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ANTIANGIOGENIC PROPERTIES OF SELECTED RUTHENIUM(III) COMPLEXES THAT ARE NITRIC OXIDE SCAVENGERS

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Angiogenesis plays an important role in physiological and pathological events like fertility, healing of injured tissue, and tumor spreading. Essential for angiogenesis is the biochemical and molecular activation of the endothelial cells of capillaries. The nitric oxide synthase (NOS) pathway has been clearly demonstrated to regulate the occurrence and progression of the angiogenic cascade. We demonstrated that the nitric oxide (NO) pathway controls the angiogenic program of the endothelial cells and that NOS inhibitors can block angiogenesis. Increased levels of NO correlate with tumor growth and spreading in different human and experimental cancers.
The aim of this study was the pharmacological characterization of some ruthenium-based NO scavengers (imidazolium trans imidazole dimethylsulphoxide tetrachloro ruthenate, ImH[trans-RuCl4(DMSO)Im], NAMI-A; sodium bis indazole tetrachloro ruthenate, Na[trans-RuCl4Ind2], KP1339, and RuEDTA) to be used as anti-angiogenic/anti-tumor agents. The potency and efficacy of the NO scavengers were evaluated on acetylcholine-induced vasorelaxation of rabbit aortic rings. The activity of these compounds on angiogenesis has been evaluated on the migration and proliferation of microvascular endothelial cells.
NAMI-A, KP1339 and RuEDTA were able to bind tightly and inactivate free NO in solution under physiological conditions. Formation of Ruthenium-NO adducts was documented by electronic absorption and FT-IR spectroscopy. Pre-treatment of rabbit aorta rings with NAMI-A, KP1339 and RuEDTA caused insensitivity to the endothelium-dependent vasorelaxant effect elicited by acetylcholine. NAMI-A, KP1339 and RuEDTA, devoid of any cytotoxic effect, completely blocked endothelial cell proliferation and migration stimulated by vascular endothelial growth factor (VEGF) or NO donor drugs.
It is likely that the antitumor properties previously observed for ruthenium-based NO scavengers as NAMI-A, are related to their antiangiogenic properties.

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