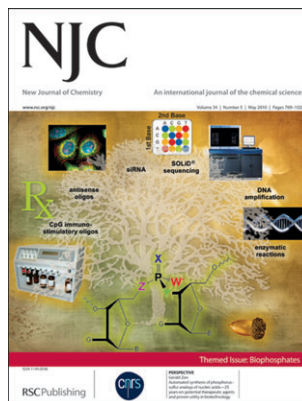


IN THIS ISSUE

ISSN 1144-0546 CODEN NJCHES 34(5) 769–1028 (2010)

**Cover**

See G. Michael Blackburn *et al.*, pp. 784–794.
Thermonuclear reactions generate phosphorus in supernovae (Kepler, 1604). Iron phosphide (Schreibersite) is a meteoritic component that enriches phosphorus abundance in primitive habitable planets. Prebiotic chemistry generates phosphate esters that, through biological evolution, make an RNA world (ribozymes and ribosomes) and life. Phosphate esters can be predicted to fulfil related roles on other habitable planets. Cover images used with permission from NASA and Prof. Venki Ramakrishnan, LMB, Cambridge, and constructed using PyMOL software. Matthew W. Bowler, Matthew J. Cliff, Jonathan P. Waltho and G. Michael Blackburn, *New J. Chem.*, 2010, **34**, 784.

**Inside cover**

See Gerald Zon, pp. 795–804.
Since 1984, fully-automated solid-phase synthesis of oligonucleotides having phosphorothioate (W or X = S) or, eventually, phosphorothiolate (Y or Z = S) linkages has enabled the continuous growth of diverse applications, such as those depicted here. Gerald Zon, *New J. Chem.*, 2010, **34**, 795.

EDITORIALS

782

Introduction to the themed issue on Biophosphates

Introducing a collection of articles on the theme of Biophosphates.



783

Introduction to the themed issue in honour of Professor Wojciech J. Stec

A 70th birthday present for Professor Wojciech J. Stec, whose work has built bridges between chemistry and biology.



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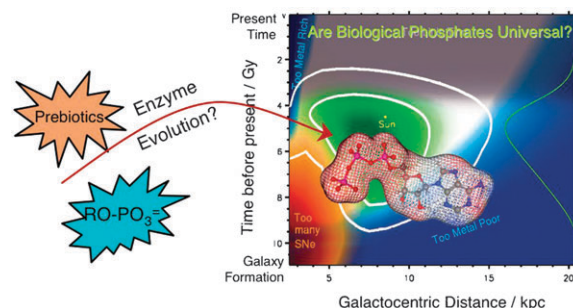
PERSPECTIVES

784

Why did Nature select phosphate for its dominant roles in biology?

Matthew W. Bowler, Matthew J. Cliff, Jonathan P. Waltho and G. Michael Blackburn*

Terrestrial pre-biotic evolution established phosphate esters in multiple roles. Enzymes have evolved to manipulate them in all parts of biology. Will this prove to be the case for life across the universe?

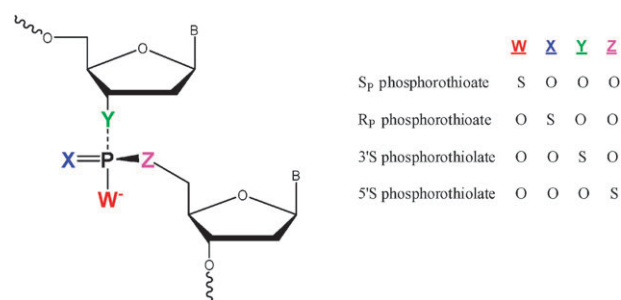


795

Automated synthesis of phosphorus–sulfur analogs of nucleic acids—25 years on: potential therapeutic agents and proven utility in biotechnology

Gerald Zon*

This account highlights how fully automated solid-phase synthesis of nuclease-resistant, chiral, phosphorothioate-modified oligodeoxynucleotides and chemically related compounds, notably 3'S and 5'S phosphorothiolates, have enabled remarkably broad advances across basic science, medical research, and biotechnology.

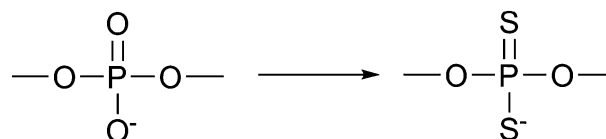


805

Synthesis of nucleoside and oligonucleoside dithiophosphates

Xianbin Yang* and Ellen Mierzejewski

Replacing the two nonbridging oxygen atoms at a phosphomonoester of a nucleotide or internucleotide phosphate moiety with two sulfurs leads to the formation of nucleoside and oligonucleoside dithiophosphates.

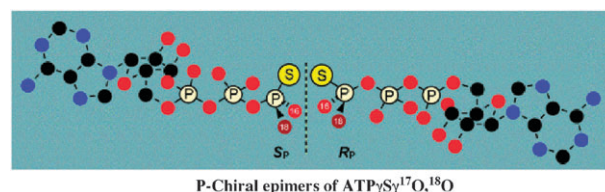


820

Sulfur as a mechanistic probe in enzymatic and non-enzymatic substitution at phosphorus

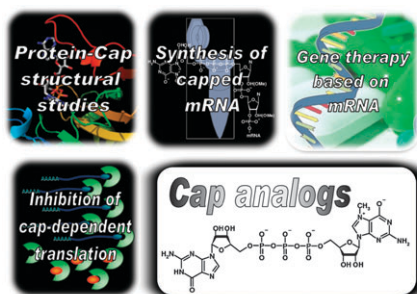
Perry A. Frey*

The principle of economy in the evolution of binding sites appears to govern whether an enzymatic phosphotransfer proceeds by a double displacement mechanism or a single displacement mechanism.



PERSPECTIVES

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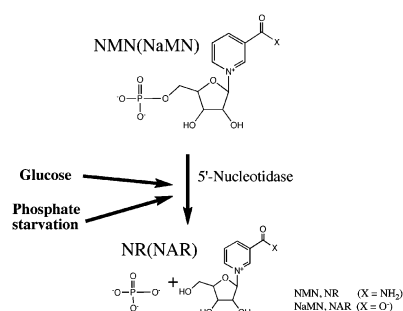


Synthetic mRNA cap analogs with a modified triphosphate bridge – synthesis, applications and prospects

Jacek Jemielity,* Joanna Kowalska, Anna Maria Rydzik and Edward Darzynkiewicz*

Recent developments in the synthesis of cap analogs modified within the 5',5'-triphosphate bridge and their utility for interdisciplinary studies on cap-dependent processes in gene expression and its regulation, as well as biotechnological applications and perspectives in medicine, are presented.

845

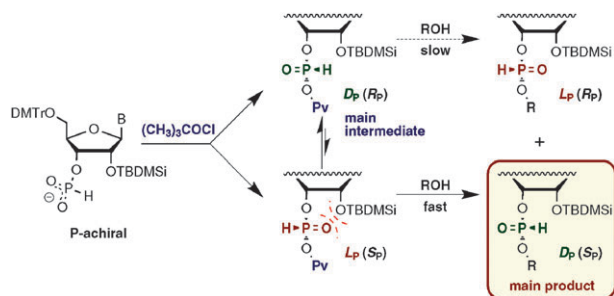


5'-Nucleotidases and their new roles in NAD⁺ and phosphate metabolism

Katrina L. Bogan and Charles Brenner*

New roles for 5'-nucleotidases have been uncovered.

854



Chemistry and stereochemistry of internucleotide bond formation by the *H*-phosphonate method

Michał Sobkowski*

Investigations on the mechanism of stereoselective ribonucleoside 3'-*H*-phosphonates condensations with alcohols and nucleosides are presented.

LETTERS

870



Stereopure oligonucleotide phosphorothioates as human telomerase substrates

Ronald Pruzan, Daria Zielinska, Beata Rebowska-Kocon, Barbara Nawrot and Sergei M. Gryaznov*

Stereopure all-Rp-phosphorothioate primer/substrates demonstrate higher affinity for purified human telomerase than those for their all-Sp-counterparts.

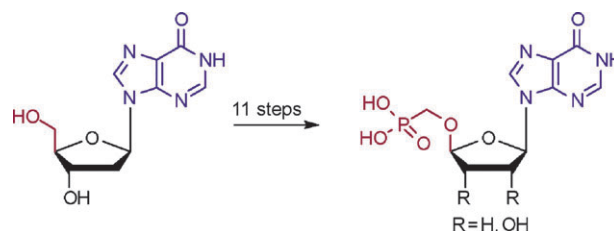
LETTERS

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Synthesis and biological evaluation of inosine phosphonates

Mikhail Abramov and Piet Herdewijn*

The 4'-phosphonomethoxy analogs of inosine and 2',3'-dideoxyinosine were synthesized and tested for their activity against HCV and HIV.

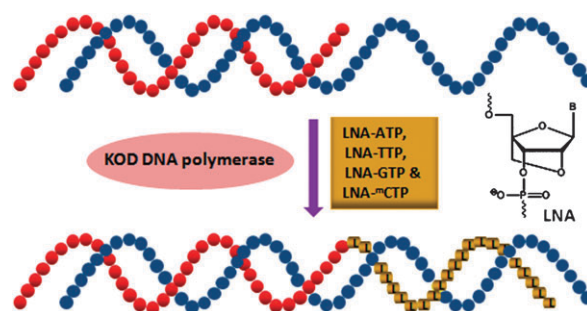


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Polymerase directed incorporation studies of LNA-G nucleoside 5'-triphosphate and primer extension involving all four LNA nucleotides

Rakesh N. Veedu, Birte Vester and Jesper Wengel*

A primer extension experiment using all four LNA nucleoside 5'-triphosphates as the only NTP source has been investigated for the first time and the results are compared with an experiment using natural DNA nucleotides.



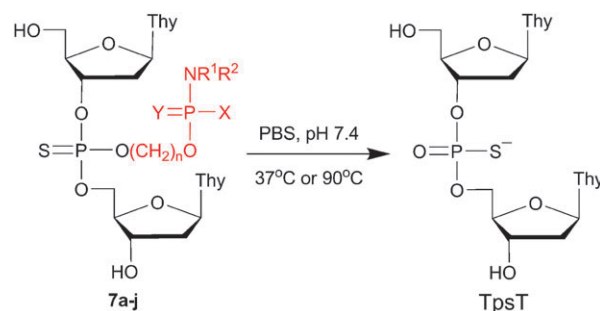
PAPERS

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Hydroxyalkylated phosphoramidate, phosphoramidothioate and phosphorodiamidothioate derivatives as thiophosphate protecting groups in the development of thermolytic DNA prodrugs

Andrzej Grajkowski, Jacek Cieślak, Alexei Gapeev and Serge L. Beaucage*

A novel class of thermosensitive thiophosphate protecting groups in the development of thermolytic DNA oligonucleotide prodrugs has been investigated.

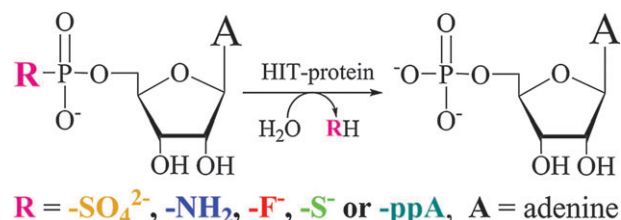


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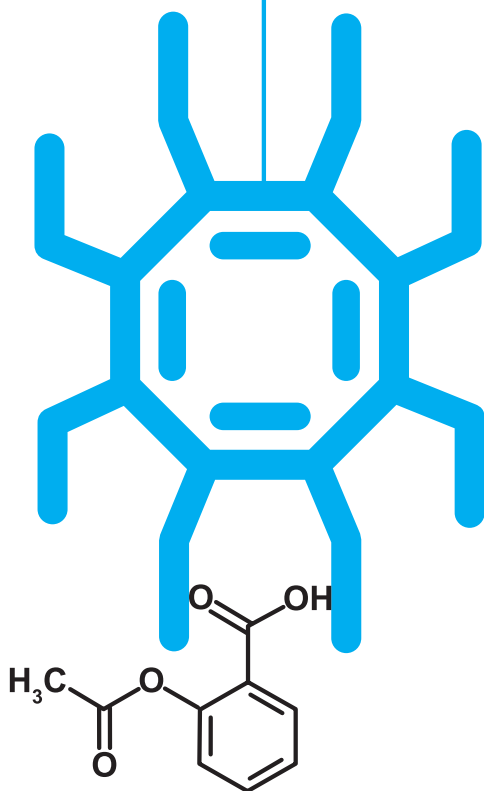
Recognition of different nucleotidyl-derivatives as substrates of reactions catalyzed by various HIT-proteins

Andrzej Guranowski,* Anna Maria Wojdyła, Jarosław Zimny, Anna Wypijewska, Joanna Kowalska, Maciej Łukaszewicz, Jacek Jemielity, Edward Darżynkiewicz, Agata Jagiełło and Paweł Bieganski

Different HIT-proteins hydrolyze different nucleotidyl-derivatives with different preference. Relevance to the metabolism of nucleotide pro-drugs.



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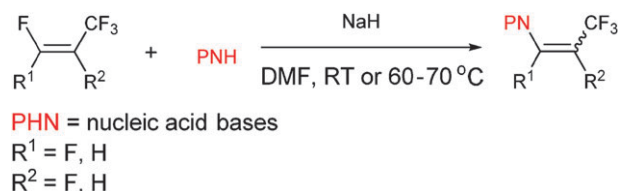
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Fluorinated enamines of nucleobases as precursors of nucleoside analogues. Synthesis, spectroscopic and structural studies

Hanna Wójtowicz-Rajchel,* Magda Pasikowska, Anna Olejniczak, Andrzej Katrusiak and Henryk Koroniak*

In fluorinated enamines of nucleic acids bases the flat conformation of the *Z* stereoisomer is stabilised by internal hydrogen bonding between C^{β/α}–H and the carbonyl oxygen in pyrimidinic bases or the endocyclic nitrogen in purinic bases.

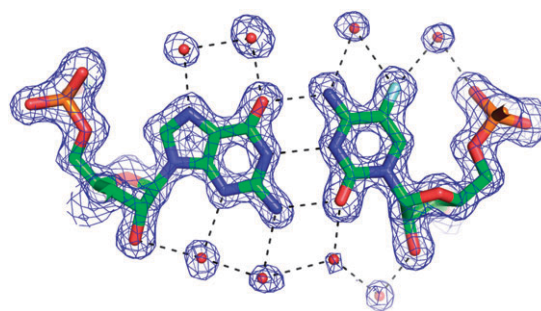


903

The hydration and unusual hydrogen bonding in the crystal structure of an RNA duplex containing alternating CG base pairs

Dorota A. Adamiak, Jan Milecki, Ryszard W. Adamiak and Wojciech Rypniewski*

The structure and hydration of 5-FC:G pair in the crystal structure of [CGCG(5-FC)G]₂ duplex. Water oxygen atoms come as close as 2.9 Å to the fluorine atom (*turquoise*) of the 5-fluorocytidine residue, indicating significant H-bonding interactions.

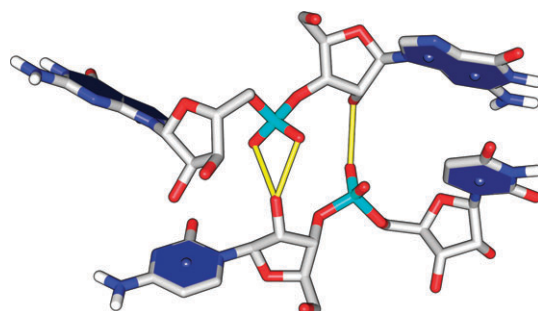


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RNA structural motifs that entail hydrogen bonds involving sugar–phosphate backbone atoms of RNA

Nikolai B. Ulyanov and Thomas L. James*

Long-range hydrogen bonds, *i.e.*, hydrogen bonds between atoms not in the same residue or sequential residues, involving sugar–phosphate backbone atoms of RNA were found to be involved in a surprising 39% of all nucleotides in eight high-resolution multi-domain crystal structures analyzed. One RNA structure-stabilizing motif, the ribose–phosphate zipper motif, is shown here.



918

Biological and physicochemical characterization of siRNAs modified with 2',2'-difluoro-2'-deoxycytidine (gemcitabine)

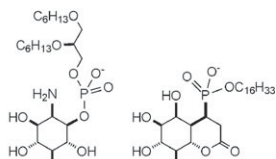
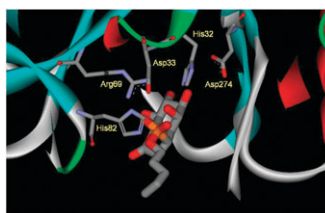
Malgorzata Sierant,* Milena Sobczak, Magdalena Janicka, Alina Paduszynska and Danuta Piotrkowska

We have synthesized and characterized siRNA duplexes with a single replacement of a cytidine unit for 2',2'-difluoro-2'-deoxycytidine (gemcitabine, dFdC).



PAPERS

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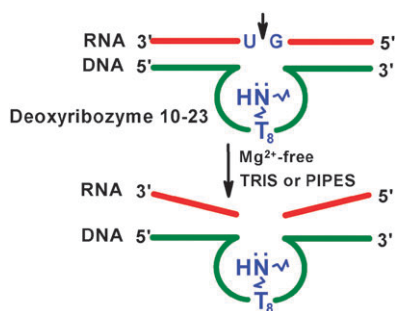


Nonhydrolyzable analogs of phosphatidylinositol as ligands of phospholipases C

Cornelia Mihai, Xiangjun Yue, Li Zhao, Alex Kravchuk, Ming-Daw Tsai and Karol S. Bruzik*

2-Deoxy-2-amino and conformationally constrained PI analogs bind to phosphatidylinositol-specific phospholipase C in low micromolar concentration range and induce a conformational change in the enzyme.

934

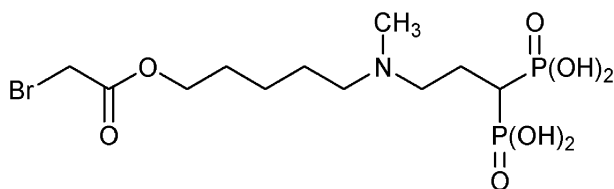


RNA-cleaving 10–23 deoxyribozyme with a single amino acid-like functionality operates without metal ion cofactors

Damian Smuga, Kinga Majchrzak, Elzbieta Sochacka* and Barbara Nawrot*

We identified protein-like modified deoxyribozymes 10–23, which in the presence of Mg^{2+} ions are more active than their parent precursor and can operate in a magnesium-free systems.

949

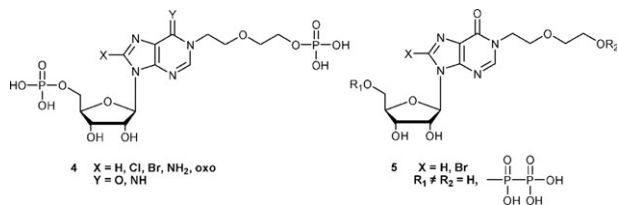


Synthesis of an analogue of the bisphosphonate drug Ibandronate for targeted drug-delivery therapeutic strategies

Nicolas Camper, Christopher J. Scott and Marie E. Migaud*

The synthesis of an Ibandronate analogue attached by a cleavable ester group to a linker with thiol specific reactivity opens the way to the targeted delivery of bisphosphonates to cancer cells.

956



Concise synthesis of novel acyclic analogues of cADPR with an ether chain as the northern moiety

Huimin Wu, Zhenjun Yang, Liangren Zhang* and Lihe Zhang

A series of novel acyclic analogues of cADPR with an ether chain as the northern moiety have been synthesized.

PAPERS

967

Preparation of benzylphosphonates *via* a palladium(0)-catalyzed cross-coupling of H-phosphonate diesters with benzyl halides. Synthetic and mechanistic studies

Gaston Lavén, Marcin Kalek, Martina Jezowska and Jacek Stawinski*

A general, efficient method for the synthesis of benzylphosphonates and benzylphosphonothioates, using Pd(0) and Xantphos as a supporting ligand, was developed.

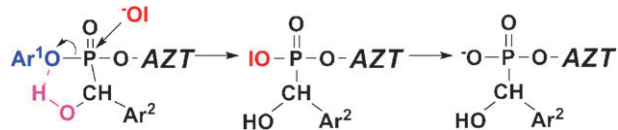


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Studies on the decomposition pathways of diastereoisomeric mixtures of aryl nucleoside α -hydroxyphosphonates under hydrolytic conditions. Synthesis of α -hydroxyphosphonate monoesters

Agnieszka Szymańska-Michalak, Jacek Stawinski and Adam Kraszewski*

α -Nucleophiles and intramolecular acid catalysis facilitate hydrolytic decomposition of diastereoisomeric mixtures of α -hydroxyphosphonate diesters.

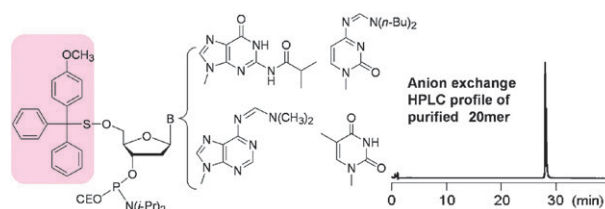


984

Synthesis of oligodeoxynucleotides using the oxidatively cleavable 4-methoxytritylthio (MMTrS) group for protection of the 5'-hydroxyl group

Kohji Seio,* Miyuki Shiraishi, Eri Utagawa, Akihiro Ohkubo and Mitsuo Sekine*

Oligodeoxynucleotides were synthesized without any acid treatment by using the oxidatively-cleavable MMTrS group.

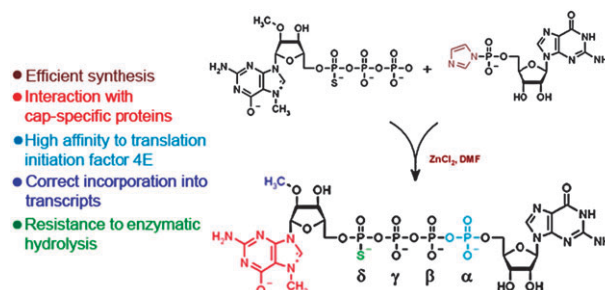


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Towards mRNA with superior translational activity: synthesis and properties of ARCA tetraphosphates with single phosphorothioate modifications

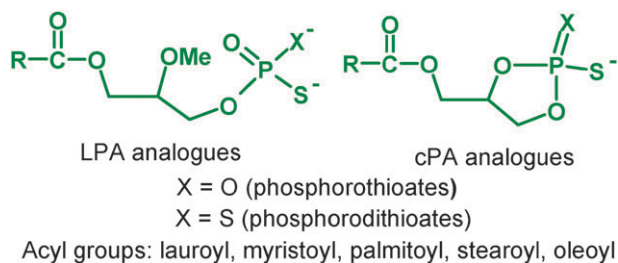
Malwina Strenkowska, Joanna Kowalska, Maciej Lukaszewicz, Joanna Zuberek, Wei Su, Robert E. Rhoads, Edward Darzynkiewicz and Jacek Jemielity*

New mRNA cap analogs have been designed, synthesized and characterized as useful reagents to obtain modified mRNA with potential therapeutic applications.



PAPERS

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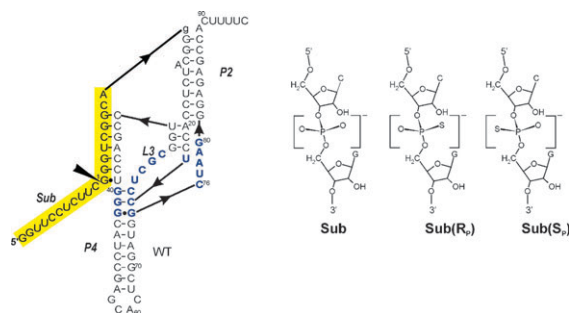


The chemical synthesis of phosphorothioate and phosphorodithioate analogues of lysophosphatidic acid (LPA) and cyclic phosphatidic acid (CPA)

Przemysław Rytczak, Maria Koziółkiewicz and Andrzej Okruszek*

New phosphorothioate and phosphorodithioate analogues of lysophosphatidic acids (LPA) and cyclic phosphatidic acids (cPA) were synthesized employing oxathiaphospholane and dithiaphospholane chemistry.

1018



Phosphate residues of antigenomic HDV ribozyme important for catalysis that are revealed by phosphorothioate modification

Jan Wrzesinski, Agnieszka Wichlacz, Danuta Nijakowska, Beata Rebowska, Barbara Nawrot and Jerzy Ciesiołka*

The NAIM (nucleotide analog interference mapping) and “metal ion rescue” methods were applied to better understand the role of phosphate groups and divalent metal ions in the formation of active structures and in the catalysis of antigenomic HDV ribozyme.

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