

Critical Adenosine Derivatives and SAR

The Reliable Leading Nucleoside Pioneer!



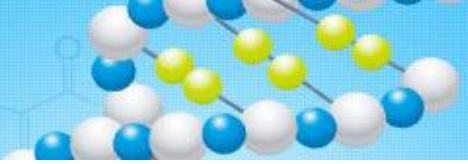
Corporate Locations



美国加州圣地亚哥
- 太平洋彼岸的“人间天堂”，
最适于居住的城市
San Diego, CA
- The **Paradise** on Earth; the
most livable city



中国郑州 - 重要交通枢纽，商
贸中心，国家园林城市
Zhengzhou, China
- The key transportation and
business central garden city



About Granlen

- Provides reliable chemistry related services for the biotech, pharmaceutical, genomic, diagnostic, and related industries with:
 - *A broad spectrum of chemistry*
 - *A wide range of drug discovery services*
 - *An integrated drug development process to IND*
 - *Specialized on nucleosides and related compounds*

Objectives – Establish the best nucleoside labs



Our History of Success

Medicinal Chemistry and Drug Development

Oncology

Microtubule polymerization inhibitor (Phase II)

Kinase inhibitor (Phase II)

Proteasome Inhibitor (Preclinical)

Antiviral

An HBV drug (Phase III)

An HIV drug (Phase II)

An HCV drug (Phase II)

An HIV drug (Phase I)

An HCV candidate (IND)





IND-Enabling Preclinical CMC Services



- *Process development research & LSS*
- *Analytical method development and stability studies*
- *Regulatory and documentation*





Nucleosides – Magic Compounds

1. Small molecule drugs

2. Genomic, RNA drugs and biotech related fields

3. Diagnostic related fields

- **>80 nucleoside drugs; >200 nucleoside drugs under investigation**
- **Antiviral, anticancer, anti-bacterial and related areas**
- **Come from body and nature, easily accepted by body with low toxicity risk**
- **Best small molecule lead compounds for drug discovery**

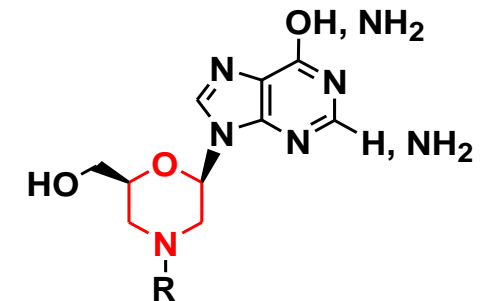
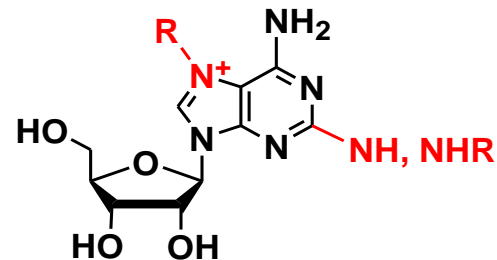
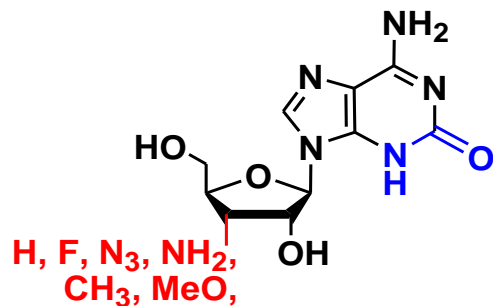
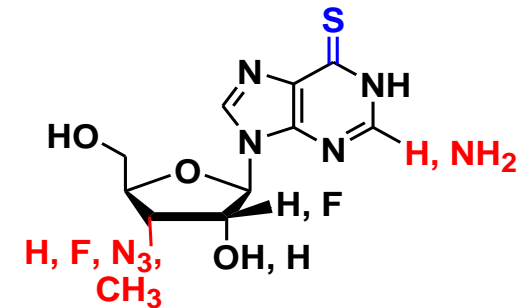
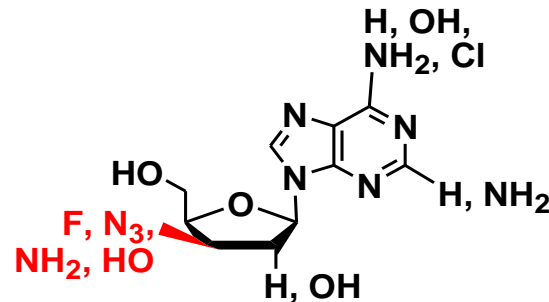
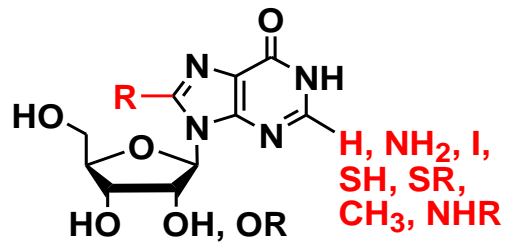
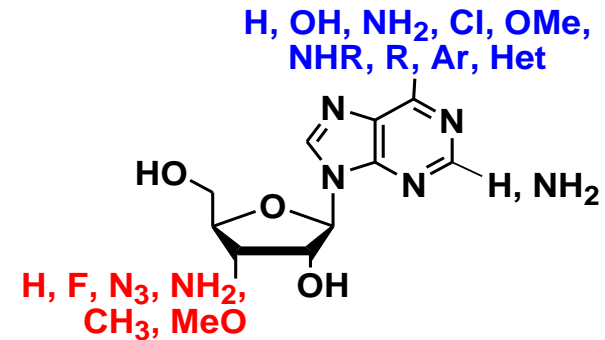
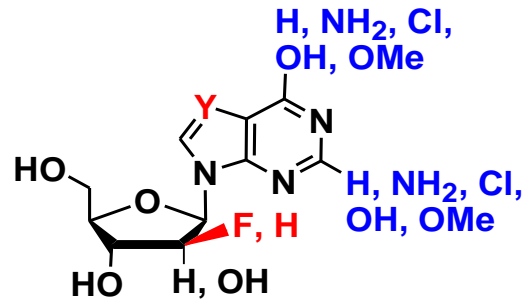
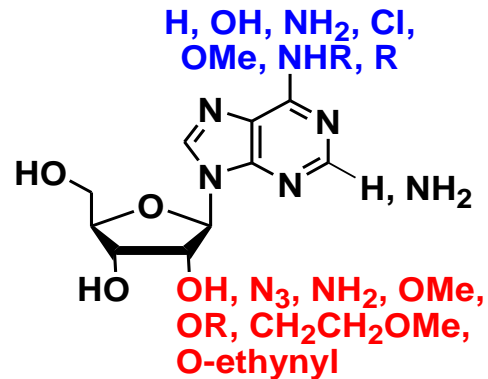


Diversified Nucleoside Library

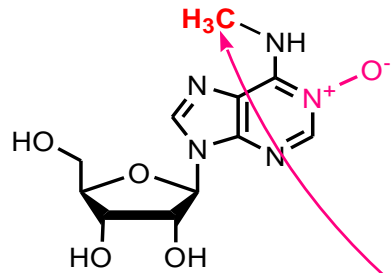
- **>1100 nucleoside compounds, including >110 novel and >400 unique ones**
- **>50 different classes of nucleosides with high diversity**
- **>200 biologically important nucleoside derivatives**
 - ✓ **Drugs, inhibitors, receptors, agonists, regulators, activators, adducts**
 - ✓ **Metabolites and drug related substances**
 - ✓ **RNA-modified nucleosides, analogues and characteristic combinations**
- **Easily design further lead optimization with open fields**
- **May get initial SAR conclusion by the first screen and enough material for further biological studies if leads are found**



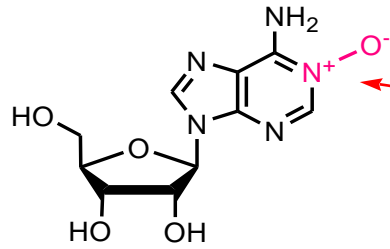
Representative Purine Nucleosides



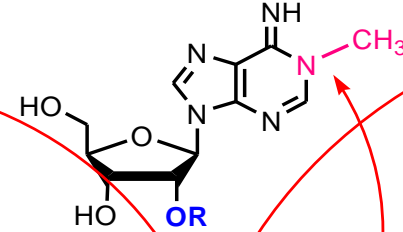
Critical Adenosine Derivatives and SAR



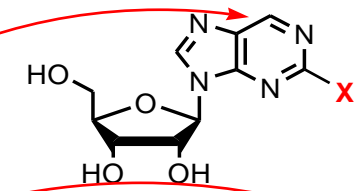
GL100909
antiviral agent



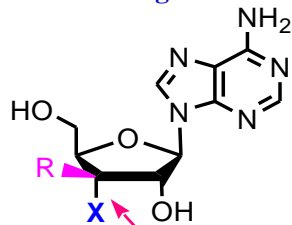
GL101125; Antiviral and anti-inflammatory agent



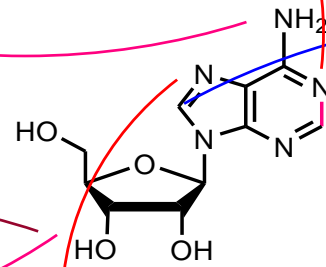
R = H: GL101125; Antiviral and anti-inflammatory agent
R = Me: GL103161, RNA nuc



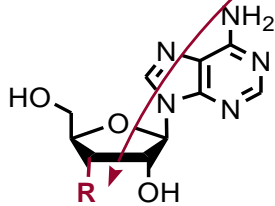
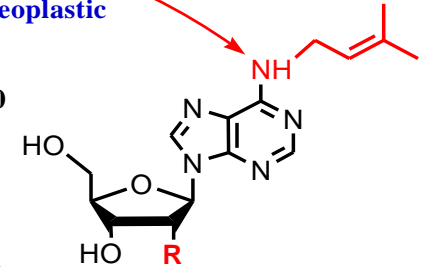
X = H, GL100428; Nebularine, Anti-bacterial Antineoplastic
X = NH₂: GL100429
X = Cl: GL102286
X = OMe: GL101960



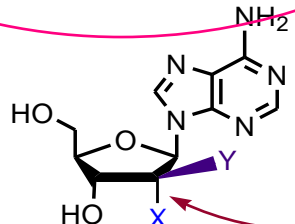
X = H, R = OH: GL101507 anticancer agent
X = H, R = F: GL101301
X = OH, R = CH₃: GL102222; Antitumor, reductase inhibitor
X = OH, R = ethynyl: GL103183



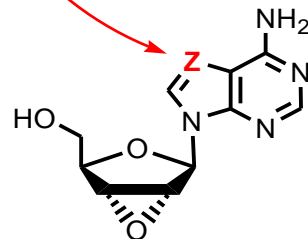
R = OH: GL102581; antiviral plant cytokinin, RNA nuc
R = H: GL102820



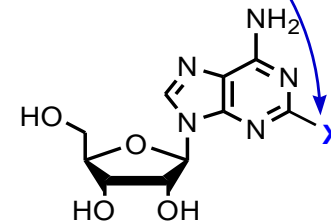
R = H, GL101316; antiviral
R = N₃, GL100826, Antiviral antineoplastic agent
R = F, GL100201
R = CH₃, GL101239
R = NH₂, GL101278
R = MeO: GL100483
R = MOE: GL102515
R = O-propargyl: GL 103325



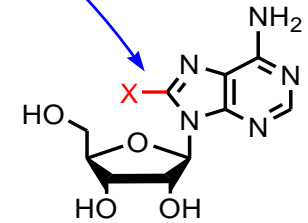
X = H, Y = OH: GL101177 antiviral drug Vidarabine
X = H, Y = F: GL100575, antiviral
X = OH, Y = CH₃: GL100687 antiviral agent
X = OH, Y = ethynyl, GL103168
X = Cl, Y = H: GL101860
X = N₃, Y = H: GL101395
X = OMe, Y = H: GL100400
X = MOE, Y = H: GL100402
X = O-propargyl, Y = H: GL101157



Z = N: GL102649 polymerase inhibitor
Z = CH: GL102636



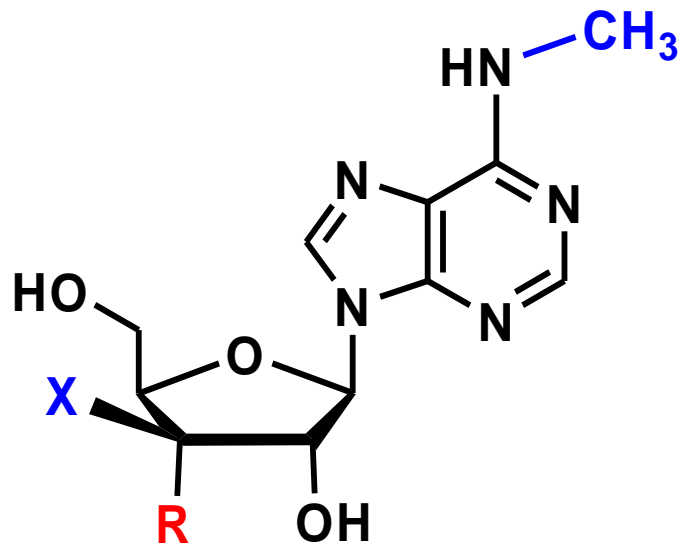
X = Cl: GL101374, DAD inhibitor, antimalarial agent
X = Br, GL101800, antimalarial
X = I, GL100870
X = OH, GL100323, inhibitor
X = MeS: GL101322 DAD inhibitor
X = Me: GL100877; RNA nuc
X = CF₃: GL101939
X = CH₂NH₂: GL103099
X = NHNH₂: GL101377
X = CN: GL101808
X = MeO: GL101375



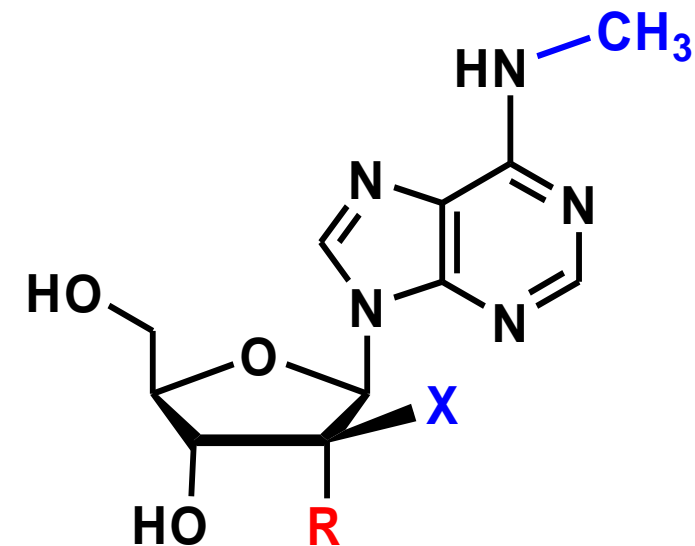
X = OH: GL101128, anticancer antibiotics
X = Cl: GL101901 anticancer antiimmune agent
X = Br, GL100681 ADA inhibitor
X = N₃: GL101679
X = NH₂: GL101680
X = NHNH₂: GL101681
X = MeNH: GL101678
X = MeS: GL102526
X = MeO: GL101677
X = Allyl-O: GL103252
X = BnO: GL101127



N^6 -Methyl Adenosine Derivatives



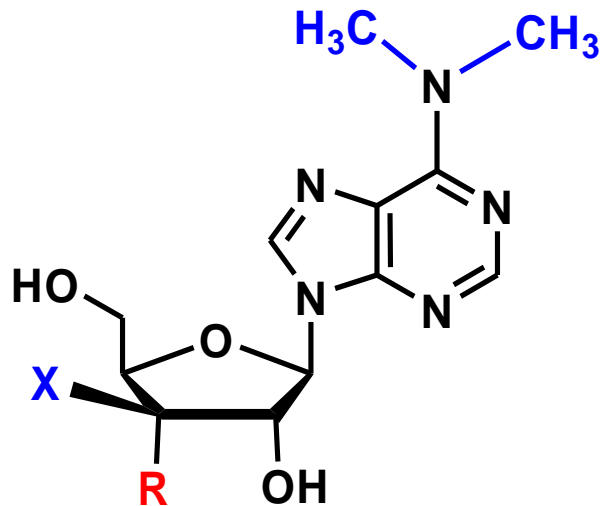
R = OH, X = H: GL100832, **RNA nuc**
 R = OH, X = Me: GL102223
 R = H, X = OH: GL103522
 R = F, X = H: GL102133
 R = N₃, X = H: GL102151



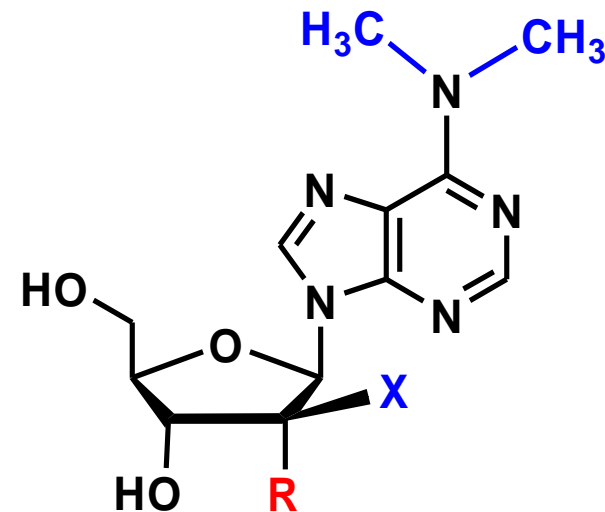
R = X = H: GL102669, **Antitumor, antibacterial, antimalarial**
 R = H, X = F: GL101912
 R = OH, X = H: GL100832, **RNA nuc**
 R = OCH₃, X = H: GL102100, **RNA nuc**
 R = OH, X = CH₃: GL101910



N^6,N^6 -Dimethyl Adenosine Derivatives



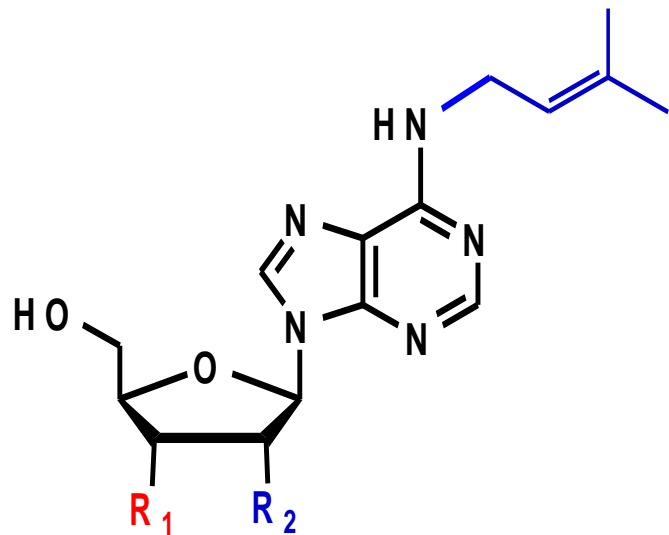
- R = X = H: GL101317
- R = H, X = OH: GL103523
- R = OH, X = H: GL102056, **antitumer, RNA nuc**
- R = OH, X = ethynyl: GL103202
- R = OH, X = Me: GL102225
- R = F, X = H, GL101815
- R = N₃, X = H, GL102512
- R = CH₃, X = H, GL101240
- R = NH₂, X = H, GL102822, **PAN**



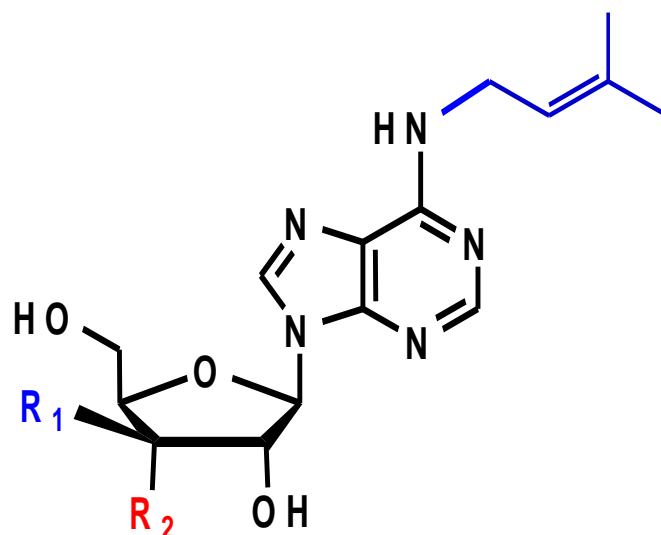
- R = X = H, GL103215
- R = H, X = F; GL101913
- R = OH, X = H: GL102056, **antitumer, RNA nuc**
- R = OH, X = CH₃: GL101911
- R = OCH₃, X = H: GL102099, **RNA nuc**



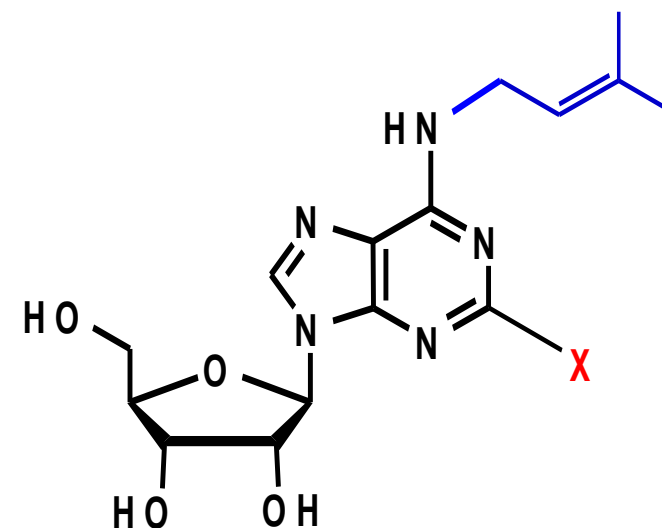
N^6 -iso-Pentenyl Adenosines and SAR



$R_2 = H, R_1 = OH$: GL102820
 $R_2 = OH, R_1 = H$: GL103085
 $R_1 = R_2 = HO$: GL102581
 antitumor antiviral agent, plant
 cytokine and RNA nuc



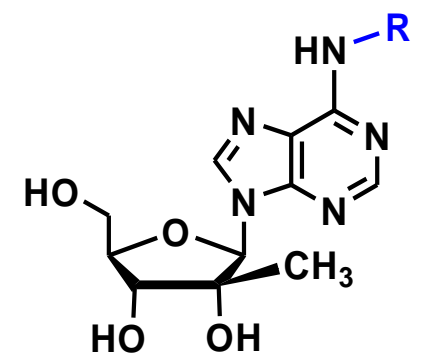
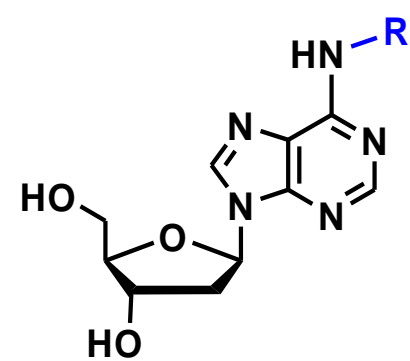
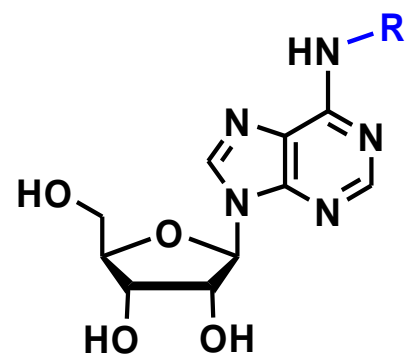
$R_1 = H, R_2 = F$: GL103692
 $R_1 = CH_3, R_2 = OH$: GL103658
 $R_1 = ethynyl, R_2 = OH$: GL103669
 $R_1 = F, R_2 = H$: GL103635
 $R_1 = OH, R_2 = H$: GL103622



$X = H$, GL102581, antitumor antiviral
 $X = NH_2$, GL102582
 $X = Cl$, GL103335
 $X = SCH_3$, GL103339, RNA nuc

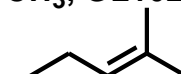


N⁶-Substituted Adenosine Derivatives and SAR



R = CH₃, GL100832, RNA nuc
R = CH₂CH₂OH, GL102900

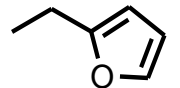
R = NH₂, GL102059
R = Ac, GL100887, RNA nuc
R = CH₂Ph, GL102055, antiviral


R = CH₃, GL102669
R =  GL102820
R = cyclopentyl GL103216

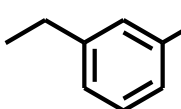
R = H, GL100687, antiviral
R = CH₃, GL101910
R = CH₂Ph, GL103091

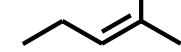
R =  GL102057

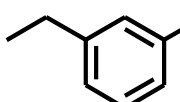
R =  GL102903

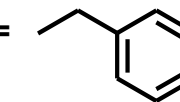
R =  GL100318
antiviral
anticancer

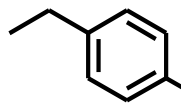
R =  GL102581
antiviral
antitumor
RNA nuc

R =  GL103219

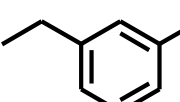
R =  GL103093

R =  GL103080

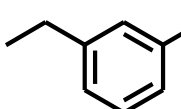
R =  GL103081

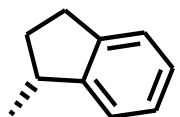
R =  GL103218

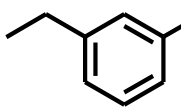
R =  GL103092

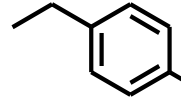
R =  GL102901

R =  GL102902

R =  GL103090

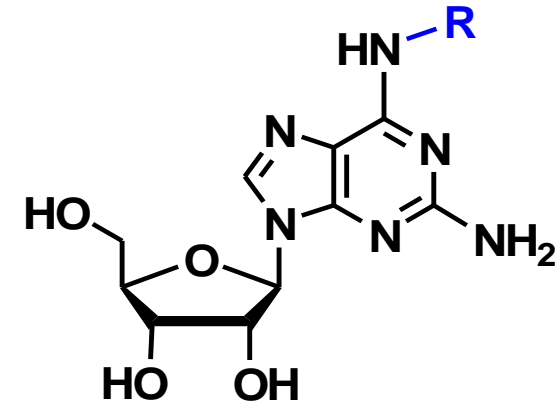
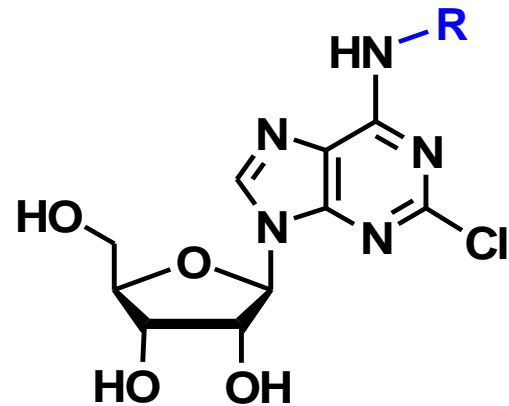
R =  GL100315
AD receptor
antihypertensive

R =  GL103095

R =  GL103096



N^6 -and 2-Substituted Adenosine Derivatives and SAR



R = H, GL101374

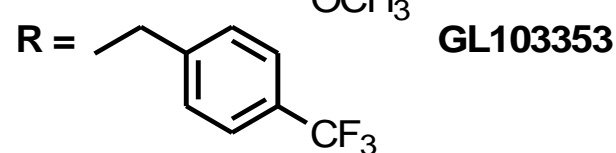
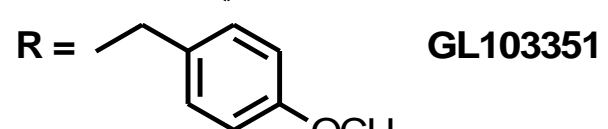
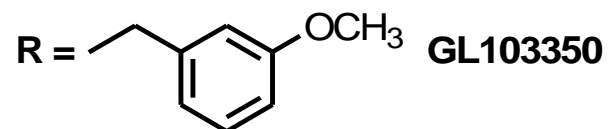
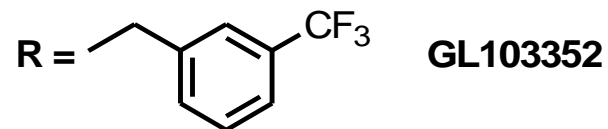
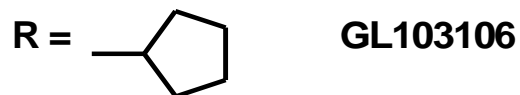
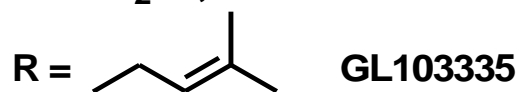
ADA inhibitor antimalarial

R = CH₃, GL103331

R = CH₂CH₃, GL103332

R = CH₂CH₂OH, GL103336

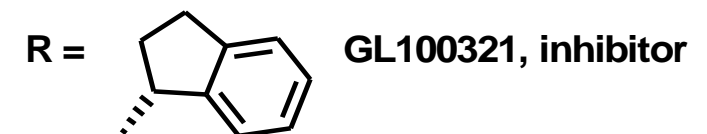
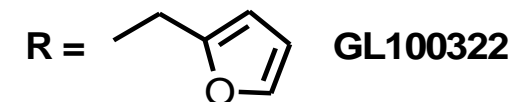
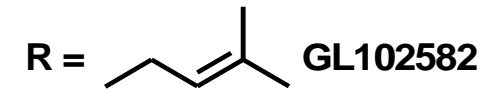
R = CH₂Ph, GL103349



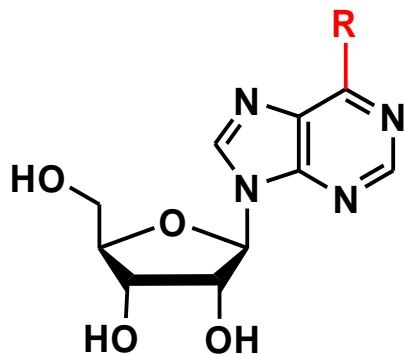
R = OCH₃, GL101398

R = SCH₃, GL103231

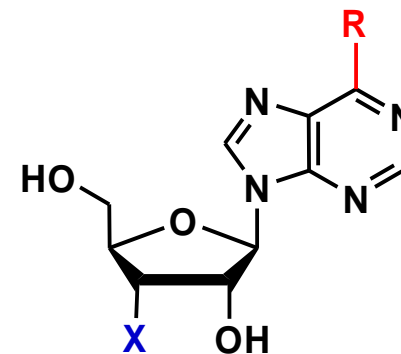
R = S-CH₂CH=CH₂, GL103232



6-Substituted Purine Nucleoside Derivatives – I



R = H, GL100428, **antibacterial and antineoplastic**
R = Me, GL100209, **antiviral antifungal antibiotics**
R = OH, GL100160, **RNA nucleoside**
R = SH, GL1010402, **anticancer**
R = Cl, GL100190, **ADA substrate**
R = OMe, GL100851; R = SMe, GL103238
R = Furfuryl-2, GL100231; R = NHH₂, GL102059
R = NHpropynyl, GL102057; R = NHCH₂CH₂OH, GL102900
R = NHAc, GL100887, **RNA nucleoside**
R = NHMe, GL100832, **RNA nucleoside**
R = NMe₂, GL102056, **RNA nucleoside, anticancer**
R = NH-isopentenyl, GL102581, **antiviral, cytokinin nuc, RNA nuc**
R = NH-isoamyl, GL102903
R = NH-furfuryl-2, GL100318, **anticancer antiviral**
R = NHCH₂Ph, G102055, **antiviral, natural cytokinin nuc**
R = NH-BnOMe-p, GL102901, **plant growth regulator**
R = NH-BnOMe-m, GL102902, **plant growth regulator**
R = NH-BnCF₃-m, GL103080, **antiviral, cytokinin nuc**
R = NH-BnCF₃-p, GL103081, **antiviral, cytokinin nuc**
R = 1-piperiziny, GL102062; R = 4-morpholinyl, GL102061



X = F

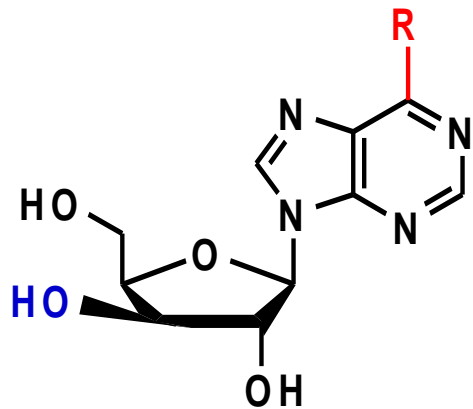
R = H, GL100466; R = CH₃, GL100213
R = OH, GL101137; R = OCH₃, GL100847
R = NH₂, GL100201; R = NHMe, GL102133
R = NMe₂, GL101815; R = C₆H₅, GL100494
R = furfuryl-2, GL100233
R = thiofuranyl-3, GL100493
R = pyridinyl-4, GL100495
R = Naphthyl-alpha, GL100496
R = NH-iso-pentenyl, GL103692
R = NH-Bn-OMe-m, GL103691
R = NH-Bn-OMe-p, GL103690
R = NH-Bn-CF₃-m, GL103689

X = N₃

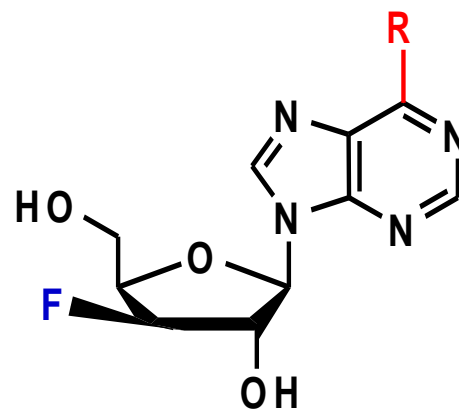
R = NH₂, GL100826
antiviral anticancer
R = CH₃, GL101224
R = NHCH₃, GL102151
R = NHMe₂, GL102152



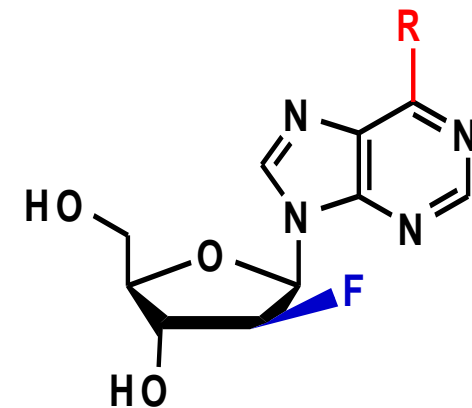
6-Substituted Purine Nucleoside Derivatives – II



R = Me, GL103203
 R = OH, GL103618
 R = NH₂, GL101507, anticancer
 R = NHCH₃, GL103522
 R = NMe₂, GL103523
 R = NH-iso-pentenyl, GL103622
 R = NH-BnOMe-p, GL103620
 R = NH-BnOMe-m, GL103619
 R = NH-BnCF₃-m, GL103621

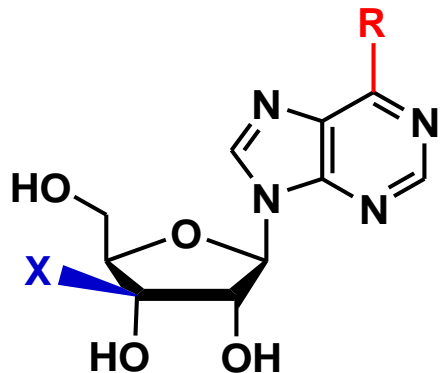


R = OH, GL103103
 R = NH₂, GL103101
 R = NH-iso-pentenyl, GL103635
 R = NH-BnOMe-p, GL103632
 R = NH-BnOMe-m, GL103631
 R = NH-BnCF₃-m, GL103633



R = H, GL100577
 R = CH₃, GL100334
 R = OH, GL103693
 R = OCH₃, GL103695
 R = SCH₃, GL103249
 R = NH₂, GL100575;
 Antiprotozoal antiviral
 R = NHMe, GL101912
 R = NMe₂, GL101913

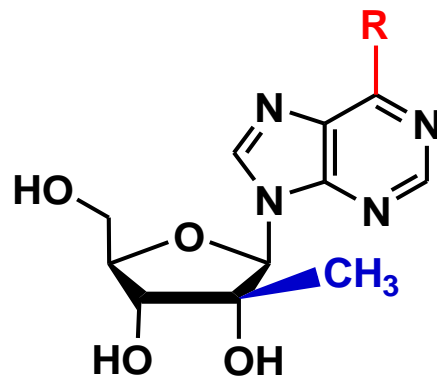
6-Substituted Purine Nucleoside Derivatives – III



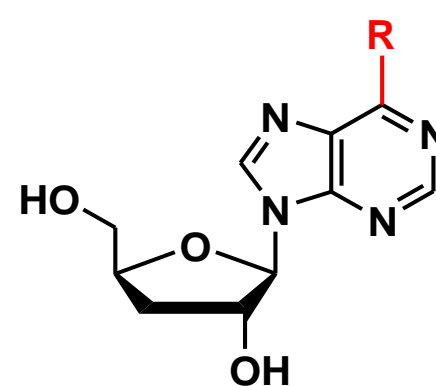
X = CH₃:
R = OH, GL103652
R = NH₂, GL102222, antitumor,
RNA reductase inhibitor
R = NHMe, GL102223
R = NMe₂, GL102225
R = NH-isopentenyl, GL103658
R = NH-BnOMe-p, GL103655
R = NH-BnOMe-m, GL103653
R = NH-BnCF₃-m, GL103656

X = —≡

R = OH, GL103665
R = NH₂, GL103183
R = NMe₂, GL103202
R = NH-isopentenyl, GL103669
R = NH-Bn-OMe-m, GL103668
R = NH-Bn-CF₃-m, GL103666



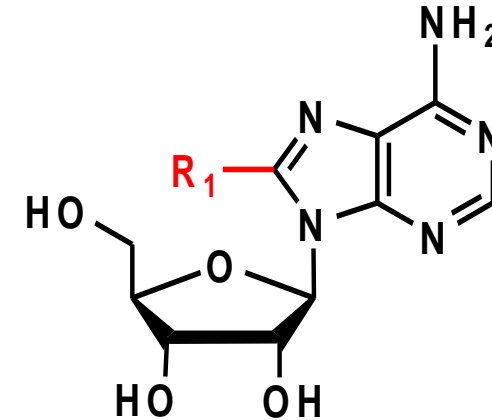
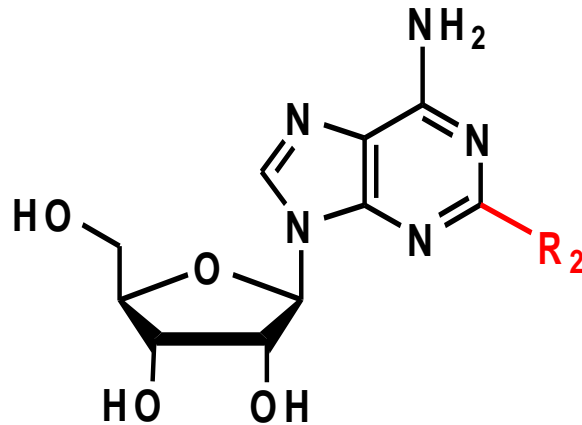
R = H, GL100623
R = CH₃, GL100634
R = OH, GL102996
R = OCH₃, GL100742
R = NH₂, GL100687, antiviral
R = NHMe, GL101910
R = NMe₂, GL101911
R = NH-iso-pentenyl, GL103093
R = NH-furfuryl-2, GL103092
R = NH-CH₂Ph, GL103091
R = NH-Bn-OMe-m, GL103095
R = NH-Bn-OMe-p, GL103096
R = NH-Bn-CF₃-m, GL103090
R = NH-Bn-CF₃-p, GL103081



R = OH, GL103680
R = OCH₃, GL103681
R = NH₂, GL101316
antiviral antibiotics
R = NMe₂, GL101317
R = NH-isopentenyl, GL103085
R = NH-Bn-OMe-m, GL103682
R = NH-Bn-CF₃-m, GL103110



2-/8-Substituted Adenosine Derivatives



$R_2 = \text{Cl}$, GL101374, **ADA inhibitor, antimalarial**

$R_2 = \text{Br}$, GL101800, **antimalarial**

$R_2 = \text{I}$, GL100870

$R_2 = \text{HO}$, GL100323, **inhibitors**

$R_2 = \text{Me}$, GL100877, **RNA nucleoside**

$R_2 = \text{OMe}$, GL101375;

$R_2 = \text{CF}_3$, GL101939

$R_2 = \text{HS}$, GL101126;

$R_2 = \text{SMe}$, GL101322

$R_2 = \text{SCH}_2\text{CN}$, GL101326;

$R_2 = \text{CN}$, GL101808

$R_2 = \text{SCH}_2\text{Ph}$, GL101327;

$R_2 = \text{NHNH}_2$, GL101377

$R_2 = \text{SBnMe-p}$, GL101333;

$R_2 = \text{CH}_2\text{NH}_2$, GL103099

$R_2 = \text{COOMe}$, GL101809;

$R_2 = \text{CONH}_2$, GL101810

$R_2 = \text{CONHMe}$, GL101811,

$R_2 = \text{C(NH)NH}_2$, GL101996

$R_1 = \text{Cl}$, GL101901, **anticancer autommune**

$R_1 = \text{Br}$, GL100681, **Ad binding inhibitor**

$R_1 = \text{OH}$, GL101128, **anticancer antibiotics**

$R_1 = \text{N}_3$, GL101679

$R_1 = \text{NH}_2$, GL101680

$R_1 = \text{NHNH}_2$, GL101681

$R_1 = \text{OMe}$, GL101677

$R_1 = \text{SMe}$, GL102526

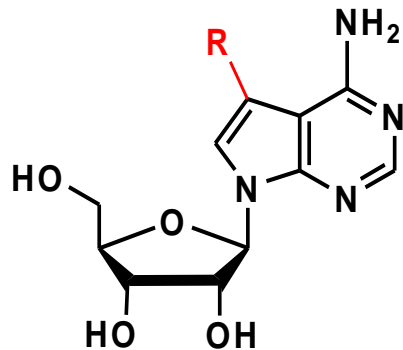
$R_1 = \text{NHMe}$, GL101678

$R_1 = \text{OCH}_2\text{Ph}$, GL101127

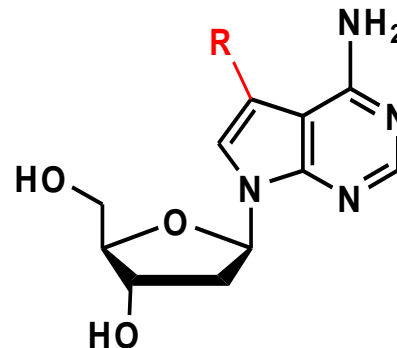
$R_1 = \text{O-allyl}$, GL102150



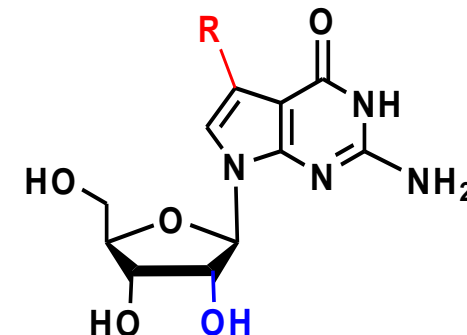
SAR of 7-Deaza Purine Nucleosides



- R = H, GL100984, **antiviral, antimalarial, anticancer, antibiotics, ADA inhibitor**
 GL100640: 2'-C-Me analogue, **antiviral**
 GL100433: 2'-F-ara analogue
 GL102639: 3'-deoxy analogue
- R = CN, GL101581, **anticancer antibiotics,**
 GL101580: 8-Br analogue
 GL101617: 3'-F analogue
 GL101590: 2'-C-Me analogue
 GL101616: 8-Br-3'-F analogue
- R = CONH₂, GL101582, **antiviral antimalarial**
 GL101618: 3'-F analogue
 GL101591: 2'-C-Me analogue
- R = I, GL100437
 GL100638: 2'-C-Me analogue
 GL100450: 3'-F analogue



- R = H, GL101535, **PNP inhibitor**
 GL102636: 2',3'-anhydro analogue
 GL102638: 2',3'-dideoxy analogue
 GL101575: 6-deamino analogue
- R = F, GL101552
 R = I, GL101538
 R = CN, GL101567

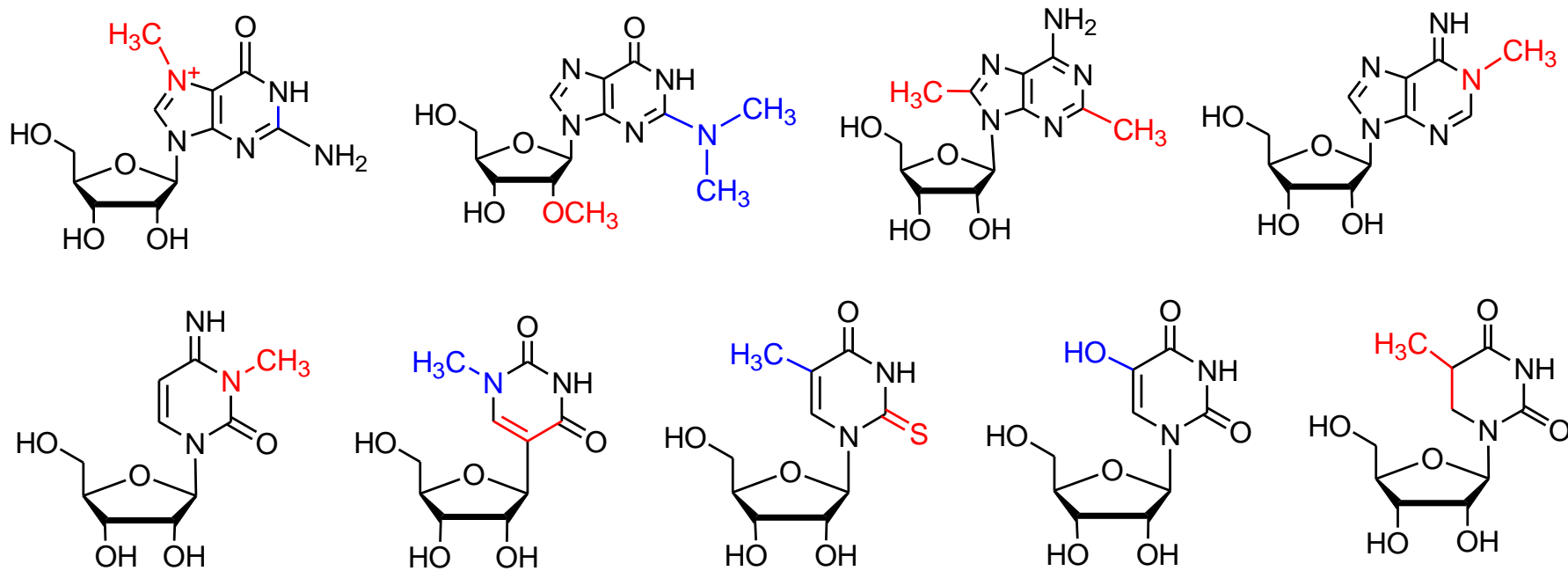


- R = H, GL100970, **antiviral agent**
 GL101553: 2'-deoxy analogue
- R = I, GL102880
 GL101555: 2'-deoxy analogue
- R = CN, GL100964, **RNA nucleoside**
 GL101516: 2'-deoxy analogue



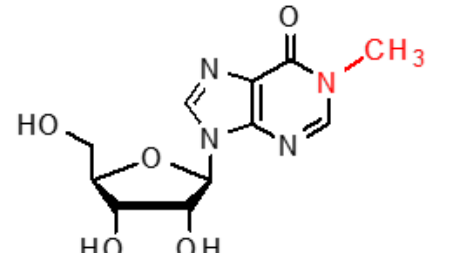
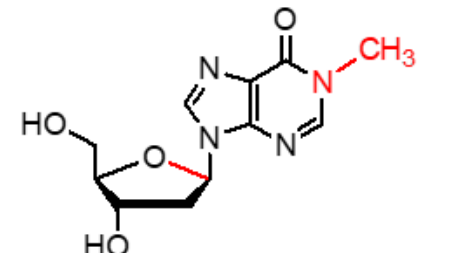
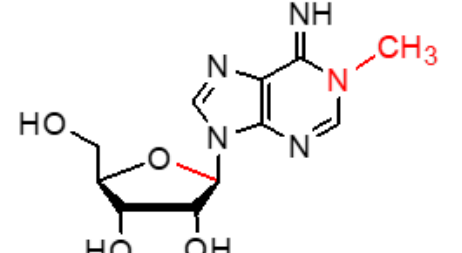
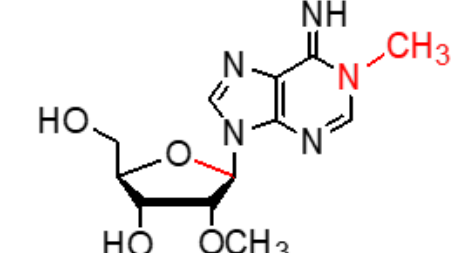
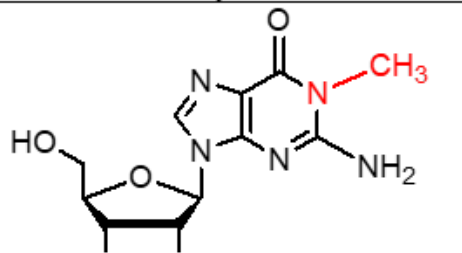
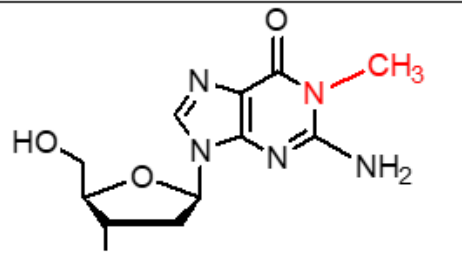
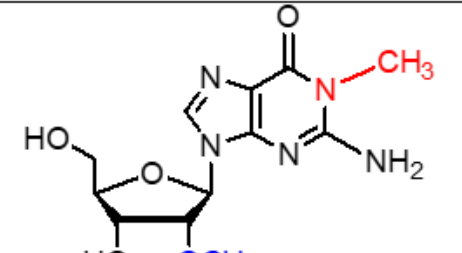
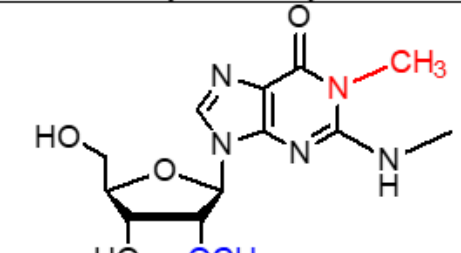
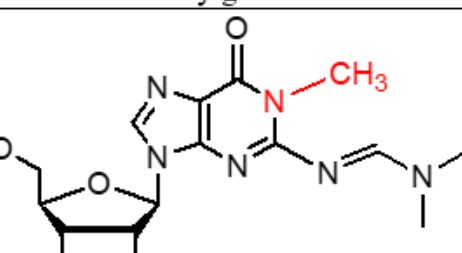
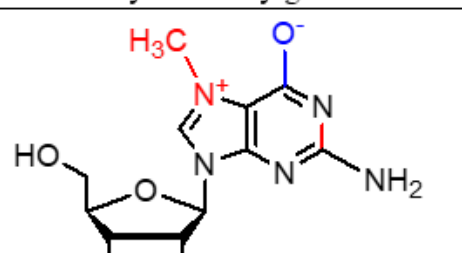
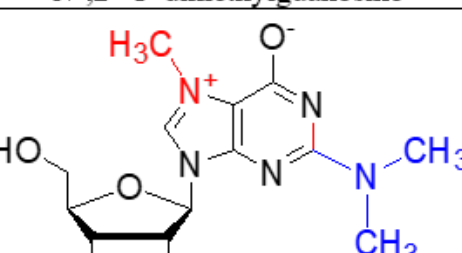
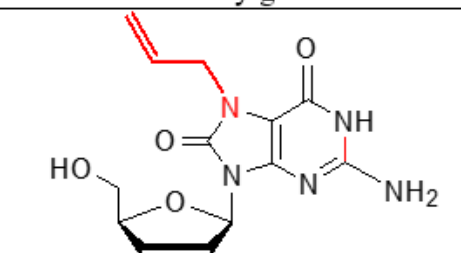
Naturally-Modified Ribo-Nucleosides

- >130 naturally-occurring nucleosides generated from various RNAs
- Important nucleosides for **mRNA, siRNA and genomic R&D etc.**
- We have most of them, and a large number of related analogues





Endo-N-Methyl/Alkylated Purine Nucleosides

 <p>GL102666; CAS#2140-73-0 <i>N</i>¹-Methylinosine</p>	 <p>GL103160; CAS#72398-31-3 <i>N</i>¹-Methyl-2'-deoxyinosine</p>	 <p>GL102303; CAS#15763-06-1 <i>N</i>¹-Methyladenosine</p>	 <p>GL103161; CAS#91101-00-7 2'-<i>O</i>-Methyl-<i>N</i>¹-methyladenosine</p>
 <p>GL102690; CAS#2140-65-0 <i>N</i>¹-Methylguanosine</p>	 <p>GL102691; CAS#5132-79-6 2'-Deoxy-<i>N</i>¹-methylguanosine</p>	 <p>GL102692; CAS#73667-71-7 <i>N</i>¹,2'-<i>O</i>-dimethylguanosine</p>	 <p>GL103259; <i>N</i>¹,<i>N</i>²-Dimethyl-2'-<i>O</i>-methylguanosine</p>
 <p>GL103260; <i>N</i>²-dmf-<i>N</i>¹-methyl-2'-<i>O</i>-methylguanosine</p>	 <p>GL102306; CAS#20244-86-4 <i>N</i>⁷-Methylguanosine</p>	 <p>GL103289; CAS#40027-70-1 <i>N</i>²,<i>N</i>²,<i>N</i>⁷-Trimethylguanosine</p>	 <p>GL102219; CAS#121288-39-9 7,8-Dihydro-8-oxo-7-allyl-guanosine</p>



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