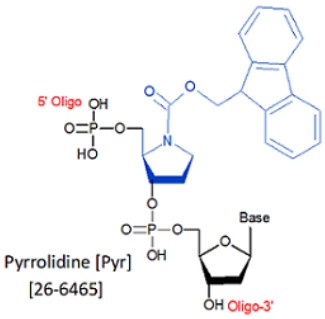
Pyrrolidine (Pyr)

Category	Structural Studies
Modification Code	Pyr
Reference Catalog Number	26-6465
5 Prime	Y
3 Prime	Y
Internal	Y
Molecular Weight(mw)	178.1



Pyrrolidine: DNA Damage & Repair new base excision repair inhibitor

DNA is constantly under attack. Alkylating agents, ionizing radiation and oxidative stress can induce base modification or strand scission that, left unchecked, can lead to the development of cancer. Our cells are equipped with DNA damage-monitoring and repair enzymes to correct the damage via base excision repair (BER) or nucleotide excision repair (NER). Ironically, though, the up-regulation of these repair enzymes in cancerous cells frequently causes the development of drug resistance against chemotherapeutic reagents.

One of the most studied repair mechanisms is probably the base excision DNA repair pathway. In this pathway, DNA glycosylases recognize the damaged bases and catalyze their excision through hydrolysis of the N-glycosidic bond. Attempts to understand the structural basis for DNA damage recognition by DNA glycosylases have been hampered by the short-lived association of these enzymes with their DNA substrates. To overcome this problem, the design and synthesis of inhibitors that form stable complexes with DNA glycosylases are essential. Complexes can then be studied biochemically and structurally.

Toward this end, the Verdine group at Harvard synthesized a pyrrolidine analog that mimics the charged transition state of the enzyme-substrate complex. When incorporated into double-stranded DNA, they found the pyrrolidine analog (PYR), introduced through a synthetic oligo forms an extremely stable complex with the DNA glycosylase AlkA, exhibiting a dissociation constant in the pM range and potently inhibited the reaction catalyzed by the enzyme (1).

References

See Glen Research Report DNA Damage & Repair.

1. O.D. Scharer, et al., J. Am. Chem. Soc., 1995, 117, 6623-6624.
2. O.D. Scharer, et al., J. Biol. Chem., 1998, 273, 8592-8597.
3. V.L. Schramm, Arch Biochem Biophys, 2005, 433, 13-26.