T = 298 K, ppm): δ 15.09, 23.38, 23.82, 25.46, 26.05, 28.96, 29.09, 69.23, 99.57, 125.25, 125.46, 127.75, 132.30, 145.70, 147.35, 160.06.

Elemental analysis calcd (%) for $C_{31}H_{47}Cl_2CuN_2O_2$: C, 60.62; H, 7.71; N, 4.56. Found: C, 60.40; H, 7.79; N, 4.65.

Complex 3b. Complex **3b** was prepared in an analogous manner to that described for **2a** starting from 70.4 mg of **1b** (0.132 mmol) and 13.7 mg of $CuCl$ (0.132 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm): δ 1.29 (m, 24H), 2.25 (m, 2H), 2.39 (m, 2H), 7.21 (s, 1H), 7.39 (m, 9H), 7.65 (q, J = 9.0, 8.6 Hz, 2H), 9.70 (s, 1H).

^{13}C NMR ($CDCl_3$, T = 298 K, ppm): δ 22.89, 24.22, 25.06, 25.83, 29.50, 29.77, 125.23, 125.25, 125.63, 127.29, 128.14, 129.68, 130.55, 130.68, 132.84, 132.89, 133.15, 134.59, 140.87, 144.75, 145.51.

Elemental analysis calcd (%) for $C_{33}H_{41}Cl_2CuN_2S$: C, 62.69; H, 6.54; N, 4.43. Found: C, 62.93; H, 6.47; N, 4.35.

Complex 3c. Complex **3c** was prepared in an analogous manner to that described for **2a** starting from 70.5 mg of **1c** (0.124 mmol) and 12.4 mg of $CuCl$ (0.124 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm): δ 1.19 (d, J = 6.6 Hz, 6H), 1.25 (d, J = 6.6 Hz, 6H), 1.30 (m, 12H), 2.22 (m, 2H), 2.39 (m, 2H), 7.37 (m, 9H), 7.62 (m, 2H), 9.88 (s, 1H).

^{13}C NMR ($CDCl_3$, T = 298 K, ppm): δ 22.79, 24.21, 24.93, 25.77, 29.53, 29.78, 31.07, 125.24, 125.28, 126.25, 126.54, 127.22, 129.61, 130.82, 132.95, 133.22, 133.57, 134.20, 137.14, 140.59, 144.76, 145.53.

Elemental analysis calcd (%) for $C_{33}H_{40}Cl_3CuN_2S$: C, 59.46; H, 6.05; N, 4.20. Found: C, 59.15; H, 6.21; N, 4.29.

Complex 3d. Complex **3d** was prepared in an analogous manner to that described for **2a** starting from 70.5 mg of **1d** (0.118 mmol) and 12.3 mg of $CuCl$ (0.118 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm): δ 1.02 (m, 6H), 1.32 (m, 18H), 2.08 (m, 2H), 2.32 (m, 2H), 7.50 (m, 10H), 8.12 (s, 1H), 10.12 (s, 1H).

^{13}C NMR (CDCl_3 , $T = 298\text{ K}$, ppm): δ 21.44, 21.48, 24.13, 24.48, 24.82, 25.26, 27.04, 27.35, 29.08, 29.51, 29.72, 30.20, 124.43, 124.75, 125.19, 125.62, 127.10, 129.99, 130.32, 130.53, 130.66, 130.85, 133.46, 133.78, 134.96, 136.46, 143.61, 144.76, 145.97.

Elemental analysis calcd (%) for $\text{C}_{33}\text{H}_{40}\text{Cl}_3\text{CuN}_2\text{O}_2\text{S}$: C, 56.73; H, 5.77; N, 4.01. Found: C, 56.98; H, 5.62; N, 3.93.

Complex 4a. Complex 4a was prepared in an analogous manner to that described for 2a starting from 23.3 mg of 1a (0.045 mmol) and 19.9 mg of $[\text{Pt}(\text{dms})_2\text{Cl}_2]$ (0.045 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (300 MHz, CDCl_3 , $T = 298\text{ K}$, ppm): δ 10.05 (s, 1H), 7.42 (t, $J = 7.7\text{ Hz}$, 2H), 7.19–7.25 (m, 4H), 5.32 (s, 2H), 3.66 (dq, $J = 9.4, 7.0\text{ Hz}$, 2H), 3.54 (dq, $J = 9.4, 7.0\text{ Hz}$, 2H), 3.14 (m, 2H), 2.86 (m, 2H), 2.40 (s, 6H), 1.26–1.34 (24H), 1.34 (d, $J = 6.7\text{ Hz}$, 6H), 1.29 (d, $J = 6.8\text{ Hz}$, 6H), 1.13–1.15 (m, 6H).

^{13}C NMR (CDCl_3 , $T = 298\text{ K}$, ppm): δ 147.59, 145.71, 131.68, 128.20, 125.14, 124.89, 99.39, 77.23, 77.02, 76.81, 68.87, 29.07, 29.01, 25.88, 25.09, 23.81, 23.50, 22.35, 15.05.

Elemental analysis calcd (%) for $\text{C}_{33}\text{H}_{53}\text{Cl}_3\text{N}_2\text{O}_2\text{PtS}$: C, 47.00; H, 6.34; N, 3.32. Found: C, 46.74; H, 6.50; N, 3.39.

Complex 4b. Complex 4b was prepared in an analogous manner to that described for 2a starting from 27.3 mg of 1b (0.052 mmol) and 20.0 mg of $[\text{Pt}(\text{dms})_2\text{Cl}_2]$ (0.052 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (300 MHz, CDCl_3 , $T = 298\text{ K}$, ppm): δ 1.18–1.41 (m, 24H), 2.30 (m, 2H), 2.53 (m, 2H), 2.58 (s, 6H), 7.19 (s, 1H), 7.27–7.63 (m, 11H), 11.49 (s, 1H).

^{13}C NMR (CDCl_3 , $T = 298\text{ K}$, ppm): δ 145.54, 144.77, 142.45, 133.17, 132.44, 132.30, 132.12, 130.33, 130.20, 130.02, 128.80, 127.67, 125.15, 124.76, 124.71, 29.67, 29.38, 25.24, 24.34, 24.15, 22.99, 22.83, 22.51, 22.34.

Elemental analysis calcd (%) for $\text{C}_{35}\text{H}_{47}\text{Cl}_3\text{N}_2\text{PtS}_2$: C, 48.81; H, 5.50; N, 3.25. Found: C, 49.08; H, 5.39; N, 3.13.

Complex 4c. Complex 4c was prepared in an analogous manner to that described for 2a starting from 29.0 mg of 1c (0.051 mmol) and 20.0 mg of $[\text{Pt}(\text{dms})_2\text{Cl}_2]$ (0.051 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (300 MHz, CDCl_3 , $T = 298\text{ K}$, ppm): δ 1.17–1.40 (24H), 2.27 (m, 2H), 2.49 (m, 2H), 2.59 (s, 6H), 7.27–7.62 (m, 10H), 11.72 (s, 1H).

^{13}C NMR (CDCl_3 , $T = 298\text{ K}$, ppm): δ 145.54, 144.78, 136.55, 133.58, 132.42, 132.09, 131.97, 130.48, 130.19, 127.66, 127.25, 125.93, 124.74, 124.69, 29.69, 29.41, 25.34, 24.41, 24.09, 22.99, 22.69, 22.53, 22.34.

Elemental analysis calcd (%) for $\text{C}_{35}\text{H}_{46}\text{Cl}_4\text{N}_2\text{PtS}_2$: C, 46.93; H, 5.18; N, 3.13. Found: C, 47.22; H, 5.01; N, 3.06.

Complex 4d. Complex 4d was prepared in an analogous manner to that described for 2a starting from 30.6 mg of 1d (0.051 mmol) and 20.0 mg of $[\text{Pt}(\text{dms})_2\text{Cl}_2]$ (0.051 mmol). The product was obtained in quantitative yield as a yellow solid.

^1H NMR (300 MHz, CDCl_3 , $T = 298\text{ K}$, ppm): δ 1.09–1.30 (24H), 2.20 (m, 2H), 2.40 (m, 2H), 2.50 (s, 6H), 7.27–7.64 (m, 10H), 10.56 (s, 1H).

^{13}C NMR (CDCl_3 , $T = 298\text{ K}$, ppm): δ 145.51, 144.72, 136.65, 133.73, 132.54, 132.51, 132.20, 130.53, 130.08, 127.53, 127.08, 126.09, 124.85, 124.78, 45.46, 44.04, 42.70, 29.65, 29.40, 25.21, 24.31, 24.21, 22.99, 22.86, 22.53, 22.34.

Elemental analysis calcd (%) for $\text{C}_{35}\text{H}_{46}\text{Cl}_4\text{N}_2\text{O}_2\text{PtS}_2$: C, 45.31; H, 5.00; N, 3.02. Found: C, 45.10; H, 5.09; N, 2.95.

Complex 5a. Complex 5a was prepared in an analogous manner to that described for 2a starting from 42.5 mg of 1a (0.082 mmol) and 30.2 mg of $[\text{PdCl}(\text{allyl})]_2$ (0.041 mmol). The product was obtained in quantitative yield as an orange solid.

^1H NMR (300 MHz, CDCl_3 , T = 298 K, ppm): δ 10.8 (s, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.32–7.27 (m, 4H), 5.19 (bs, 1H), 3.76 (m, 2H), 3.60 (m, 2H), 3.20 (m, J = 6.8 Hz, 2H), 2.93 (m, 2H), 2.72 (bs, 2H), 1.40 (d, J = 6.8 Hz, 6H), 1.37–1.31 (m, 18H), 1.20 (t, J = 7.0 Hz, 6H).

^{13}C NMR (CDCl_3 , T = 298 K, ppm): δ 161.04, 147.60, 145.78, 131.64, 128.27, 125.10, 124.86, 99.27, 77.35, 77.24, 77.04, 76.72, 68.78, 30.93, 29.03, 28.95, 28.72, 25.95, 25.15, 23.73, 23.49, 15.05.

Elemental analysis calcd (%) for $\text{C}_{34}\text{H}_{52}\text{Cl}_2\text{N}_2\text{O}_2\text{Pd}$: C, 58.50; H, 7.51; N, 4.01. Found: C, 58.83; H, 7.39; N, 3.92.

Complex 5b. Complex 5b was prepared in an analogous manner to that described for 2a starting from 70.3 mg of 1b (0.132 mmol) and 24.1 mg of $[\text{PdCl}(\text{allyl})]_2$ (0.066 mmol). The product was obtained in quantitative yield as an orange solid.

^1H NMR (300 MHz, CDCl_3 , T = 298 K, ppm): δ 1.10–1.18 (m, 6H), 1.18–1.27 (m, 6H), 1.33 (d, J = 6.4 Hz, 6H), 1.38 (d, J = 6.4 Hz, 6H), 2.22–2.40 (m, 2H), 2.50 (sept, J = 7.2 Hz, 2H), 2.74 (m, 2H), 3.40–4.11 (m, 2H), 4.88–5.43 (m, 1H), 7.18 (s, 1H), 7.36 (m, 9H), 7.63 (m, 2H), 10.99 (s, 1H).

^{13}C NMR (CDCl_3 , T = 298 K, ppm): δ 22.9, 24.1, 24.5, 25.2, 29.4, 29.6, 61.2, 110.4, 124.8, 124.9, 125.4, 127.7, 128.9, 129.9, 130.3, 130.3, 132.2, 132.4, 132.5, 133.0, 142.2, 144.7, 145.6.

Elemental analysis calcd (%) for $\text{C}_{36}\text{H}_{46}\text{Cl}_2\text{N}_2\text{PdS}$: C, 60.38; H, 6.47; N, 3.91. Found: C, 60.06; H, 6.59; N, 4.06.

Complex 5c. Complex 5c was prepared in an analogous manner to that described for 2a starting from 69.7 mg of 1c (0.122 mmol) and 22.4 mg of $[\text{PdCl}(\text{allyl})]_2$ (0.061 mmol). The product was obtained in quantitative yield as an orange solid.

^1H NMR (300 MHz, CDCl_3 , T = 298 K, ppm): δ 0.48–1.53 (m, 24H), 2.19 (m, 2H), 2.42 (m, 2H), 2.62 (s, 2H), 3.74 (s, 2H), 5.11 (s, 1H), 7.20 (s, 3H), 7.47 (m, 8H), 10.26 (s, 1H).

^{13}C NMR (CDCl_3 , T = 298 K, ppm): δ 22.9, 24.2, 24.6, 25.4, 29.4, 29.6, 65.8, 109.4, 125.0, 125.1, 126.8, 127.2, 127.5, 130.0, 130.5, 132.2, 132.7, 132.9, 133.7, 136.5, 141.9, 144.6, 145.5.

Elemental analysis calcd (%) for $\text{C}_{36}\text{H}_{45}\text{Cl}_3\text{N}_2\text{PdS}$: C, 57.61; H, 6.04; N, 3.73. Found: C, 57.87; H, 5.93; N, 3.61.

Complex 5d. Complex 5d was prepared in an analogous manner to that described for 2a starting from 70.0 mg of 1d (0.116 mmol) and 21.1 mg of $[\text{PdCl}(\text{allyl})]_2$ (0.058 mmol). The product was obtained in quantitative yield as an orange solid.

^1H NMR (300 MHz, CDCl_3 , T = 298 K, ppm): δ 1.15 (m, 6H), 1.24–1.39 (m, 18H), 2.38 (m, 4H), 2.58–3.05 (m, 2H), 3.83 (s, 2H), 5.20 (s, 1H), 7.28 (s, 3H), 7.35–7.91 (m, 8H), 10.57 (s, 1H).

^{13}C NMR (CDCl_3 , T = 298 K, ppm): δ 22.8, 24.2, 24.3, 25.3, 29.3, 29.6, 61.2, 109.6, 124.8, 124.8, 124.9, 126.5, 126.5, 127.2, 127.5, 130.1, 130.3, 130.4, 130.5, 130.6, 132.2, 132.5, 133.7, 136.4, 139.9, 140.6, 141.6, 143.8, 144.6, 144.7, 145.5.

Elemental analysis calcd (%) for $\text{C}_{36}\text{H}_{45}\text{Cl}_3\text{N}_2\text{O}_2\text{PdS}$: C, 55.25; H, 5.80; N, 3.58. Found: C, 55.50; H, 5.69; N, 3.48.

Complex 5e. Complex 5e was prepared in an analogous manner to that described for 2a starting from 66.0 mg of 1e (0.186 mmol) and 33.6 mg of $[\text{PdCl}(\text{allyl})]_2$ (0.093 mmol). The product was obtained in quantitative yield as an orange solid.

^1H NMR (300 MHz, CDCl_3 , T = 298 K, ppm): δ 10.43 (t, J = 1.5 Hz, 1H), 7.63 (dt, J = 2, 8 Hz, 2H), 7.45 (t, J = 2 Hz, 1H), 7.05–7.00 (m, 3H), 6.95 (s, 2H), 5.90 (s, 2H), 5.27 (sept, J = 8 Hz, 1H), 3.89 (d, J = 8 Hz, 2H), 2.79 (d, J = 12 Hz, 2H), 2.30 (s, 3H), 2.06 (s, 6H).

^{13}C NMR (CDCl_3 , T = 298 K, ppm): δ 141.3, 141.2, 139.4, 134.5, 131.1, 130.9, 130.1, 129.8, 122.7, 121.6, 119.9, 109.7, 61.3, 53.4, 21.1, 17.8.

Elemental analysis calcd (%) for $\text{C}_{22}\text{H}_{25}\text{Cl}_2\text{N}_5\text{Pd}$: C, 49.23; H, 4.69; N, 13.05. Found: C, 49.44; H, 4.56; N, 12.98.

Complex 5f. Complex 5f was prepared in an analogous manner to that described for 2a starting from 100.8 mg of 1f (0.220 mmol) and 39.2 mg of [PdCl(allyl)]₂ (0.110 mmol). The product was obtained in quantitative yield as a yellow solid.

¹H NMR (300 MHz, CDCl₃, T = 298 K, ppm): δ 11.63 (s, 1H), 9.79 (s, 1H), 6.55 (br s, 2H), 6.32 (d, J = 3 Hz, 1H), 5.95 (dd, J = 3 Hz, 2 Hz, 1H), 5.79 (t, J = 6 Hz, 1H), 5.44 (sept, J = 6 Hz, 1H), 4.54–4.43 (m, 3H), 4.25 (s, 3H), 4.07 (d, J = 6.6 Hz, 2H), 3.00 (d, J = 12 Hz, 2H), 2.14 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H).

¹³C NMR (CDCl₃, T = 298 K, ppm): δ 170.8, 169.7, 169.7, 155.8, 152.9, 148.8, 138.1, 110.9, 108.5, 89.4, 80.7, 73.2, 70.2, 63.1, 62.5, 36.7, 21.0, 20.7, 20.6.

Elemental analysis calcd (%) for C₂₀H₂₇Cl₂N₅O₈Pd: C, 37.37; H, 4.23; N, 10.90. Found: C, 37.11; H, 4.35; N, 10.99.

Complex 6a. Complex 6a was prepared in an analogous manner to that described for 2a starting from 70.2 mg of 1a (0.136 mmol) and 41.8 mg of [Ru(*p*-cymene)Cl₂]₂ (0.068 mmol). The product was obtained in quantitative yield as an orange solid.

¹H NMR (400 MHz, CD₃CN, T = 298 K, ppm): δ 1.19 (m, 24H), 1.30 (d, J = 7.0 Hz, 3H), 1.33 (d, J = 6.7 Hz, 6H), 1.40 (d, J = 6.7 Hz, 6H), 2.96 (m, 3H), 3.23 (p, J = 6.8 Hz, 2H), 3.62 (m, 2H), 3.75 (m, 2H), 5.29 (d, J = 5.8 Hz, 2H), 5.48 (s, 2H), 5.54 (d, J = 5.8 Hz, 2H), 7.41 (m, 4H), 7.57 (m, 2H), 9.13 (s, 1H).

¹³C NMR (CD₃CN, T = 298 K, ppm): δ 15.26, 18.88, 22.31, 23.01, 23.67, 25.44, 25.51, 29.53, 29.61, 31.70, 68.41, 99.42, 125.82, 126.10, 129.11, 132.72, 147.32, 148.76.

Elemental analysis calcd (%) for C₄₁H₆₁Cl₃N₂O₂Ru: C, 59.95; H, 7.49; N, 3.41. Found: C, 60.28; H, 7.35; N, 3.33.

Complex 6b. Complex 6b was prepared in an analogous manner to that described for 2a starting from 70.4 mg of 1b (0.132 mmol) and 40.4 mg of [Ru(*p*-cymene)Cl₂]₂ (0.066 mmol). The product was obtained in quantitative yield as an orange solid.

¹H NMR (400 MHz, CD₃CN, T = 298 K, ppm): δ 1.08 (d, J = 6.8 Hz, 6H), 1.13 (d, J = 6.9 Hz, 6H), 1.21 (d, J = 6.8 Hz, 6H), 1.27 (d, J = 6.8 Hz, 6H), 1.29 (d, J = 7.8 Hz, 6H), 2.18 (s, 3H), 2.46 (m, 3H), 2.90 (sept, J = 6.9 Hz, 2H), 5.29 (d, J = 5.8 Hz, 2H), 5.54 (d, J = 5.8 Hz, 2H), 7.32 (m, 2H), 7.39 (m, 3H), 7.45 (m, 4H), 7.66 (q, J = 8.0 Hz 2H), 7.99 (d, J = 1.5 Hz, 1H), 9.88 (d, J = 1.7 Hz, 1H).

¹³C NMR (CD₃CN, T = 298 K, ppm): δ 18.86, 22.29, 22.52, 23.83, 24.49, 25.41, 29.92, 30.14, 31.69, 82.10, 84.48, 125.69, 125.80, 128.44, 129.88, 130.00, 130.45, 130.73, 131.18, 132.32, 133.19, 133.49, 141.15, 146.23, 146.89.

Elemental analysis calcd (%) for C₄₃H₅₇Cl₃N₂RuS: C, 61.38; H, 6.83; N, 3.33. Found: C, 61.59; H, 6.65; N, 3.26.

Complex 6c. Complex 6c was prepared in an analogous manner to that described for 2a starting from 70.4 mg of 1c (0.124 mmol) and 37.8 mg of [Ru(*p*-cymene)Cl₂]₂ (0.062 mmol). The product was obtained in quantitative yield as an orange solid.

¹H NMR (400 MHz, CD₃CN, T = 298 K, ppm): δ 1.10 (d, J = 6.5 Hz, 15H), 1.21 (d, J = 6.7 Hz, 6H), 1.29 (m, 12H), 2.46 (m, 4H), 2.89 (sept, J = 7.3 Hz, 2H), 5.29 (d, J = 5.6 Hz, 2H), 5.54 (d, J = 5.7 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.45 (m, 7H), 7.65 (t, J = 7.6 Hz, 3H), 8.02 (s, 1H), 9.62 (s, 1H).

¹³C NMR (CD₃CN, T = 298 K, ppm): δ 1.08, 1.35, 1.63, 18.89, 22.30, 22.50, 23.91, 24.52, 25.47, 29.92, 30.10, 31.68, 82.16, 84.53, 125.75, 125.90, 128.30, 128.69, 130.56, 130.64, 131.22, 132.46, 133.30, 133.63, 134.25, 136.32, 146.23, 146.84.

Elemental analysis calcd (%) for C₄₃H₅₆Cl₄N₂RuS: C, 58.97; H, 6.44; N, 3.20. Found: C, 59.23; H, 6.32; N, 3.15.

Complex 6d. Complex 6d was prepared in an analogous manner to that described for 2a starting from 70.5 mg of 1d (0.118 mmol) and 35.8 mg of [Ru(*p*-cymene)Cl₂]₂ (0.059 mmol). The product was obtained in quantitative yield as an orange solid.

^1H NMR (400 MHz, CD_3CN , T = 298 K, ppm): δ 9.51 (s, 1H), 8.01 (s, 1H), 7.69–7.63 (m, 2H), 7.49–7.40 (m, 6H), 7.31–7.29 (m, 2H), 5.55 (d, J = 5.7 Hz, 2H), 5.30 (d, J = 5.7 Hz, 2H), 2.91 (m, 2H), 2.45 (m, 3H), 1.29 (t, J = 6.8 Hz, 12H), 1.21 (d, J = 6.9 Hz, 9H), 1.11 (t, J = 6.8 Hz, 12H).

^{13}C NMR (CD_3CN , T = 298 K, ppm): δ 146.13, 145.91, 145.29, 135.44, 133.32, 132.69, 132.35, 131.61, 130.83, 130.54, 130.27, 129.69, 129.26, 128.89, 127.72, 127.35, 126.22, 124.97, 124.94, 124.81, 124.79, 83.58, 81.21, 30.76, 29.90, 29.41, 29.17, 28.98, 25.46, 24.49, 23.70, 23.54, 23.37, 22.94, 22.89, 21.55, 21.36, 20.49, 17.93, 0.97, 0.77, 0.56, 0.35, 0.15.

Elemental analysis calcd (%) for $\text{C}_{43}\text{H}_{56}\text{Cl}_4\text{N}_2\text{O}_2\text{RuS}$: C, 56.89; H, 6.22; N, 3.09. Found: C, 56.67; H, 6.37; N, 3.21.

Complex 6e. Complex 6e was prepared in an analogous manner to that described for 2a starting from 55.2 mg of 1e (0.156 mmol) and 47.8 mg of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (0.078 mmol). The product was obtained in quantitative yield as an orange solid.

^1H NMR (400 MHz, CDCl_3 , T = 298 K, ppm): δ 9.80 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.21 (d, 2H, J = 8.4 Hz), 7.14 (s, 2H), 5.82 (d, J = 6.2 Hz, 2H), 5.78 (d, J = 6.2 Hz, 2H), 5.56 (s, 2H), 2.83 (sept, J = 6.8 Hz, 1H), 2.33 (s, 3H), 2.08 (s, 3H), 2.00 (s, 6H), 1.19 (d, J = 6.9 Hz, 6H).

^{13}C NMR (CDCl_3 , T = 298 K, ppm): δ 140.3, 140.0, 137.7, 134.2, 131.5, 131.1, 130.2, 129.3, 124.3, 123.1, 119.8, 106.3, 100.1, 86.4, 85.5, 51.6, 30.0, 21.5, 20.6, 17.9, 16.9.

Elemental analysis calcd (%) for $\text{C}_{29}\text{H}_{34}\text{Cl}_3\text{N}_5\text{Ru}$: C, 52.77; H, 5.19; N, 10.61. Found: C, 53.03; H, 5.05; N, 10.49.

Complex 6f. Complex 6f was prepared in an analogous manner to that described for 2a starting from 100.8 mg of 1f (0.220 mmol) and 34.6 mg of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (0.110 mmol). The product was obtained in quantitative yield as a red solid.

^1H NMR (400 MHz, CD_3CN , T = 298 K, ppm): δ 12.75 (s, 1H), 8.68 (s, 1H), 6.13 (d, J = 3.68 Hz, 1H), 5.80 (dd, J = 4 Hz, 2 Hz, 1H), 5.60 (t, J = 6 Hz, 1H), 5.58 (d, J = 5.45, 2H), 5.33 (d, J = 5.63, 2H), 4.50 (dd, J = 5.24 Hz, 2.82 Hz, 1H), 4.44 (dd, J = 3.0 Hz, 9.53 Hz, 1H), 4.36 (dd, J = 4.92 Hz, 7.48 Hz, 1H), 4.05 (s, 3H), 2.94 (sept, 1H), 2.21 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 1.33 (d, J = 6.7 Hz, 6H).

^{13}C NMR (CD_3CN , T = 298 K, ppm): δ 171.3, 170.5, 170.4, 158.0, 154.4, 149.9, 136.6, 109.8, 89.4, 84.5, 82.1, 74.2, 70.8, 66.2, 63.7, 36.7, 31.7, 22.3, 21.0, 20.7, 20.6, 18.9.

Elemental analysis calcd (%) for $\text{C}_{27}\text{H}_{36}\text{Cl}_3\text{N}_5\text{O}_8\text{Ru}$: C, 42.33; H, 4.74; N, 9.14. Found: C, 42.60; H, 4.51; N, 9.04.

3.4. Crystal Structure Determination

2a, 2b, 5b, 5c, 5e and 6e diffraction data were collected at XRD2 beamline of Elettra Synchrotron, Trieste (Italy) [49], using a monochromatic wavelength of 0.620 Å, at 100 K or 298 K. The data sets were integrated, scaled and corrected for Lorentz, absorption and polarization effects using XDS package [50]. Data from two random orientations of the same crystals have been merged to obtain complete datasets for the triclinic crystal forms, using CCP4-Aimless code [51,52]. SADABS program [53] has been used to scale and apply semi-empirical absorption corrections on 6e and 2a datasets, exploiting multiple measures of symmetry-related reflections. The structures were solved by direct methods using SHELXT program [54] and refined using full-matrix least-squares implemented in SHELXL-2019/3 [55]. Thermal motions for all non-hydrogen atoms have been treated anisotropically. Hydrogens have been included on calculated positions, riding on their carrier atoms. Geometric and thermal restraints (SAME, SADI, SIMU) have been applied to disordered fragments (e.g., allyl ligands and solvent molecules). The Coot program was used for structure building [56]. The crystal data are given in Tables S1. Pictures were prepared using Ortep3 v2.02 and Pymol v2.5 software [57].

Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and allocated the CCDC deposition numbers: 2518446 (**5b** at 100 K), 2518447 (**5b** at 298 K), 2518448 (**5c** at 100 K), 2518449 (**5c** at 298 K), 2518450 (**5e** at 100 K), 2518451 (**5e** at 298 K), 2518452 (**6e** acetonitrile solvate at 100 K), 2518453 (**6e** diethyl ether solvate at 100 K), 2518454 (**6e** diethyl ether solvate at 298 K), 2518455 (**2a** at 100 K) and 2518456 (**2b** at 100 K). These data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures> (accessed on 4 June 2026).

3.5. Cytotoxicity Assay

Two ovarian cancer cell lines, A2780 and A2780*cis*, together with the non-cancerous MRC-5 cell line, were cultured according to the manufacturer's instructions and maintained at 37 °C in a humidified incubator with 5% CO₂. For viability assays, 1×10^3 ovarian cancer cells and 8×10^3 MRC-5 cells were seeded into 96-well plates. After a 24 h incubation period, cells were exposed to six concentrations of the metal-based compounds (0.001, 0.01, 0.1, 1, 10, and 100 µM). Stock solutions of all compounds were prepared at 10 mM using DMSO as solvent.

Following 96 h of treatment, cell viability was quantified using the CellTiter-Glo assay (Promega, Madison, WI, USA) and measured with either a Tecan M1000 or a Synergy H1 microplate reader. IC₅₀ values were obtained by fitting logistic dose–response curves with GraphPad Prism v10 software. Experiments were performed in triplicate, and results are presented as mean values with standard deviation indicated by error bars.

4. Conclusions

In summary, this work repositions azolium-derived metallates from transient intermediates in the synthesis of metal–NHC complexes to a promising and largely untapped class of standalone anticancer agents. Through a comparative investigation involving five late transition metals and three families of functionalized azolium salts, we established clear structure–activity and structure–selectivity relationships, demonstrating that variations in both the metal center and ligand architecture strongly influence the biological profile of these compounds.

From a synthetic perspective, all metallates were obtained through straightforward, atom-economical, and operationally simple procedures performed under aerobic conditions in green solvents, without chromatographic purification. Such synthetic accessibility represents a significant advantage for future medicinal applications. In addition, this study reports the first isolation and crystallographic characterization of ruthenate species within this family, further expanding the structural diversity of azolium-derived metallates.

Biological evaluation against cisplatin-sensitive and cisplatin-resistant ovarian cancer models revealed that backbone-functionalized azolium salts generate the most potent derivatives, frequently surpassing cisplatin while retaining activity in resistant cells. Unlike cisplatin, whose efficacy dramatically decreases in the A2780*cis* model, the synthesized metallates displayed nearly unchanged IC₅₀ values across sensitive and resistant cell lines, suggesting the involvement of alternative mechanisms of action.

Ligand functionalization also strongly influenced selectivity toward tumour cells. Ethoxide-substituted derivatives and several platinum-based metallates combined high antiproliferative activity with reduced toxicity toward noncancerous fibroblasts, whereas benzyl azido- and methyl guanosine-derived compounds generally showed lower cytotoxicity toward both cancerous and normal cells. These findings demonstrate that the azolium framework plays a key role in modulating both efficacy and tolerability.

Overall, the present study establishes azolium-derived metallates as a versatile platform for the development of nonclassical metal-based chemotherapeutics against ovarian

cancer. The most promising derivatives, namely **2a**, **2e**, **2f**, **3a**, **4a–d**, **5a**, **5c**, **5e**, **5f**, **6a**, and **6e**, emerged as valuable lead compounds for further mechanistic and biological investigations. Future studies will focus on elucidating their molecular targets and evaluating their efficacy in more advanced biological models, including organoids and in vivo systems.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/inorganics14060155/s1>, Figure S1. ^1H NMR spectra of imidazolium salt **1a** (blue) and complex **2a** (red) in CDCl_3 ; Figure S2. ^1H NMR spectrum of complex **2a** in CDCl_3 ; Figure S3. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **2a** in CDCl_3 ; Figure S4. ^1H NMR spectrum of complex **2b** in CDCl_3 ; Figure S5. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **2b** in CDCl_3 ; Figure S6. ^1H NMR spectrum of complex **2c** in CDCl_3 ; Figure S7. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **2c** in CDCl_3 ; Figure S8. ^1H NMR spectrum of complex **2d** in CDCl_3 ; Figure S9. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **2d** in CDCl_3 ; Figure S10. ^1H NMR spectrum of complex **2e** in CDCl_3 ; Figure S11. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **2e** in CDCl_3 ; Figure S12. ^1H NMR spectrum of complex **2f** in CD_3CN ; Figure S13. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **2f** in CD_3CN ; Figure S14. ^1H NMR spectrum of complex **3a** in CDCl_3 ; Figure S15. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **3a** in CDCl_3 ; Figure S16. ^1H NMR spectrum of complex **3b** in CDCl_3 ; Figure S17. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **3b** in CDCl_3 ; Figure S18. ^1H NMR spectrum of complex **3c** in CDCl_3 ; Figure S19. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **3c** in CDCl_3 ; Figure S20. ^1H NMR spectrum of complex **3d** in CDCl_3 ; Figure S21. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **3d** in CDCl_3 ; Figure S22. ^1H NMR spectrum of complex **4a** in CDCl_3 ; Figure S23. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **4a** in CDCl_3 ; Figure S24. ^1H NMR spectrum of complex **4b** in CDCl_3 ; Figure S25. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **4b** in CDCl_3 ; Figure S26. ^1H NMR spectrum of complex **4c** in CDCl_3 ; Figure S27. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **4c** in CDCl_3 ; Figure S28. ^1H NMR spectrum of complex **4d** in CDCl_3 ; Figure S29. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **4d** in CDCl_3 ; Figure S30. ^1H NMR spectrum of complex **5a** in CDCl_3 ; Figure S31. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **5a** in CDCl_3 ; Figure S32. ^1H NMR spectrum of complex **5b** in CDCl_3 ; Figure S33. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **5b** in CDCl_3 ; Figure S34. ^1H NMR spectrum of complex **5c** in CDCl_3 ; Figure S35. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **5c** in CDCl_3 ; Figure S36. ^1H NMR spectrum of complex **5d** in CDCl_3 ; Figure S37. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **5d** in CDCl_3 ; Figure S38. ^1H NMR spectrum of complex **5e** in CDCl_3 ; Figure S39. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **5e** in CDCl_3 ; Figure S40. ^1H NMR spectrum of complex **5f** in CDCl_3 ; Figure S41. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **5f** in CDCl_3 ; Figure S42. ^1H NMR spectrum of complex **6a** in CD_3CN ; Figure S43. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **6a** in CD_3CN ; Figure S44. ^1H NMR spectrum of complex **6b** in CD_3CN ; Figure S45. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **6b** in CD_3CN ; Figure S46. ^1H NMR spectrum of complex **6c** in CD_3CN ; Figure S47. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **6c** in CD_3CN ; Figure S48. ^1H NMR spectrum of complex **6d** in CD_3CN ; Figure S49. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **6d** in CD_3CN ; Figure S50. ^1H NMR spectrum of complex **6e** in $\text{DMSO}-d_6$; Figure S51. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **6e** in $\text{DMSO}-d_6$; Figure S52. ^1H NMR spectrum of complex **6f** in CD_3CN ; Figure S53. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **6f** in CD_3CN . Table S1. Crystallographic data. Table S2. Selected metal distances and angles for **5b** at 100 K and 298 K. Corresponding naming scheme in use is reported (hydrogens omitted for clarity). Table S3. Selected metal distances and angles for **5c** at 100 K and 298 K. Corresponding naming scheme in use is reported (hydrogens omitted for clarity). Table S4. Selected metal distances and angles for **5e** at 100 K and 298 K. Corresponding naming scheme in use is reported (hydrogens omitted for clarity). Table S5. Selected metal distances and angles for **6e** acetonitrile and diethyl ether solvates at 100 K and 298 K. Corresponding naming scheme in use is reported (hydrogens omitted for clarity). Table S6. Selected metal distances and angles for **2a** at 100 K and 298 K. Corresponding naming scheme in use is reported (hydrogens omitted for clarity). Table S7. Selected metal distances and angles for **2b** at 100 K. Corresponding naming scheme in use is reported (hydrogens omitted for clarity).

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