GENERATION AND STUDY OF A NOVEL DNA BASE LESION

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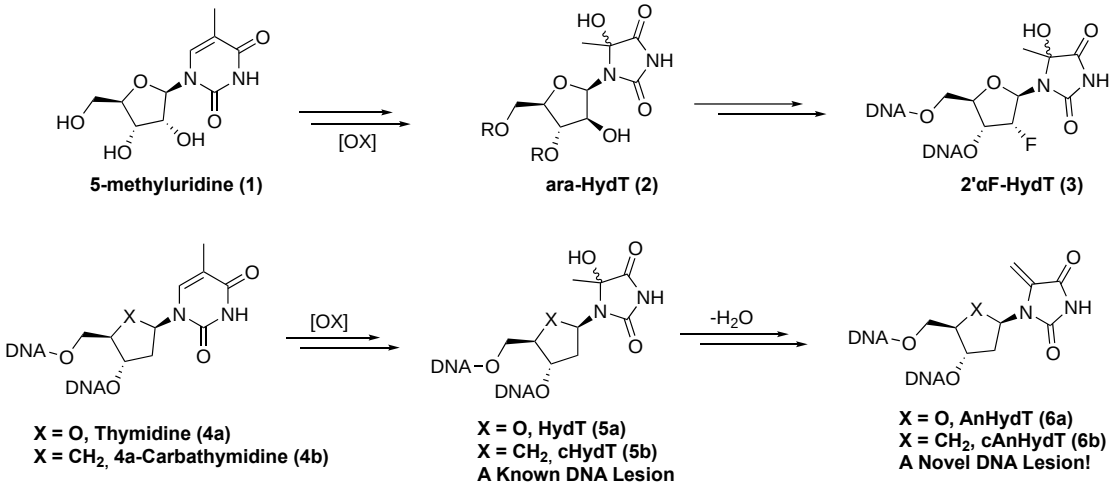
In aerobic organisms, oxidative stress occurs when the balance between Reactive Oxygen or Nitrogen Species (ROS/RNS) production and antioxidant defenses is severely disrupted. This imbalance may lead to DNA damage through the oxidation of nucleobases and sugar moieties in nucleotides. The main DNA base alteration repair mechanisms include Base Excision Repair (BER) and Nucleotide Excision Repair (NER), which may operate simultaneously on the same lesion.[1] Within our laboratory, research has been focused on the role of these mechanisms in cell function, with studies, utilizing synthetic nucleotides with oxidized bases, linked to the sugar through stable BER-resistant glycosidic bonds, that allow the study of NER processes.[2,3]



We present herein the synthesis of a BER-resistant derivative of 5-hydroxy-5-methylhydantoin (**3**), a DNA lesion derived from thymidine (**4a**) oxidation, together with the first observation of a previously unreported lesion which have been termed AnhydroHydantoin (AnHydT, **6a**). This lesion results from an unexpected dehydration of HydT (**5a**), leading to the formation of an exocyclic double bond. AnHydT displays an enhanced reactivity as a Michael acceptor. Details are provided on the isolation, characterization, and derivatization of both the carbacyclic and natural forms of the novel AnHydT lesion.

References

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(3) Psykarakis, E. E.; Chatzopoulou, E.; Gimisis, T. First Characterisation of Two Important Postulated Intermediates in the Formation of a HydT DNA Lesion, a Thymidine Oxidation Product. *Org. Biomol. Chem.* **2018**, *16*(13), 2289–2300.