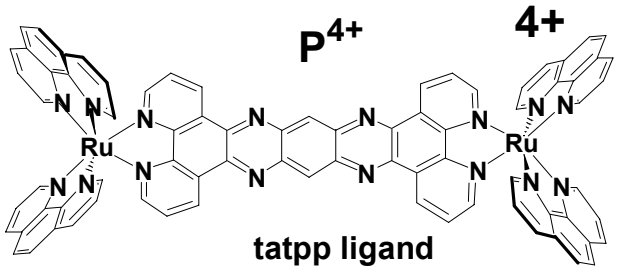
Topoisomerase I and II Inhibition by the DNA-Intercallating Ruthenium Dimers, $[Ru_2(phen)_4tatpp]^{4+}$ and $[Ru_2(phen)_4tatpq]^{4+}$

Thamara K. Janaratne, Frederick M. MacDonnell, Sanjay Awasthy, Sharad S. Singhal

Department of Chemistry and Biochemistry, The University of Texas at Arlington

DNA topoisomerases are ubiquitous enzymes that alter the configuration or topology of duplex DNA. Two types of topoisomerases, I and II, have been isolated from mammalian cells. Topoisomerase I catalyzes a transient single-stranded break of the DNA double helix during DNA relaxation whereas topoisomerase II catalyzes transient double-stranded breaks. They are essential for many vital DNA functions during cell growth, such as replication, transcription, etc. and are therefore attractive targets for chemotherapy. Several clinically used anticancer drugs are potent inhibitors of either topoisomerase I or II or both.



Currently, we are working with the ruthenium dimer, $[Ru_2(phen)_4tatpp]^{4+}$, $\mathbf{P}^{4+}$ (tatpp = 9,11,20,22 -tetraazatetrapyrido[3,2-*a*: 2′,3′-*c*: 3′′,2′′ -*1*: 2′′′,3′′′-*n*]-pentacene and phen = 1,10-phenanthroline) and its quinone analog, $[Ru_2(phen)_4tatpq]^{4+}$, $\mathbf{Q}^{4+}$ (tatpq = 9,11,20,22 -tetraazatetrapyrido[3,2-*a*: 2′,3′-*c*: 3′′,2′′ -*1*: 2′′′,3′′′-*n*]-pentacene-10,21-quinone), both of which show good toxicity against non small cell lung carcinoma (IC_{50} for $\mathbf{P}^{4+}$ 8.25±0.5 μM and $\mathbf{Q}^{4+}$ 0.85 ±0.1 μM) in vitro.

The ability of $\mathbf{P}^{4+}$ and $\mathbf{Q}^{4+}$ to inhibit mammalian topoisomerase I and II was assessed using gel shift assays with supercoiled plasmid DNA. Even at low concentration (15 μM), $\mathbf{P}^{4+}$ as well as $\mathbf{Q}^{4+}$ inhibit the relaxation activity of both enzymes. These results taken in combination with the relatively low animal toxicity suggest these complexes have potential as a new class of selective chemotherapeutic drugs.