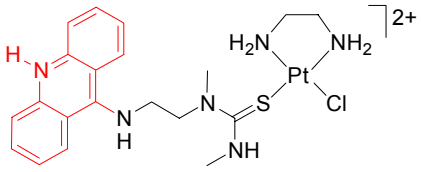
DNA Sequence and Groove Recognition by Platinum–Acridine Conjugates

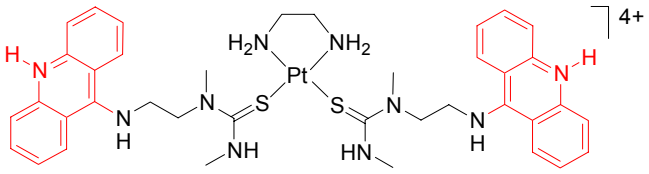
Jayati Roy Choudhury, Michael E. Budiman, Rebecca W. Alexander, and Ulrich Bierbach

Department of Chemistry, Wake Forest University

Nuclear DNA is the primary cellular target for anticancer therapies. The majority of chemotherapeutic agents bind to DNA by intercalation, groove binding, or formation of adducts, thereby inhibiting vital cellular processes such as replication and transcription. Platinum–intercalator conjugates have proven to be potential DNA-targeted anticancer agents. Our lab has designed and synthesized the experimental drug PT-ACRAMTU, which forms monofunctional adducts with guanine and adenine bases with preferential intercalation of the acridine chromophore into 5′-CG/CG, 5′-TA/TA, and 5′-GA/TC base-pair steps. Most strikingly, PT-ACRAMTU forms minor-groove adducts at adenine-N3. On the other hand, the reversible DNA bisintercalator PT-BIS(ACRAMTU) binds to DNA from the minor groove with a significant preference for $(TA)_n$ sequences. Adducts of both agents inhibit transcription of DNA by prokaryotic T7 RNA polymerase. The DNA binding mode of PT-BIS(ACRAMTU) was studied by high-resolution NMR spectroscopy/molecular modeling, ethidium fluorescence quenching and equilibrium dialysis assays, and thermal melting experiments. Ongoing research utilizes transcriptional footprinting to establish the driving force behind the unusual platination of adenine in the minor-groove of DNA by PT-ACRAMTU.



PT-ACRAMTU



PT-BIS(ACRAMTU)