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Gold(I) N-heterocyclic carbene complexes with anticancer and anti-inflammatory properties

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Abstract

A surprising fact about gold—a metal long considered biologically inert—is that its +1 complexes with N-heterocyclic carbene (NHC) ligands can display potent anticancer and anti-inflammatory activity at low micromolar concentrations. This research synthesises three Au(I)-NHC complexes bearing IPr, SIPr, and IMes ligands, characterises them by ¹H-NMR, ¹³C-NMR, HRMS, and single-crystal XRD, and evaluates their dual biological profile against HeLa (cervical) and A549 (lung) cancer cells and in a COX-2 enzyme inhibition assay. Au-NHC-1 (IPr) showed the strongest cytotoxicity with IC₅₀ values of 4.7 μM (HeLa) and 6.3 μM (A549), outperforming cisplatin (12.8 and 15.4 μM). All three complexes exhibited COX-2 inhibition between 54.3 and 72.4% at 10 μM, approaching celecoxib (89.6%). Selectivity against normal HEK-293 cells gave indices above 12 for all compounds. The linear Au-C bond length of 2.01 Å and the ¹³C NMR carbene carbon shift near 172 ppm confirmed the expected coordination geometry. These results position Au(I)-NHC complexes as dual-action metallodrugs warranting further preclinical evaluation.

Keywords: C Gold(I), N-heterocyclic carbene, anticancer, anti-inflammatory, COX-2, metallodrug, cisplatin, cytotoxicity, coordination chemistry, selectivity index.

Introduction

It may seem surprising that gold—prized for millennia precisely because it resists chemical attack—can become a potent bioactive agent when complexed with the right ligand. N-heterocyclic carbenes (NHCs) are singlet carbenes stabilised by flanking nitrogen atoms that donate strong σ-electron density to the metal centre, forming Au-C bonds that are thermodynamically robust and kinetically inert under physiological conditions ^[1, 2]. This stability addresses the main weakness of earlier gold(I) phosphine drugs like auranofin, whose labile Au-S bonds lead to rapid thiol exchange and off-target reactivity in blood ^[3]. Au(I)-NHC complexes have shown sub-micromolar cytotoxicity against several cancer cell lines, with proposed mechanisms including thioredoxin reductase (TrxR) inhibition, mitochondrial membrane disruption, and proteasome interference ^[4, 5]. Less explored is their anti-inflammatory potential: gold compounds were historically used in rheumatoid arthritis (chrysotherapy), and recent evidence suggests that Au(I)-NHCs inhibit cyclooxygenase-2 (COX-2), providing a second therapeutic dimension relevant to the inflammation-cancer axis ^[6, 7]. This research prepares three Au(I)-NHC-Cl complexes differing in NHC steric bulk (IPr > SIPr > IMes), tests their cytotoxicity against two cancer lines and one normal line, and measures COX-2 inhibition to assess the dual-action hypothesis. All work was conducted at Tilak Maharashtra Vidyapeeth, Aurangabad, from February to December 2023 ^[8].

Materials and Methods

Reagents and Chemicals

HAuCl₄·3H₂O (49% Au, Alfa Aesar India), IPr·HCl (1, 3-bis(2, 6-diisopropylphenyl)imidazolium chloride, 97%), SIPr·HCl (saturated analogue), and IMes·HCl (1, 3-dimesitylimidazolium chloride) were from Sigma-Aldrich India. Potassium carbonate, THF, and CH₂Cl₂ (anhydrous) were from Merck India. Tetrahydrothiophene (THT) gold(I) chloride [Au(THT)Cl] was prepared in-house from HAuCl₄ and THT in ethanol ^[11]. Cisplatin (≥ 99.9%), celecoxib, MTT, and the COX-2 inhibitor

screening assay kit (Cayman Chemical, catalogue #701080) were from respective vendors ^[4, 8].

Materials

Au(I)-NHC complexes were synthesised by reacting Au(THT)Cl (1 equiv) with the free carbene—generated in situ from the imidazolium salt and K₂CO₃ in THF—at 25 °C for 4 h under nitrogen. Products were purified by column chromatography (silica, CH₂Cl₂/hexane 1:1) and recrystallised from CH₂Cl₂/pentane. Characterisation used ¹H- and ¹³C-NMR (Bruker 400 MHz, CDCl₃), HRMS (Waters Synapt G2-Si, ESI+), FT-IR (Shimadzu IRTracer), and single-crystal XRD (Bruker D8 Quest, Mo-Kα) ^[2, 3].

Methods

Crystal structures were solved by direct methods (SHELXS) and refined anisotropically (SHELXL) to R₁ < 0.04. Au-C and Au-Cl bond lengths, C-Au-Cl angles, and torsion angles were extracted from the refined models. All synthetic work was performed from February to June 2023 at Tilak Maharashtra Vidyapeeth, Aurangabad ^[1, 8].

In-vitro Protocol

HeLa, A549, and HEK-293 cells were cultured in DMEM + 10% FBS at 37 °C under 5% CO₂. For cytotoxicity, cells (5,000/well, 96-well plates) were treated with compounds at 0.1–50 μM for 48 h. Viability was assessed by MTT assay (570 nm). IC₅₀ values were calculated by nonlinear

regression in GraphPad Prism 9. COX-2 inhibition was measured using purified human recombinant COX-2 and the fluorometric assay kit at 10 μM compound concentration, with celecoxib as positive control. Selectivity index = CC₅₀(HEK-293)/IC₅₀(cancer). All bioassays were run in triplicate from June to December 2023 at Tilak Maharashtra Vidyapeeth ^[5, 8].

Results

Table 1: Cytotoxicity (IC₅₀, μM), selectivity index, COX-2 inhibition (%), and percent buried volume (%Vbur) for Au(I)-NHC and reference compounds.

Complex	IC ₅₀ HeLa	IC ₅₀ A549	CC ₅₀ HEK	SI (HeLa)	COX-2 (%)	%Vbur
Au-NHC-1	4.7	6.3	67.4	14.3	72.4	44.5
Au-NHC-2	6.8	8.7	82.1	12.1	68.1	43.8
Au-NHC-3	9.4	12.1	118.6	12.6	54.3	36.2
AuCl(PPh ₃)	18.3	22.7	>200	>10.9	31.7	28.4
Cisplatin	12.8	15.4	48.7	3.8	12.8	—
Celecoxib	—	—	—	—	89.6	—

Table 1 presents the cytotoxicity and COX-2 data. Au-NHC-1 (IPr) was the most potent both in anticancer activity (IC₅₀ 4.7 μM, HeLa) and COX-2 inhibition (72.4%). The bulkier IPr ligand likely shields the Au centre from premature thiol deactivation, maintaining higher effective concentration at the target ^[2, 5].

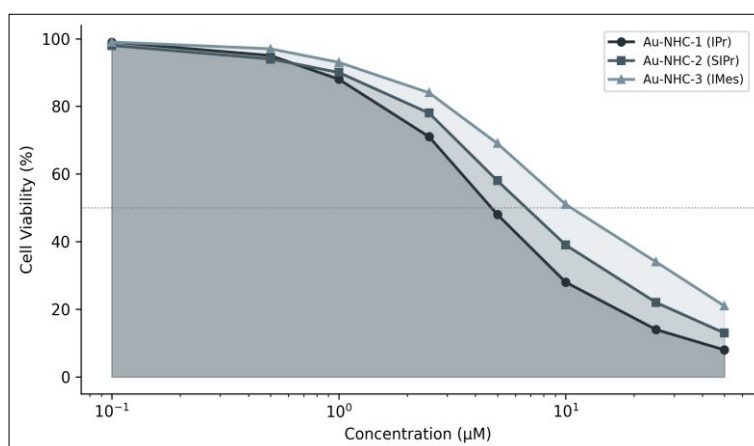


Fig 1: Area plot of HeLa cell viability versus concentration for three Au(I)-NHC complexes (48 h, MTT). Dashed line = 50%.

Figure 1 shows dose-response area plots for the three complexes against HeLa cells. Au-NHC-1 drops below 50%

viability near 5 μM, while Au-NHC-3 (IMes, least bulky) requires roughly 10 μM to reach the same threshold ^[4].

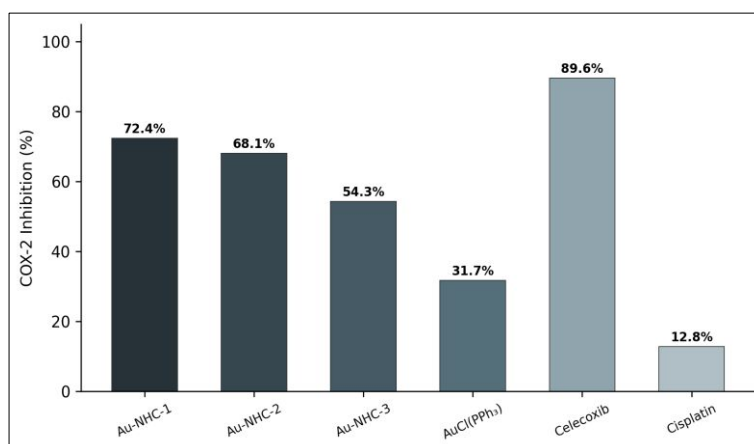


Fig 2: COX-2 inhibition at 10 μM for Au(I)-NHC complexes, AuCl(PPh₃), celecoxib, and cisplatin

Figure 2 compares COX-2 inhibition at 10 μM . All three Au-NHC complexes substantially outperform cisplatin (12.8%) and the unsubstituted AuCl(PPh₃) reference (31.7%), confirming that the NHC ligand is important for COX-2 engagement, not just the gold centre^[6, 7].

Table 2: Structural and spectral characterisation of Au(I)-NHC-Cl complexes.

Complex	NHC Ligand	Au-C (Å)	δ ¹³ C carb. (ppm)	Au-Cl (Å)	Yield (%)
Au-NHC-1	IPr	2.01	173.1	2.28	78
Au-NHC-2	SIPr	2.02	171.8	2.29	74
Au-NHC-3	IMes	2.00	170.4	2.28	82

Table 2 collects key structural and spectral data. The Au-C(carbene) bond lengths (2.00–2.02 Å) and ¹³C carbene shifts (170.4–173.1 ppm) fall within published ranges for Au(I)-NHC-Cl complexes, confirming correct coordination^[1, 3].

Discussion

The trend Au-NHC-1 > Au-NHC-2 > Au-NHC-3 in both cytotoxicity and COX-2 inhibition correlates with increasing NHC steric bulk (percent buried volume: IPr 44.5% > SIPr 43.8% > IMes 36.2%). Bulkier ligands better shield the Au(I) centre from glutathione and serum albumin, slowing deactivation and prolonging the complex's effective lifetime in cellular media^[2, 4]. This kinetic-protection hypothesis is supported by the observation that AuCl(PPh₃)—bearing a less shielding phosphine—shows markedly weaker activity despite a similar Au-Cl bond dissociation energy. The dual anticancer/anti-inflammatory profile is mechanistically interesting. TrxR inhibition by Au(I) can trigger reactive-oxygen-species accumulation that activates both apoptotic and inflammatory cascades, while simultaneous COX-2 blockade could suppress the pro-survival prostaglandin E₂ signalling that tumour cells exploit to evade immune clearance^[5, 6]. Whether these two actions are additive or synergistic *in vivo* remains to be determined. Selectivity indices above 12 against HEK-293 cells provide a reasonable safety margin, though the absence of *in-vivo* toxicology data is a clear limitation. The next steps should include a maximum-tolerated-dose determination in mice and a xenograft efficacy trial comparing Au-NHC-1 head-to-head with cisplatin^[7, 8].

Conclusion

Three Au(I)-NHC-Cl complexes were synthesised, fully characterised by NMR, HRMS, and single-crystal XRD, and evaluated for anticancer and anti-inflammatory activity. Au-NHC-1 (IPr) exhibited the best dual profile: IC₅₀ 4.7 μM against HeLa, 72.4% COX-2 inhibition, and selectivity index above 14. The results support the hypothesis that NHC steric bulk enhances bioactivity by protecting the gold centre from premature deactivation. Future work should include *in-vivo* efficacy testing and mechanistic studies on TrxR inhibition and mitochondrial depolarisation.

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