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Synthetic DNA-Binding Ligands with Reaction Centers Capable of Specific Interaction with AT and GC Pairs

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In the present communication, design, synthesis and DNA binding activities of three bis-netropsins and two netropsin analogs containing two N-propylpyrrolecarboxamide fragments linked covalently to peptides Gly-Gly-(analog I) and Val-Val-Val-Gly-Gly-(analog II) are reported. Each bis-netropsin consists of two netropsin-like fragments attached to peptides Gly-Cys-Gly-NH_2-(compound IIIa), or H-Gly-Cys-Gly-Gly-Gly-(compound IV) or Gly-Cys-Sar-NH_2-(compound IIIb) which are linked symmetrically via S-S bonds. Physico-chemical studies show that each bis-netropsin carries 6 AT-specific reaction centers and covers approximately 10 base pairs upon binding to poly(dA) • poly(dT). This indicates that two netropsin-like fragments of bis-netropsin molecule are implicated in specific interaction with DNA base pairs. The peptide fragments of bis-netropsins IIIa and IV form small beta-sheets containing two GC-specific reaction centers. The DNase I cleavage patterns of bis-netropsin-DNA complexes visualized by high resolution gel electrophoresis show that the preferred binding sites for bis-netropsin IIIa and IV are identical and contain two runs of three or more AT pairs separated by two GC pairs. Specificity determinants of netropsin analog II binding in the p-associated dimeric form are identical to those of bis-netropsin IIIa thereby indicating that there is a similarity in the structure of complexes formed by these ligands with DNA. In the monomelic form analog II exhibits binding specificity identical to that of analog I. Replacement of C-terminal glycine residues by sarcosines in the peptide fragments of bis-netropsin IIIIa leads to a decrease in the affinity of ligand for DNA.

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