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Synthesis of (2´-5´)-triadenylates and their analogues using O-nucleophilic catalysis of internucleotide coupling reaction

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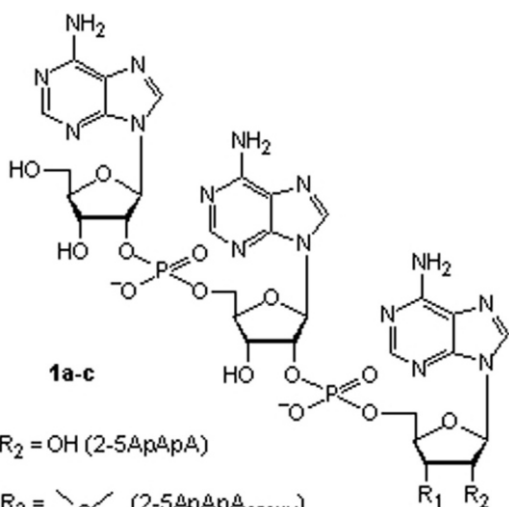Academicain Zabolotnog str., 150, Kyiv, 03680 Ukraine

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(2´-5´)-triadenylate and its analogues containing 3´-terminal epoxyadenosine or cordycepin residue were obtained by phosphotriester approach in the presence of 4-ethoxypyridine N-oxide (EPO) as O-nucleophilic catalyst of coupling reaction. The coupling reactions proceeded with high speed (below 5 min) and efficiency (yield 86-92%). The reaction yields achieved in the presence of N-methylimidazole were substantially lower (80-85%), and the final yields of triadenylates were only 21-25%, as compared to 29-35% obtained with N-oxide.

Keywords: (2´-5´)-oligoadenylates, oligonucleotide analogues, phosphotriester synthesis, nucleophilic catalysis, pyridine N-oxides

Introduction. 2´-5´-oligoadenylates (2-5A) play the key role in the mechanism of antiviral activity of interferon. The presence of 2-5A is of great importance in the processes of cell growth and differentiation, apoptosis, pathogenesis of diabetes and atherosclerosis, moreover, they are considered to be very promising preparations for tumor and hematological diseases [1–5]. Unfortunately, natural (2´-5´)-oligoadenylates 1a (Figure) are rapidly cleaved in the cell by phosphodiesterases. 2-5A analogues with chemical modifications, including those that increase the nuclease resistance, often reveal higher biological activity. A broad variety of 2-5A analogues with modified carbohydrate residues, internucleotide phosphates, and heterocyclic bases has been obtained [1, 2, 6–12].

Thus, triadenylate 1b modified with epoxyadenosine is known to be the inhibitor of post-transplantation tissue rejection [12] and was shown to possess cardioprotecting features [13]. Adenylate 1a and its analogue 1b stimulate proliferation of bone marrow stem cells and influence their apoptosis [14]. It was previously shown that oligoadenylates are closely connected with cAMP system (cyclic adenosine monophosphate) [15]. Type 1c analogues containing cordycepin (3´-deoxyadenosine) demonstrate antiviral activity, in particular against HIV-1 virus [16, 17]. The mechanism of their antiviral activity includes activation of RNAse L [17], inhibition of reverse transcriptase [16], and DNA-polymerase [17]. Antiproliferative activity of cordycepin analogues of 2-5A is connected with the activation of natural killer cells [18] and activity of nucleoside metabolites of "core" oligomers [19].

1a-c

a: $R_1 = R_2 = OH$ (2-5ApApA)

b: $R_1 + R_2 = $ _O_ (2-5ApApA$_{epoxy}$)

c: $R_1 = H$, $R_2 = OH$ (2-5ApApCord)

Structure of triadenylates

Most often 2-5A are prepared by phosphotriester synthesis in the solution, yet solid-phase phosphoramidite approach is also used to synthesize 2-5A in small quantities [1, 2]. Usually arylsulfonyl chlorides and nitrotriazolides are used in the presence of N-methylimidazole or tetrazole catalysts as coupling reagents in phosphotriester method. Pyridine N-oxides, especially those containing -electronodonor groups at *para*-position, are so called hypernucleophiles which catalyze acyl, phosphoryl and sulfonyl transfer reactions efficiently [20]. N-oxide-based reagents were proposed as coupling reaction catalysts in the synthesis of oligodeoxyribonucleotides [21–23]. Current work describes the first synthesis of 2-5A using O-nucleophilic catalysis. We have developed an efficient method of the preparation of (2 -5)-triadenylates and their analogues 1a–c by phosphotriester approach with 4-ethoxypyridine N-oxide (EPO) as a coupling reaction catalyst.

Materials and Methods. Experiments were performed using adenosine (*Fluka*, Germany), 4,4 -dimethoxytrityl chloride, 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCL), trimethylchlorosilane, 2-chlorophenyldichlorophosphate, 2-nitrobenzaldoxime (*Alrdich* USA). Other reagents and solvents were purchased from *Macrochim*, Ukraine. Acetonitrile was distilled over P_2O_5 and cal-

cium hydride; pyridine was dried by distillation over NaOH, ninhydrin and calcium hydride. ^{1}H NMR spectra were obtained on Bruker WM-300 spectrometer (300 MHz, internal standard tetramethylsilane), UV spectra were recorded using Specord UV-Vis spectrophotometer (*Karl Zeiss Jena*, Germany). Mass-spectra were obtained on Perkin-Elmer SCIEX API-100 instrument using electrospray ionization technique, ESI-MS, with detection of positive ions. Thin layer chromatography was performed on Silica gel 60F$_{254}$ plates (*Merck*, Germany) in the following systems: chloroform-methanol 9:1 (A), isopropanol–concentrated NH_3–water 5:1:2 (B). High performance liquid chromatography (HPLC) was performed on Waters system (USA) equipped with DAD-440 Kontron detector, using Nucleosil-C18 column (10 m, 4.6 250 mm, *Interchrom*, France) in the gradient of CH_3CN (5–40%) in 0.1 M triethylammonium acetate buffer (pH 6.5). EPO was synthesized according to [24, 25]. Nucleotide component 2 was prepared by phosphorylation of 6-N,3 -O-dibenzoyl-5 -O-dimethoxytrityladenosine [26, 27] with *o*-chlorophenylphosphoditriasolide using standard procedure [28].

6-N-benzoyl-9-(2,3-anhydro- -D-ribofuranosyl)adenine (3b)

2 ,3 -anhydroadenosine [29] (498 mg, 2 mmol) was evaporated with dry pyridine (2 5 ml), dissolved in 10 ml of the same solvent and trimethylchlorosilane was added (762 l, 6 mmol). The mixture was stirred for 5 hours at room temperature, benzoyl chloride (464 l, 4 mmol) was added and left overnight. The mixture was cooled to ~5°C, then 2 ml of water, and 10 min later 4 ml of 25% of aqueous ammonia were added. In 15 min the mixture was evaporated, and the residue was co-evaporated with 5 ml of pyridine. Then 50 ml of chloroform were added, the precipitate was filtered off, washed with CHCl$_3$ (2 10 ml), and filtrate was evaporated. The product was isolated by silica gel chromatography in the gradient of methanol (0–8%) in chloroform. Product 3b was crystallized from ethanol. 522 mg of white powder were obtained (74%). M.p. 186–187°C (lit. data 185–188°C [12]). ^{1}H NMR (DMSO-d_6): 11.20 (br.s, 1H, NH), 8.77 (s, 1H) and 8.65 (s, 1H) (H-2, H-8), 8.06 (d, J=6.9 Hz, 2H, Bz), 7.5-7.7 (m, 3H, Bz), 6.35 (s, 1H, H-1), 5.06 (m, 1H, 5 -OH), 4.57 (br.s, 1H, H-2), 4.26 (m, 2H, H-3 , H-4),

3.56 (m, 2H, H-5´,5″). Found, %: C 57.46, H 4.38, N 20.05. Calculated for $C_{17}H_{15}N_5O_4$, %: C 57.80, H 4.28, N 19.72.

Adenylyl-(2´-5´)-adenylyl-(2´-5´)-(2´,3´-anhydroadenosine)(1b). Synthesis using EPO.

P-component 2 (1.34 g, 1.25 mmol), OH-component 3b (353 mg, 1 mmol) and EPO (1.31 g, 9.4 mmol) were evaporated with dry pyridine (2 10 ml), dissolved in 10 ml of dry pyridine and TPSCl (948 mg, 3.13 mmol) was added. In 5 min the reaction mixture was diluted with 50 ml of chloroform and washed with aqueous $NaHCO_3$ (2 30 ml) and water (30 ml), organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. Excess pyridine was removed by evaporating with toluene (2 10 ml). Dinucleotide 4b was isolated by silica gel chromatography in the gradient of methanol in chloroform (0–3%). 1.18 g of dimer 4b was obtained (yield 91%). It was dissolved in 75 ml of 2% solution of *p*-toluenesulfonic acid (TsOH) in chloroform-methanol (7:3) mixture. In 5 min the mixture was diluted with 50 ml of chloroform and washed with aqueous $NaHCO_3$ (3 50 ml) and water (50 ml), organic layer was dried over Na_2SO_4 and evaporated. Detritylated dimer 5b was isolated by silica gel chromatography in the gradient of methanol (0–3%) in chloroform to get 820 mg of the product (90%). 820 mg of 5b (0.82 mmol), 1.10 g of P-component 2 (1.03 mmol), and 1.08 g of EPO (7.74 mmol) were evaporated with absolute acetonitrile (2 10 ml), dissolved in 10 ml of this solvent, and TPSCl (782 mg, 2.58 mmol) was added. In 5 min the mixture was diluted with 50 ml of chloroform, washed with aqueous $NaHCO_3$ (2 25 ml) and water (25 ml), organic layer was dried over Na_2SO_4 and evaporated. After silica gel chromatography in the 0-3% methanol gradient in chloroform, 1.38 g of fully protected trimer was obtained (86%). It was dissolved in 75 ml of 2% TsOH solution (chloroform-methanol 7:3). In 5 min the mixture was treated as described above, and detritylated trimer was isolated by silica gel chromatography in the gradient of methanol (0–3.5%) in chloroform. The yield of the product was 1.03 g (0.62 mmol, 88%). 2.08 g of 2-nitrobenzaldoxime (12.5 mmol) and dioxane, triethylamine and water (30 ml each) were added, and the solution was kept overnight at room temperature. The mixture was evaporated; the residue was evaporated with 10 ml of pyridine and

treated with 100 ml of ether. The precipitate was filtered, washed with ether and dried in vacuum. It was dissolved in 50 ml of conc. aqueous ammonia and left for 48 h at room temperature. The solution was evaporated, the residue was treated with 20 ml of ether and 20 ml of 0.01 M triethylammonium bicarbonate (TEAB, pH 7.5) and aqueous layer was separated. Trimer 1b was isolated by chromatography on Molselect DEAE-25 sorbent (*Reanal*, Hungary, HCO_3^- form) in the gradient 0.01–0.3 M TEAB (pH 7.5). Corresponding fractions were evaporated in vacuum, then evaporated with ethanol (3 20 ml). The residue was dissolved in the minimum volume of ethanol and precipitated with saturated potassium iodide solution in acetone (200 ml). Potassium salt was filtered, washed with acetone (5 5 ml) and dried. The yield of 1b was 344 mg (0.35 mmol). Yield after deblocking equaled 56%, overall yield was 35% based on starting OH-component 3b. R_f 0 (A), 0.72 (Б). UV (H_2O): $_{max}$ 259 nm (3.73 10^4). ESI-MS: *m/z* 908.3 $[(M+H)^+]$.

Adenylyl-(2´-5´)-adenylyl-(2´-5´)-adenosine(1a). Synthesis using MeIm. 1.45 g (2.50 mmol) of OH-component 3a, 3.34 g (3.13 mmol) of P-component 2 and 2.24 ml (28 mmol) of MeIm were evaporated with dry pyridine (2 20 ml), dissolved in 30 ml of dry pyridine and TPSCl was added (2.85 g, 9.4 mmol). In 15 min the mixture was treated as described for 1a. Protected dinucleotide 4a was isolated by silica gel chromatography in the gradient of methanol in chloroform (0–2%) to get 3.40 g (2.08 mmol, 83%) of 4a. It was dissolved in 200 ml of $CHCl_3$-MeOH 7:3 mixture, 3.95 g of TsOH (20.8 mmol) were added and the mixture was kept for 5 min. After the standard work-up the product was isolated by chromatography in the gradient of methanol (0-2%) in $CHCl_3$. The yield of detritylated dimer 5a was 2.34 g (1.76 mmol, 85%). P-component 2 (2.35 g, 2.2 mmol, 1.25 eq.) and 1.58 ml of methylimidazole (19.8 mmol) were added and the mixture was evaporated with absolute CH_3CN (2 20 ml), dissolved in 30 ml of the same solvent and 2.0 g of TPSCl (6.6 mmol) were added. In 15 min the mixture was treated as described above. Chromatography in the gradient 0-2% MeOH in chloroform allowed obtaining 3.21 g (1.41 mmol, 80%) of fully protected trimer. It was detritylated by the treatment with 2.68 g of TsOH (14.1 mmol) in 150 ml of the mixture $CHCl_3$-MeOH 7:3. In 5 min the mixture was

treated as described above. Detritylated trimer was isolated by chromatography in the gradient 0-2% of methanol in CHCl₃ (yield 2.32 g, 1.17 mmol, 83%). The product was dissolved in dioxane-conc. NH₃ 2:3 mixture (100 ml) and left for 3 days at room temperature. Solution was evaporated, the residue was treated with 25 ml of 0.01M TEAB (pH 7.5) and 25 ml of CHCl₃. Organic layer was separated. Product was isolated by ion-exchange chromatography and transformed into potassium salt as described in 1b. 632 mg of 1a (0.63 mmol) were obtained. Deblocking yield equaled 54%, overall yield was 25% from OH-component 3a. R_f 0 (A), 0.70 (B). $_{max}$ (H₂O) 259 nm (3.76 10⁴). ESI-MS: *m/z* 926.4 [(M+H)⁺].

Adenylyl-(2′-5′)-adenylyl-(2′-5′)-(3′-deoxyadenosine)(1c). Cordycepin analogue was obtained by both methods described above using EPO or MeIm nucleophilic catalysts. R_f 0 (A), 0.71 (B). $_{max}$ (H₂O) 259 nm (3.75 10⁴). ESI-MS: *m/z* 910.3 [(M+H)⁺].
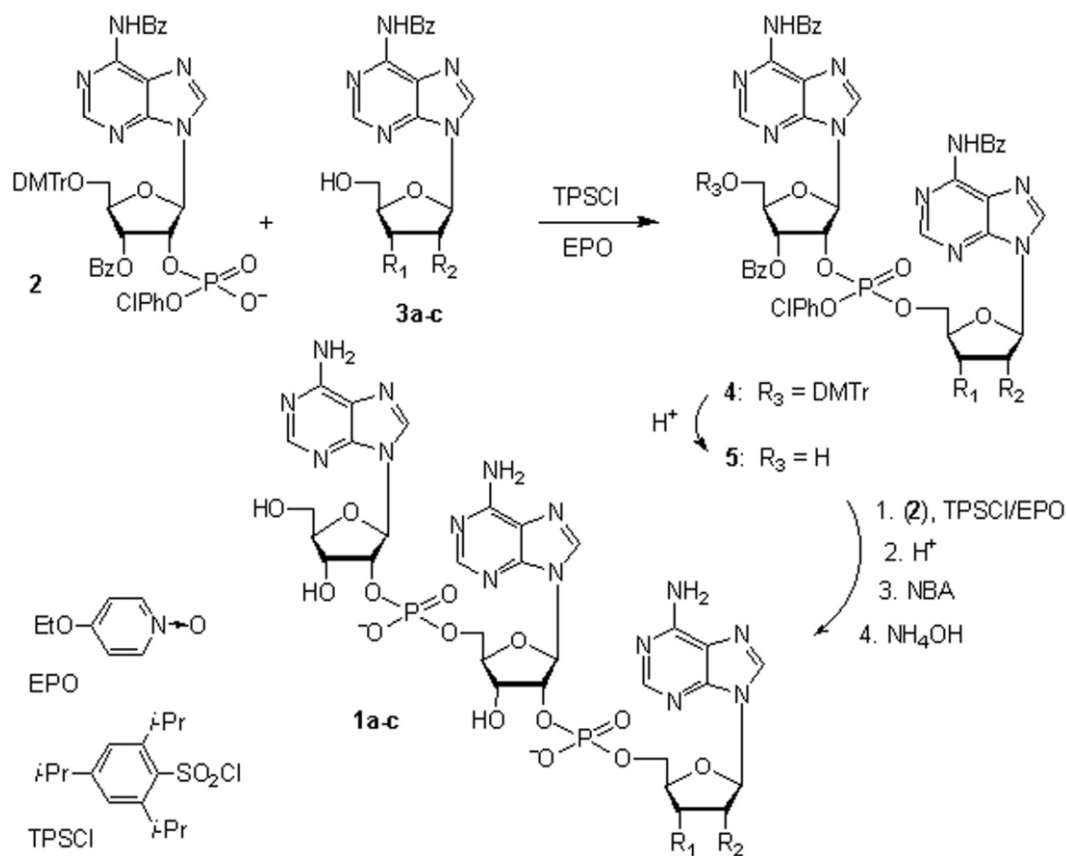
Results and Discussion. O-nucleophilic catalysis of coupling reactions in oligonucleotide synthesis has some advantages over traditional N-nucleophilic catalysis with the reagents like methylimidazole. First of all, it is much higher reaction speed, and lower level of side reactions resulting from low basicity of reagents. N-oxides are much less basic compounds than corresponding pyridines (pK_a = 4-6), but at the same time they are 50-100 times more reactive catalysts [20]. High efficiency of O-nucleophilic catalysis was previously demonstrated in the synthesis of oligodeoxyribonucleotides. In this case, almost quantitative coupling is achieved in 2-3 min, as compared to 10-15 min with methylimidazole catalysis [21] (for intramolecular catalysis the speed is even higher [22, 23]). Synthesis conditions in the preparation of quite labile oligoribonucleotides should be as mild as possible which can be provided by O-nucleophilic catalysts combining high nucleophilicity with low basicity. In the present work O-nucleophilic catalysis was applied to the synthesis of triadenylate 1a and its analogues containing an epoxy group or cordycepin residue at 3′-end (1b, 1c).

Trinucleotides 1a-c were synthesized by modified phosphotriester approach in the solution (Scheme). 6-N,5′,3′-O-protected phosphodiester 2 was used as a nucleotide component in all cases. To prepare it,

5′-O-dimethoxytrityl-N-6-benzoyladenosine was selectively benzoylated at 3′-hydroxyl [26, 27], and then 2′-hydroxy group of 3′-benzoate was phosphorylated by *o*-chlorophenylphosphoditriazolide in acetonitrile [28]. OH-components were suitably protected nucleosides 3a-c. Protected adenosine 3a was 3′-terminal nucleoside in the synthesis of natural trimer 1a, and 3′-O,N-protected cordycepin 3c in the synthesis of cordycepin analogue of 2-5A. These nucleosides were obtained by known methods of nucleoside chemistry. In the synthesis of epoxy-2-5A N-protected anhydroadenosine 3b was used as OH-component. It was obtained by selective benzoylation of 2′,3′-anhydroadenosine [29] at exocyclic amino group using silyl transient protection method [28]. In our case trimethylchlorosilane was used as silylating agent, whereas patent [12] applied more expensive hexamethldisilazane for this purpose.

Activating reagent triisopropylbenzenesulfonyl chloride (TPSCl, 2.5 eq. to P-component) and coupling catalyst 4-ethoxypyridine N-oxide (EPO, [21]) were used in the synthesis of triadenylates from synthons 2 and 3a-c. 3 eq. of N-oxide to TPSCl and 25% excess of P-component over nucleoside component were introduced in the reaction. Reactions were performed in pyridine or acetonitrile. The second coupling was carried out in acetonitrile, whereas the first one was performed in pyridine due to insufficient solubility of starting nucleosides in CH₃CN. Coupling reactions were fast (less than 5 min), and high yields were achieved. Dimethoxytrityl group was removed by *p*-toluenesulfonic acid. At all stages the products were isolated by silica gel chromatography. Deblocking of detritylated epoxy-trimer was performed in 2 stages: it was treated with 0.15 M solution of 2-nitrobenzaldoxime (NBA) in dioxane-triethylamine water 1:1:1 mixture (10 eq. of oxime per phosphate group) to remove chlorophenyl phosphate-protecting groups [28, 30], and then O- and N-benzoyl groups were cleaved by ammonolysis. Experiments showed that the epoxy group in 2′,3′-anhydroadenosine was stable both to oximate treatment and ammonolysis.

Protocol of the synthesis of epoxy derivative 1b with EPO is presented in Materials and Methods. Natural trimer 1a and its analogue 1c containing 3′-terminal cordycepin residue were synthesised in the same way.

General scheme of the synthesis of (2'-5')-oligoadenylates. Bz – benzoyl, ClPh – o-chlorophenyl, DMTr – dimethoxytrityl, NBA – 2-nitrobenzaldoxime.

High rate and yields of the reaction were observed in all cases. Final deblocking of 1a and 1c was performed in one stage without oximate treatment, using only the ammonolysis of detritylated trimers. Additional treatment with oxime resulted in insignificant increase of the yield of deblocked oligomers (this was the case for epoxy analogue 1b as well). After complete removal of protecting groups trimers 1a-c were purified by anion-exchange chromatography on Molselect DEAE-25 sorbent in 0.01-0.3 M gradient of concentration of TEAB (pH 7.5). Potassium salts of (2'-5')-triadenylates were obtained by the precipitation of ethanolic solutions of triethylammonium salts of trimers with potassium iodide solution in acetone. The yields of trimers 1a-c were 29-35% based on corresponding starting nucleoside components 3a-c.

For comparison, trimers 1a-c were prepared also by classic method [31] using coupling reagent TPSCl and N-nucleophilic catalyst methylimidazole. The repre-

sentative synthetic protocol for trimer 1a is provided in experimental part. The synthesis of 1a-c with MeIm was generally performed as we described before [14]. At all stages the same reagents, their concentration and ratio were used as in the EPO-catalyzed synthesis of corresponding trimers. Under the same synthetic conditions, methylimidazole provided substantially lower coupling yields (up to 85%) and total yields of final oligomers (21-25%), as compared with EPO. Couplings in the presence of MeIm resulted in the formation of less clean reaction mixtures, with several times longer coupling reactions (10-15 min). Thus, overall efficiency of 2-5A synthesis using N-oxide catalysis appeared to be considerably higher than that with MeIm.

The data on the yields of individual coupling reactions and final products synthesized under various conditions are presented in the Table. All triadenylates are white powders soluble in water and practically insoluble in organic solvents. The purity of compounds pre-

Yields of individual coupling reactions and final yields of (2'-5')-trinucleotides

Compound	Yield, %					
	Synthesis with EPO			Synthesis with MeIm		
	1st coupling	2nd coupling	final	1st coupling	2nd coupling	final
2-5ApApA (1a)	90	87	31	83	80	25
2-5ApApA$_{epoxy}$ (1b)	91	86	35	85	81	24
2-5ApApCord (1c)	92	88	29	82	83	21

pared by both methods was 95-96%, according to reverse-phase HPLC. Their structures were confirmed by mass-spectrometric analysis (ESI-MS).

In conclusion, the use of O-nucleophilic catalysis of internucleotide coupling reaction in the phosphotriester synthesis of oligoribonucleotides allowed achieving a high speed and yield of coupling reactions and overall synthesis efficiency. The effectiveness of this reagent in the synthesis of (2 -5)-oligoadenylates exceeds that of the classical nucleophilic catalyst of nucleic acids chemistry, N-methylimidazole, substantially.

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Синтез (2'-5')-триаденилатов и их аналогов с использованием О-нуклеофильного катализа реакции межнуклеотидной конденсации

Резюме

Осуществлен синтез (2'-5')-триаденилата и его аналогов, содержащих 3'-концевой остаток эпоксиаденозина и кордицепина, фосфотриэфирным методом в присутствии О-нуклеофильного катализатора реакции конденсации – N-оксида 4-этоксипиридина (EPO). Реакции конденсации проходили с высокой скоростью (до 5 мин) и выходом (86–92 %). Выходы реакций в присутствии N-метилимидазола были заметно ниже (80–85 %), а суммарный выход триаденилатов в этом случае составлял 21–25 % против 29–35 % при использовании EPO.

Ключевые слова: (2 -5)-олигоаденилаты, аналоги олигонуклеотидов, фосфотриэфирный синтез, нуклеофильный катализ, N-оксиды пиридинов.

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