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*A Reliable and Innovative Partner  
to Speed up Your Success*

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## Expertise

### Nucleosides and Nucleotides

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## About Granlen

Granlen is a preclinical contract research organization that specializes in the “*more difficult*” chemistries of nucleosides, peptides, phosphorous, heterocyclic, and related chemistry. Our research facility is located in Zhengzhou, China and we offer project management and business development support from San Diego. We can offer made-to-order compound libraries, hit-to-lead optimization, medicinal chemistry, and a wide range of chemistry services including custom synthesis, intermediates, references compounds, metabolites and impurities, route scouting, process development, and scale-up. We can provide nucleosides, peptide conjugates, disaccharides, haptens, antigens, and bioreagents. Heterocyclic chemistry is easy and always a welcome change. Teams at Granlen are also specialized in macrocyclic compounds used as super-chelating and MRI contrast agents.

Apart from our expertise in chemistry, as a preclinical CRO we offer an integrated development platform in order to speed projects toward clinical trials. We have developed relationships with some specialized facilities that may be able to assist with your preclinical and clinical development.



Our management team has led a number of compounds into clinical trials and we have expertise in every step toward Phase I. In conjunction with our drug discovery services we provide expertise in:

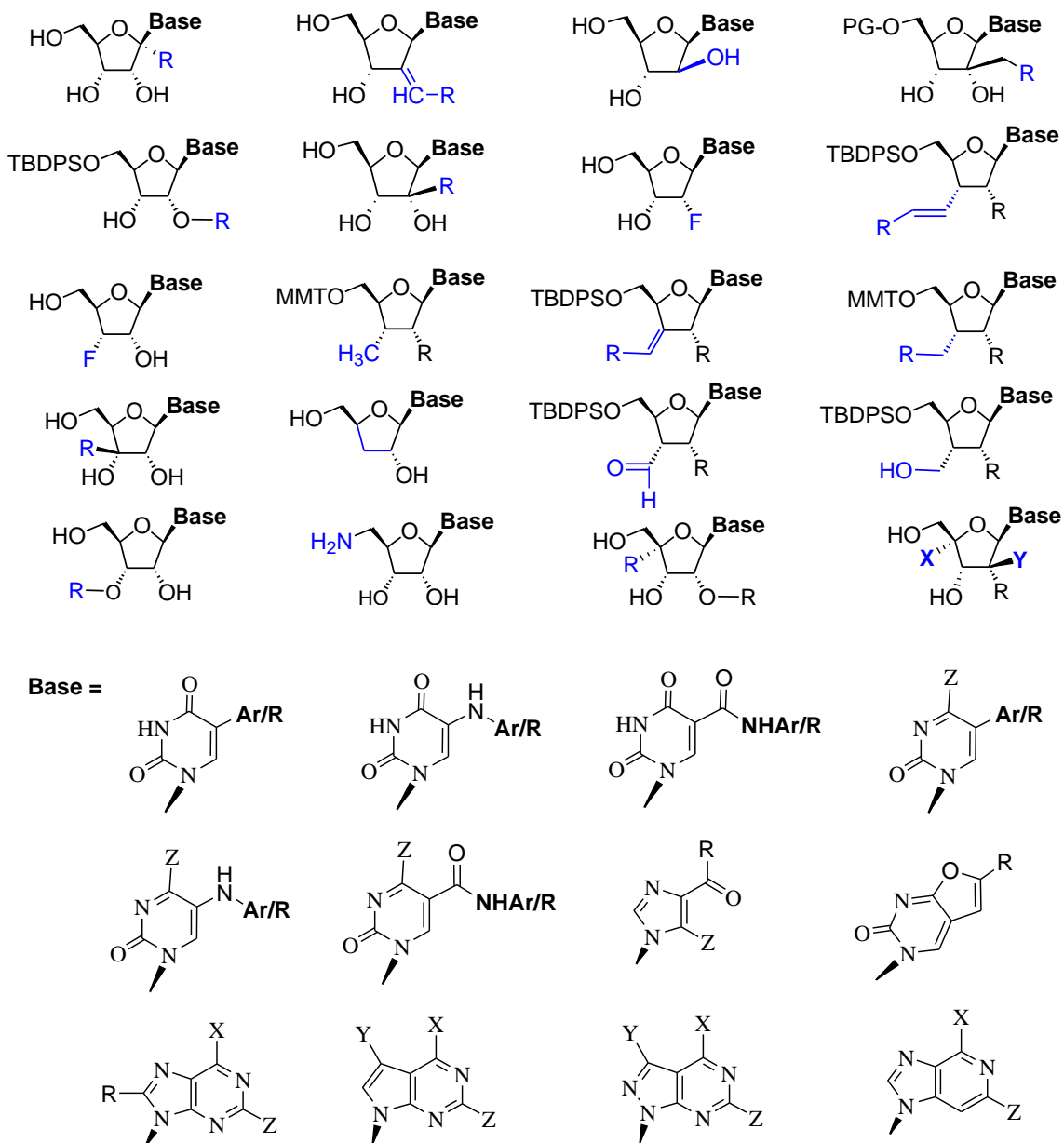
- Nucleosides, nucleotides, nucleic acids, and libraries
- Di-nucleotides, aminoacylated dinucleotides, triphosphates, methylene-phosphonates, phosphoramidites, and other organophosphorus derivatives
- Novel amino acids, dipeptides, and glycopeptides
- Bio-reagents, bio-materials, immunogens
- Macrocyclic compounds as super-chelating and MRI contrast agents





## Ribose-Modified Nucleosides

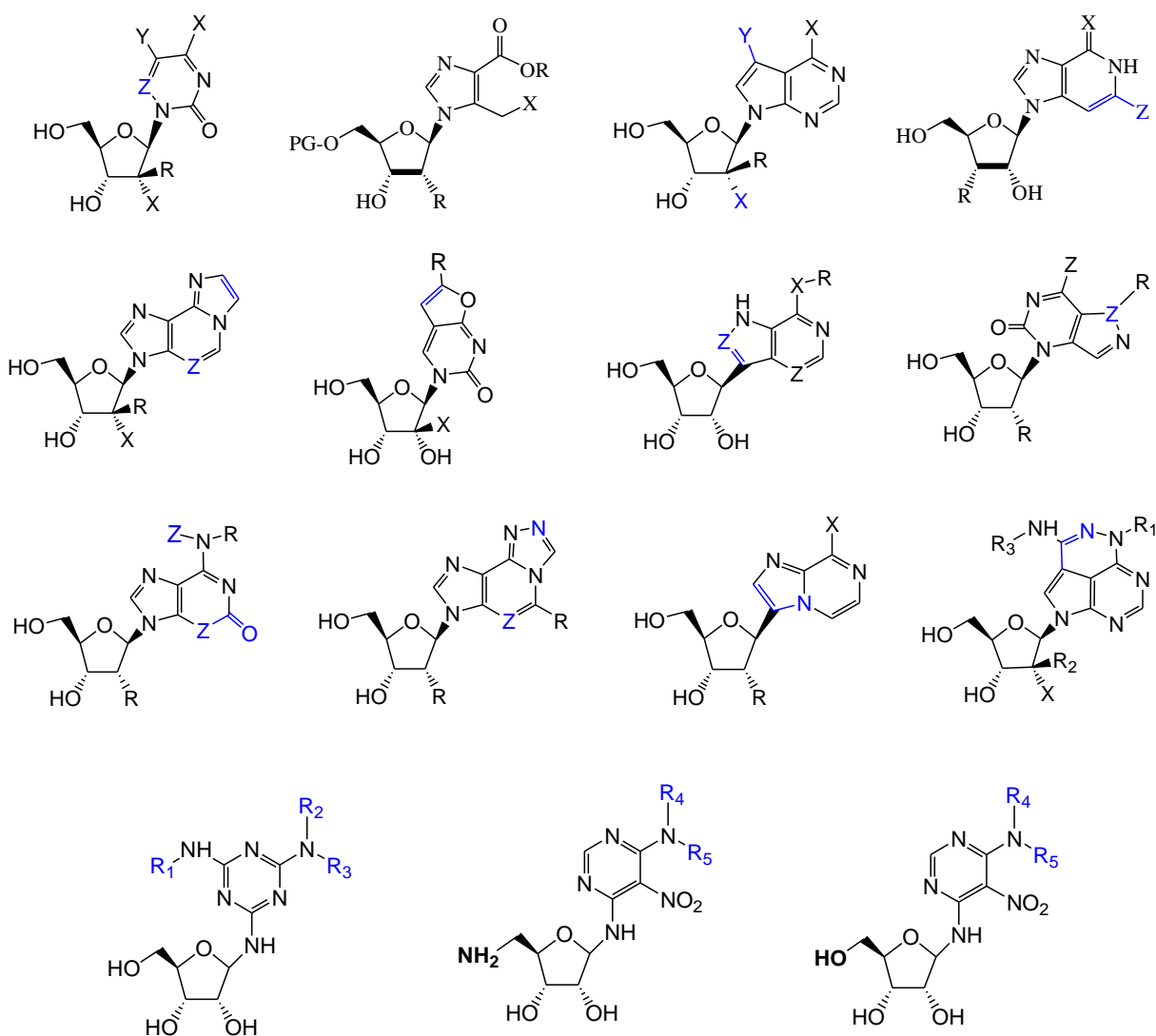
Systematic modification of the ribofuranosyl ring generated a variety of new ribofuranose modified nucleosides for antiviral, anticancer, and immunomodulating drug discovery. The conformation effect of the carbohydrate ring system, phosphorylation mechanism, molecular modeling, and medicinal chemistry principles were effectively utilized during lead discovery and optimization processes. Various ribofuranose modified nucleosides with different purine, deaza-purine and pyrimidine bases were synthesized as illustrated below.





## Heterocyclic Base-Modified Nucleosides

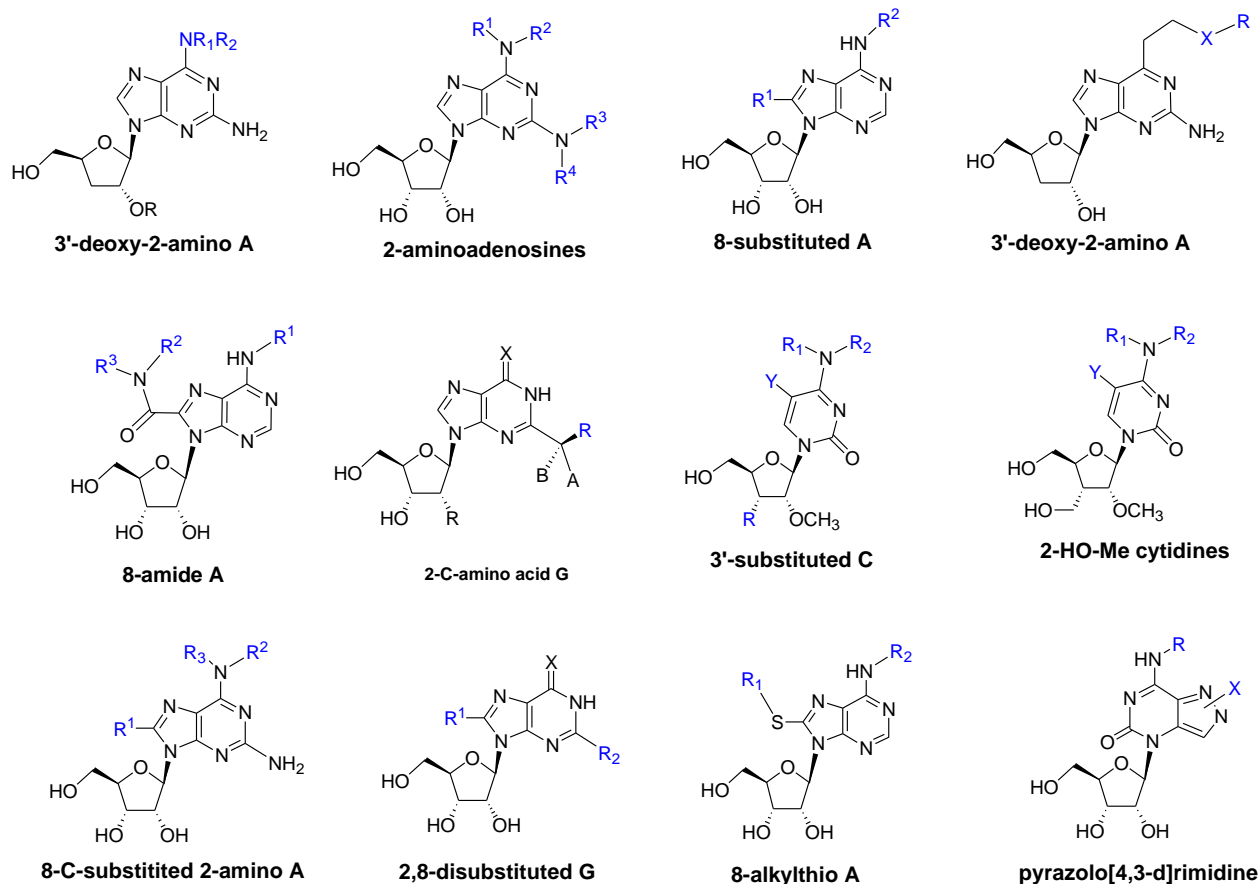
Modification of various purine, pyrimidine, and other heterocycles resulted in the creation of novel nucleoside pharmacophores for new drug discovery. The modified bases include 7-deaza-purine, 3-deaza-purine, 5-aza-pyrimidine, triciribine and others. In addition to traditional SAR used for anticancer and antiviral drug discovery, the structure-PK-property relationships were evaluated using the data from dozens of advanced lead compounds. The leads with higher lipophilic substituents demonstrated better PK properties and bioavailability. The exocyclic, natural product mimic nucleosides were also synthesized based on the triazine and nitropyrimidine heterocyclic moieties.





## Diverse Nucleoside Libraries

There are tremendous difficulties in applying solid-phase combinatorial strategies to nucleoside chemistry such that large numbers of nucleoside analogues can be made in a short period of time to explore a wide range of biological activities. The executives at Granlen pioneered and established many of these solid-phase techniques, and built the largest nucleoside libraries for anticancer, antiviral and other drug discovery screening. Below are listed some representative examples with library sizes ranging from 96-3000 for various scaffolds.

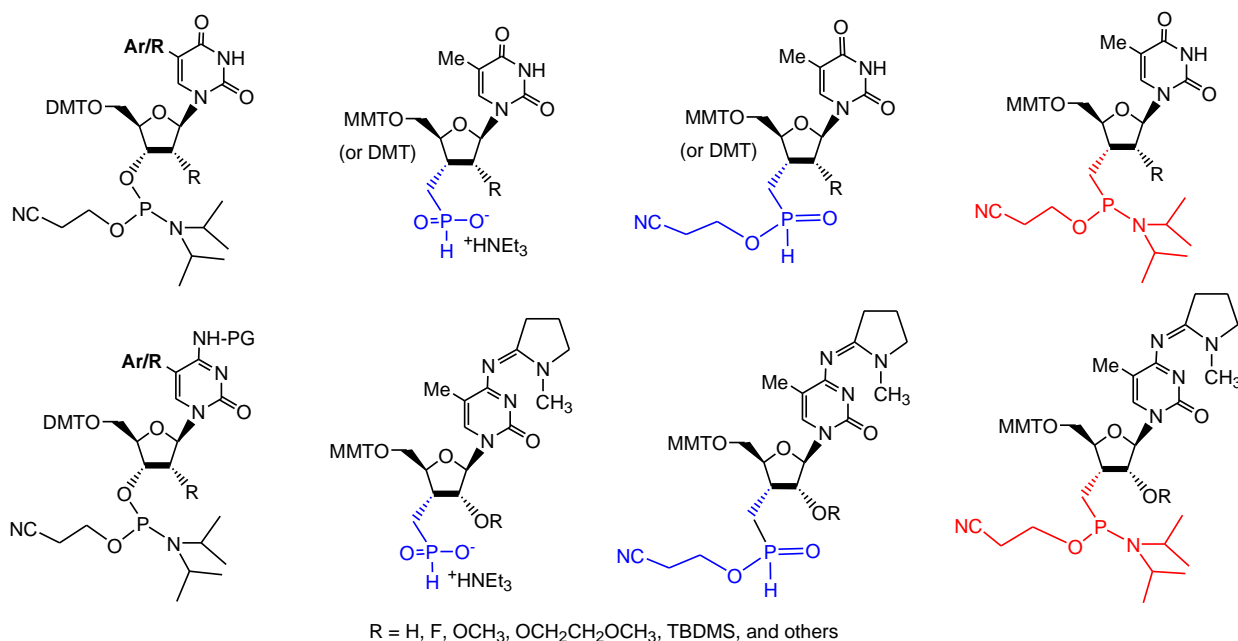


Our expertise is also represented by our modification of a variety of natural nucleoside analogues, such as toyocamycin, sangivamycin, cordycepin, cliticine, tubercidin, ladakamycin, and formycin. Our team is highly experienced in the synthesis of nucleoside and base-derived drugs such as cytarabine, gemcitabine, azacitidine, decitabine, fludarabine, capecitabine, cladribine, acyclovir, adefovir, prafefovir, and other derivatives. Synthesis of various modified 7- and 3-dezaadenosine as well as modified triciribine derivatives further demonstrate Granlen's capabilities to face great scientific challenges.



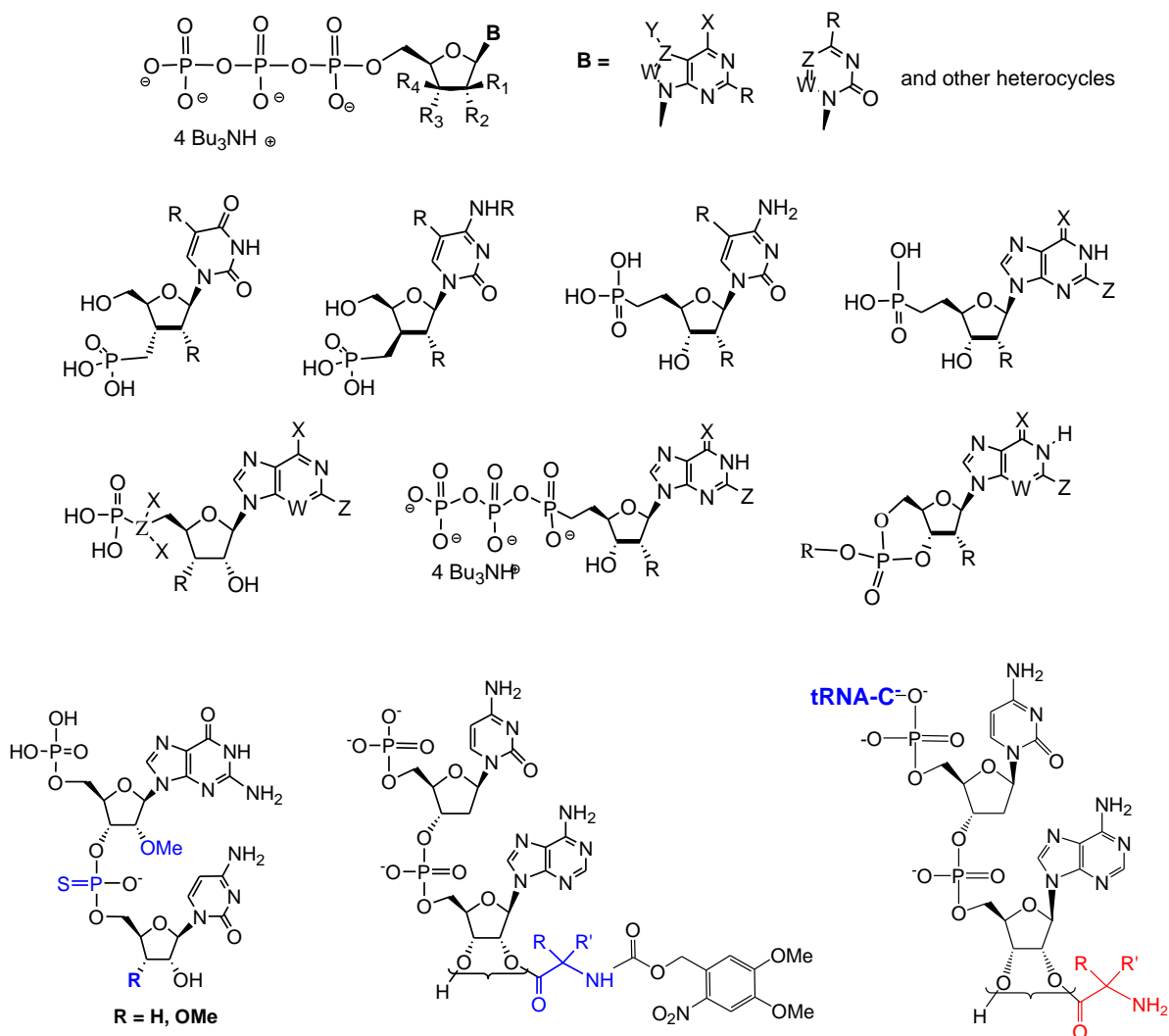
## Phosphorous Chemistry

Granlen has expertise preparing triphosphates, phosphonates, phosphoramidites, phosphonamidites, and dinucleotide diphosphates. We have synthesized novel nucleoside triphosphates and 5'-C-triphosphonates for RdRp polymerase activity studies. The successful syntheses of 3'-methylene modified nucleoside *H*-phosphonates and corresponding 3'-C-phosphonamidites for novel modified antisense drug discovery are considered the most challenging chemistry in the nucleic acid field. Challenging phosphorus chemistry and the very challenging Arbuzov reaction were required for these accomplishments.



In addition to this type of phosphorus chemistry, our team is also experienced with the synthesis of various novel 3'- and 5'-C-modified nucleoside phosphonates, halo-phosphonates and their corresponding triphosphates, as well as dinucleotides and phosphate prodrugs. Triphosphates of the active nucleosides are essential for many mechanistic studies. Therefore, a number of triphosphates were synthesized from advanced lead compounds, which also resulted in good SAR. In order to further study the biological properties of novel nucleosides, a number of 3'- and 5'-C-phosphonates were synthesized, and converted to the corresponding C-triphosphates.

A series of phosphothioate dinucleotides were designed and synthesized to explore new drug discovery opportunities (the 1<sup>st</sup> structure below). Our team also synthesized dinucleotide pCpA, converted it to well protected and activated aminoacylated dinucleotides (the structure in the middle), which were then ligated onto t-RNA for enzyme modifications.



## Summary

The management and employees of Granlen have significant expertise in the areas of ribofuranoses, modified nucleosides, nucleotides, and related phosphorus compounds. In a bulleted fashion, the team at Granlen can assist with:

- Modified ribofuranoses
- Nucleosides, nucleotides, nucleic acids
- Novel nucleoside libraries
- H-Phosphonates, C-phosphonates, C-phosphoramidites, phosphoramidites
- Triphosphates, C-triphosphonates
- Dinucleotides, and other organophosphorus derivatives
- Solid-supported ribose or nucleoside derivatives