Nuclease activity of heterodinuclear platinum/copper complexes, a novel approach in drug design

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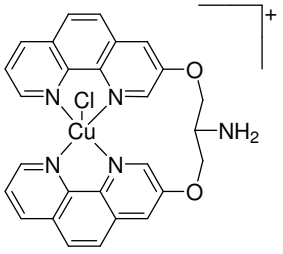
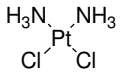
cis-Diamminedichloroplatinum(II), generally referred to as cisplatin (see figure), is widely used as a chemotherapeutic agent to cure solid tumor cancers, such as testicular and ovarian cancer [1]. The clinical use of cisplatin is beyond any doubt very successful, but the treatment is accompanied by serious side effects and acquired tumor resistance. In order to decrease or to overcome these problems, a new strategy is envisaged where two entities with different mechanisms of action are linked by a tunable spacer. Cisplatin derivatives, which are known to cause distortions in DNA upon binding in the major-groove are linked to the minor-groove binding nuclease-active Cu-3-Clip-Phen [2] (see figure).



Cu-3-Clip-Phen



Cisplatin

The syntheses of heterodinuclear complexes able to interact both from the major groove and minor groove of DNA are presented. To further investigate the effect of such an unusual interaction, a complex that is not able to cross the phosphate backbone of DNA has been synthesized. Both complexes are able to cleave supercoiled DNA in a direct double-stranded fashion in contrast to Cu-3-Clip-Phen alone. This synergism between the platinum and the copper parts is related to the kinetically inert coordination bond between the platinum moiety and DNA. Therefore, the platinum moiety has two tasks: distortion of the DNA double strand and anchoring of the Cu-3-Clip-Phen moiety to DNA.

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References

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