Enhanced DNA double strand cleavage with non-heme iron complexes

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Natural non-heme systems such as bleomycin (BLM) have served as a rich source of inspiration in ligand design, both in terms of ligand environment and redox chemistry.[1] We have developed the pentadentate ligand N4Py as a functional model for the active site of BLM.[2] After ligation to iron, *FeN4Py* is able to oxidise a wide variety of organic substrates efficiently with either H_2O_2 or *m*CPBA.[3,4]

FeN4Py, as with iron-BLM, is capable of oxidising DNA using O_2 as terminal oxidant.[5] Moreover, this system is distinctive in that it does not require the addition of an external reductant. However, only single strand (ss) cleavage events are observed, *i.e.* only one of the DNA strands is oxidised. From a therapeutic perspective double strand (ds) cleavage, *i.e.* where both DNA strands are oxidised in close proximity, is more relevant, as this is the mode of action of many anti-tumor drugs such as BLM. In order to meet this requirement, two N4Py's are linked covalently (Figure 1). In a competition experiment between *FeN4Py* and *double-FeN4Py*, the latter was found to be, significantly, more active towards double strand cleavage (Figure 2).

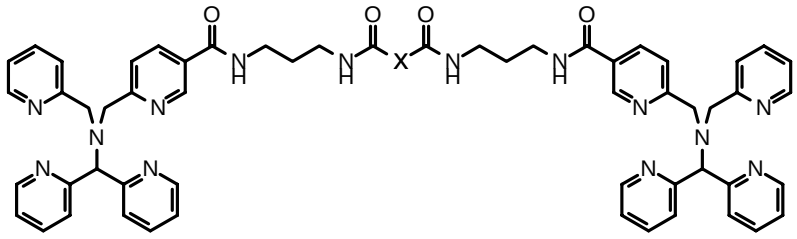

Figure 1, Two covalently linked N4Py ligands (*double-FeN4Py)*

Figure 2, DNA cleavage with FeN4Py (left) and double FeN4Py (right)

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