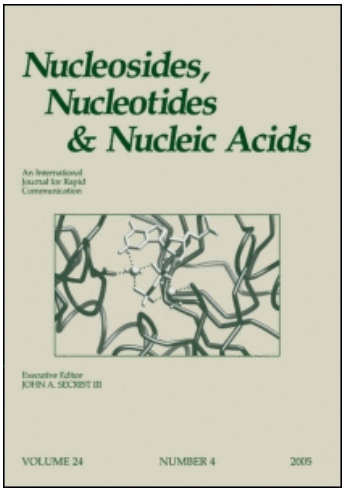

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A Solid-Phase Synthesis of 2',5'-Linked Oligoadenylates (2-5A)

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To cite this Article Lesiak, Krystyna , Uznanski, Bogdan and Terrence, Paul F.(1989) 'A Solid-Phase Synthesis of 2',5'-Linked Oligoadenylates (2-5A)', Nucleosides, Nucleotides and Nucleic Acids, 8: 5, 1055 — 1056
To link to this Article: DOI: 10.1080/07328318908054279
URL: http://dx.doi.org/10.1080/07328318908054279

NUCLEOSIDES & NUCLEOTIDES, 8(5&6), 1055-1056 (1989)

A SOLID-PHASE SYNTHESIS OF 2',5'-LINKED OLIGOADENYLATES (2-5A)

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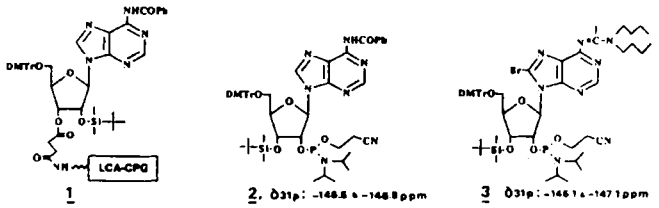
2',5'-Oligoadenylate 5'-triphosphates (2-5A) as products of 2-5A synthetase and activators of ribonuclease L (RNase L), are mediators in one of the mechanisms of interferon's antiviral action. Upon activation, RNase L inhibits protein synthesis due to the degradation of RNAs. This activity of 2-5A could possibly find an application in virus or cancer chemotherapy, but two major barriers prevent the use of 2',5'-linked oligoadenylates as therapeutic agents. The 2-5A is readily degraded by a 2',5'-phosphodiesterase and as a highly negatively charged molecule, is not readily taken up by cells. One possible solution to this latter limitation might be found in chemical modifications of the 2-5A structure. Many analogues of 2-5A have been already obtained with modified base, ribose or phosphate moieties. While these have provided some important information about the enzyme-activator interactions, the cell permeability problem still remains unsolved. One of the major obstacles in this study is lack of a convenient method of synthesis of 2',5'-ribonucleotides of widely varying structure.

The recent progress in the automated synthesis of DNA, as well as first reports on the applications of this technique in the RNA area prompted us to apply the solid-phase method to the synthesis of 2',5'-linked oligonucleotides.

The approach used in this work is based on the phosphodiester-phosphite method of the solid phase DNA synthesis. The syntheses were performed manually in commercially available microcolumns (Applied Biosystems, Inc.) as described by Uznanski et al[1]. Preparation of protected nucleosides, their phosphoramidites and a derivatized CPG-LCA solid support was performed, with some modifications, according to procedures used in DNA / RNA synthesis[2-4].

The chain elongation was carried on in the 2' to 5' direction. N^6-Benzoyl-5'-O-(dimethoxytrityl)-2'-O-(t-butyldimethylsilyl)-adenosine (1) attached to CPG-LCA support was used as a starting nucleoside and phosphoramidites 2 or 3 for chain elongation (Scheme 1). Due to an instability of N^6-benzoyl-8-bromoadenosine,depurination resistant di-(n-butyl)formamidine protection of N^6-amino group was chosen in compound 3.



Scheme 1

Table 1. Yields of synthesized 2',5'-linked oligonucleotides

	Compound	Total yield	Av. coupling efficiency
I	(2-5) ApApApApA	73%*	93%
	(2-5) ApApApApA	76%**	94%
II	(2-5) pApApApA	65%*	93%
III	(2-5) pApApApApApApApApApA	31%*	99%
IV	(2-5) pApAp(br^{8}A)p(br^{8}A)pA	44%*	97% (br^{8}A) 90% (A)
V	(2-5) pAp(br^{8}A)pA	27%*	94% (A)

*) 0.5 umol scale
**) 5.0 umol scale

5'-Terminal phosphorylation was achieved with bis-(2-cyanoethyl)-N,N-diisopropylphosphoramidite / tetrazole.

Synthesized oligomers are listed in Table 1. The structure of each oligoadenylate was confirmed by the results of its ezymatic hydrolyses. The compounds I, II, III and V were also compared by means of reversed-phase HPLC to corresponding compounds obtained in independent ways.

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