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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

Synthesis and Characterization of Artificial Ribonucleases

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To cite this Article Zhdan, N. S. , Kuznetsova, I. L. , Zenkova, M. A. , Vlassov, A. V. , Silnikov, V. N. , Giege, R. and Vlassov, V. V.(1999) 'Synthesis and Characterization of Artificial Ribonucleases', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 6, 1491 – 1492

To link to this Article: DOI: 10.1080/07328319908044764

URL: <http://dx.doi.org/10.1080/07328319908044764>

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SYNTHESIS AND CHARACTERIZATION OF ARTIFICIAL RIBONUCLEASES

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ABSTRACT: RNA cleaving molecules were synthesized by conjugating components of ribonucleases A and T1 catalytic centers (imidazole, aliphatic amino and/or carboxy residues) to intercalating and cationic structures. The artificial ribonucleases were shown cleave RNA at Py-Pu sites in single-stranded regions.

Small molecules capable of cleaving nucleic acids are useful tools for probing RNA structure in solution and can find applications in design of antisense oligonucleotide

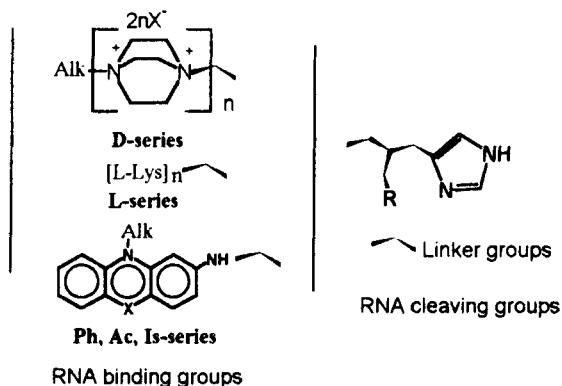


FIG.1. R = imidazole, carboxy, carboxymethyl, amino groups; Ph = phenazine; Ac = acridine; Is = isoalloxazine

conjugates. We synthesized small RNA cleaving catalytic groups mimicking catalytic centers of ribonucleases A and T1. The groups have one or two imidazole residues, amino and carboxy groups in different combinations connected by linkers of variable length and flexibility [1-3].

The groups have been conjugated to different molecules capable of binding to RNA: to cationic structures (**D** [3] and **L**) series with different number of charges and to studied in experiments with 3'-[32 P]-tRNA^{Phe} (FIG. 2). It was found that some of the synthesized compounds cleave RNA in physiological conditions (37 °C, pH 7). The compounds display similar cleavage specificity with some variations. Sensitivity of phosphodiester bonds to the synthetic ribonucleases decreases in the order: CA>UA>CG>UG>>CC, UU, GG, AA. The compounds of **D** and **L** display very strong

preference to the single-stranded RNA regions. Compounds of the **Ph** and **Ac** series can attack some sites within double-stranded regions although with slower rate. The

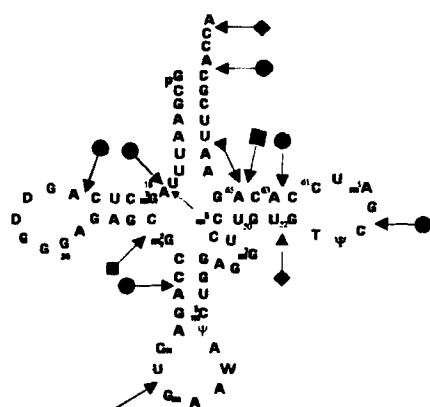


FIG. 2. Sites of cleavage of the tRNA^{Phe} by the artificial ribonucleases: ○→ - all compounds, except for Is series; ◆→ - **D** and **L** series; ▲→ - **Ph** and **Ac** series

highest specificity was demonstrated by compounds of the **Is** series which cleaved the RNA at U₈ and U₃₃ only. Highest cleavage efficiency was displayed by the compounds containing two imidazole residues or imidazole and carboxy group, with linker groups including more than 8 chemical bonds. After 6 h. incubation of the tRNA (10⁻⁷ M) with these compounds (10⁻⁴-10⁻⁵ M) at 37 °C and pH 7.0 resulted in complete depolymerization of the RNA.

The compounds provide new probes for the investigation of RNA structure in solution and potential reactive groups for antisense oligonucleotide derivatives.

This work was supported by grants: INTAS 96-1418, RFBR 95-03-32361, RFBR 96-15-97732.

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