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Indenyl and Allyl Palladates: Synthesis, Bonding, and Anticancer Activity

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Abstract : Organopalladium compounds have recently attracted attention for their high stability even under physiological conditions and, above all, for their remarkable in vitro cytotoxicity towards cisplatin-resistant cell lines. Among the organopalladium derivatives, those bearing at least one N-heterocyclic carbene ligand (NHC) and the Pd(II)-η^3-allyl fragment have exhibited IC_{50} values in the micro and sub-micromolar range towards several cancer cell lines in vitro and in some cases selectivity towards cancerous vs. non-tumorigenic cells. Herein, a selection of allyl and indenyl palladates were synthesized using a solvent-free method consisting of grinding the corresponding palladium precursors with different saturated and unsaturated azolium salts. All compounds have been fully characterized by NMR, XRD and elemental analyses. The intramolecular H, Cl interaction has been elucidated and quantified using the Voronoi Deformation Density scheme. Most of the complexes showed excellent cytotoxicity towards ovarian cancer cell lines, with I_{50} values comparable to or even lower than cisplatin. Interestingly, the potent anticancer activity was also confirmed in a high-serous ovarian cancer (HGSOC) patient-derived tumoroid, with a clear superiority of this class of compounds over classical platinum-based agents. Finally, preliminary enzyme inhibition studies of the synthesized palladate complexes against the model TrxR show that the compounds have high activity comparable to or even higher than auranofin and classical Au(I) NHC complexes. Based on such promising data, further in vitro and in vivo experiments and in-depth mechanistic studies are ongoing in our laboratories.

Keywords : anticancer activity, palladium complexes, organoids, indenyl and allyl ligands
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