mcguigan@cf.ac.uk

Chris McGuigan
School of Pharmacy & Pharmaceutical Sciences
Cardiff University

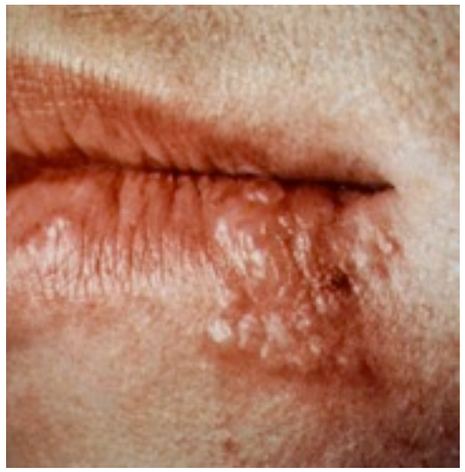
ProTides and phosphorodiamidates as nucleotide pro-drug forms: from the lab to clinical use

Royal Society of Chemistry, 17th April 2015

McGuigan Group Mission

Innovative small molecule drug discovery, particularly for viruses and cancer

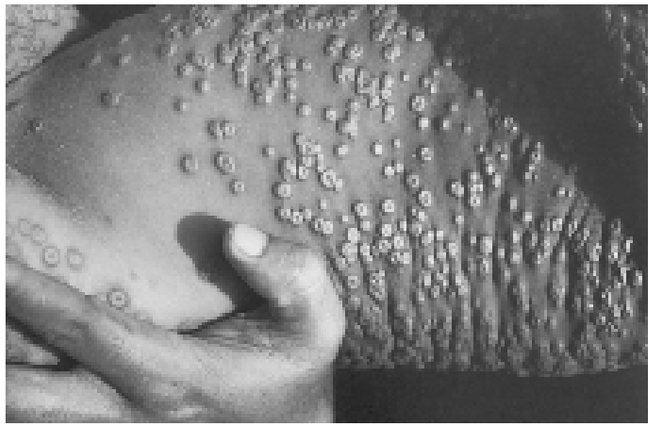
HSV



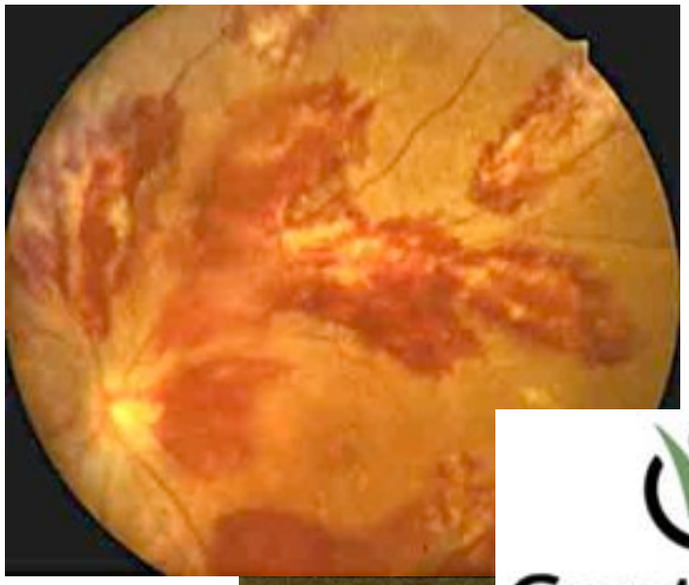
Cancer

flu

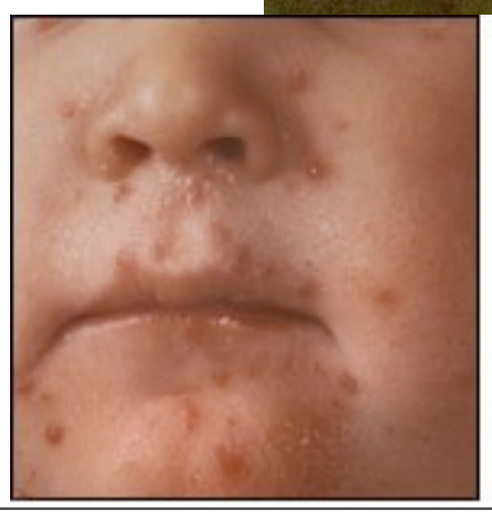
VV/Smallpox

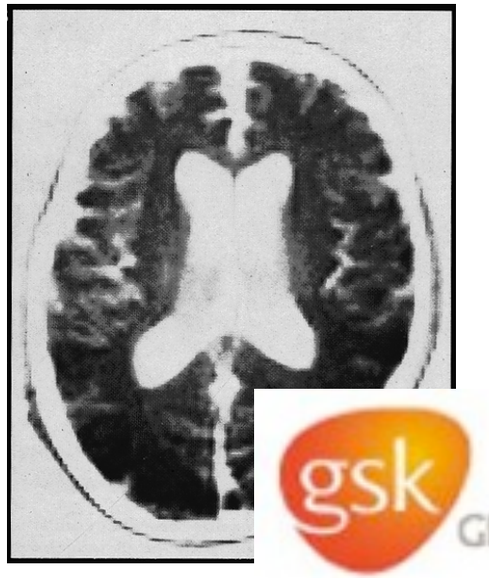


CMV



All nucleosides





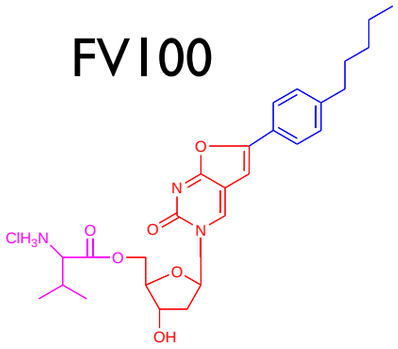
VZV

HIV/AIDS

Hepatitis B/C

NCEs from McGuigan lab that have entered human trials

FV100



Shingles

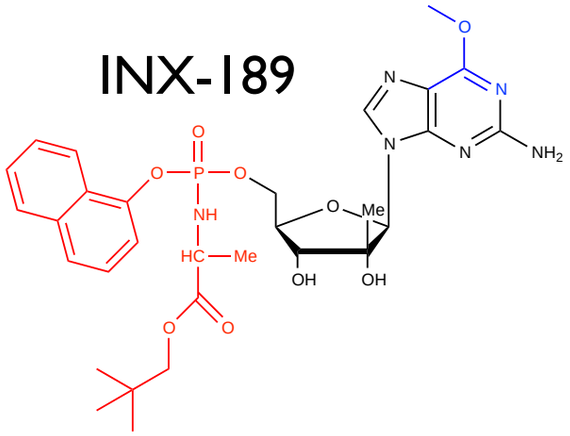
Most potent agent ever vs VZV

inhibitex

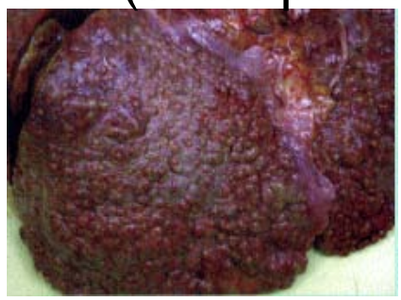
Completed phase 2:
safe and effective (2010).
Phase 3 to start 2015.

ContraVir PHARMACEUTICALS, INC.

INX-189



HCV (180M patients)



Most potent agent in class

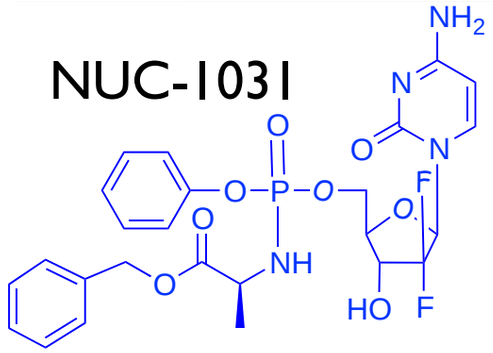
inhibitex

Completed phase 2a
safe and effective (2011).

$2.5Bn buyout Jan 2012
2 NCEs: both from Cardiff

Bristol-Myers Squibb

NUC-1031

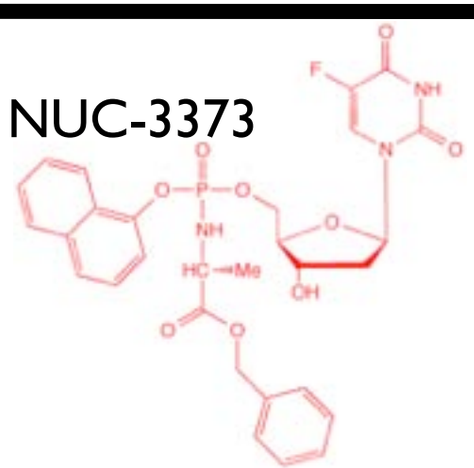


Pancreatic cancer.
Registration trials in
ovarian, pancreas,
lung and biliary

NUCANA BIOMED

First in man. Oct 2012.
Early positive data ASCO 2013, 2014.

NUC-3373



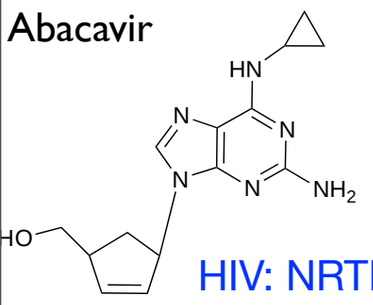
Colon cancer.

NUCANA BIOMED

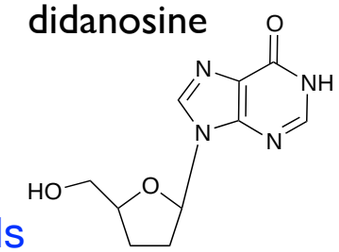
First in man. mid 2015

Antivirals

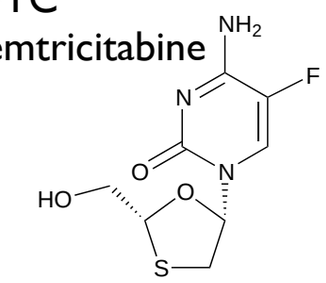
Abacavir



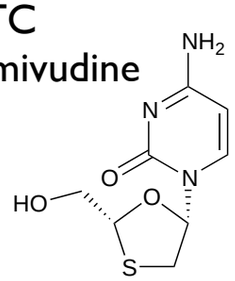
ddI
didanosine



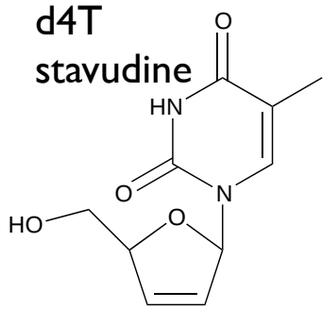
FTC
emtricitabine



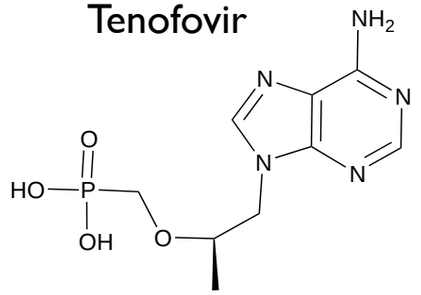
3TC
lamivudine



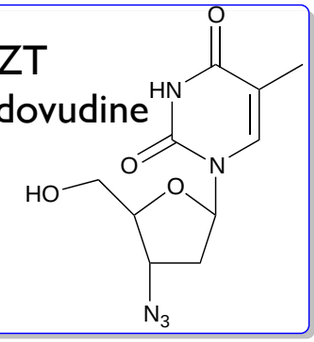
d4T
stavudine



Tenofovir



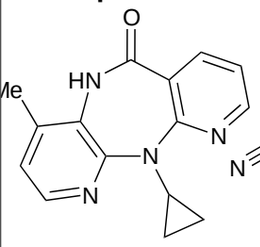
AZT
zidovudine



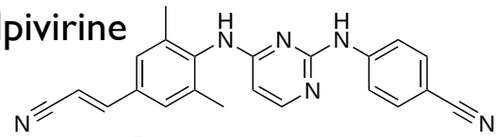
HIV: NRTIs

HIV: NNRTIs

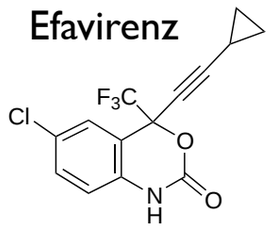
Nevirapine



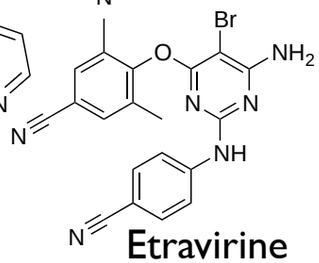
Rilpivirine



Efavirenz



Etravirine

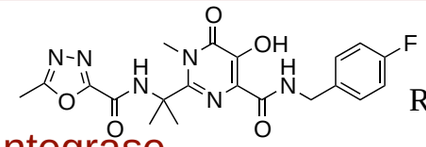


Antivirals: BNF Jan 2014

Ac-{TYR}{THR}{SER}{LEU}{ILE}{HIS}{SER}{LEU}{ILE}{GLU}{GLU}{SER}{GLN}{ASN}{GLN}{GLN}{GLU}{LYS}{ASN}{GLU}{GLN}{GLU}{LEU}{LEU}{GLU}{LEU}{ASP}{LYS}{TRP}{ALA}{SER}{LEU}{TRP}{ASN}{TRP}{PHE}-NH_2

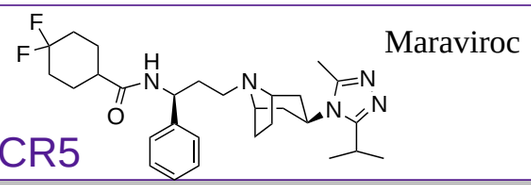
Enfuvirtide
fuzeon

HIV: Fusion



Raltegravir

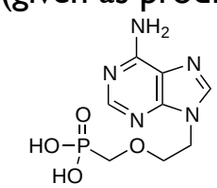
HIV: Integrase

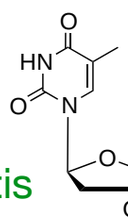


Maraviroc

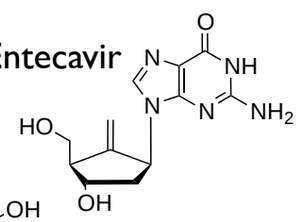
HIV: CCR5

PMEA Adefovir
(given as prodrug)





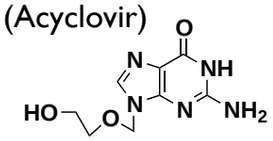
Entecavir



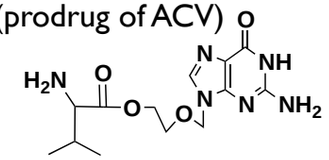
Viral hepatitis

Telbivudine

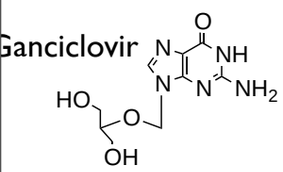
Aciclovir
(Acyclovir)



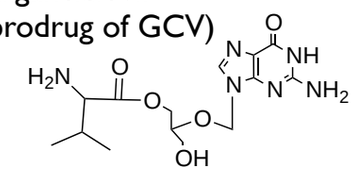
Valaciclovir
(prodrug of ACV)

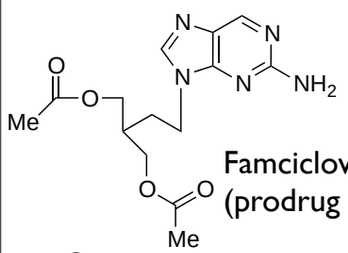


Ganciclovir



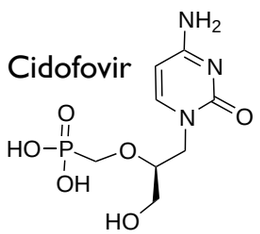
Valganciclovir
(prodrug of GCV)

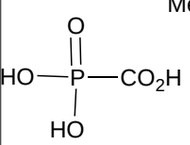




Famciclovir
(prodrug of PCV)

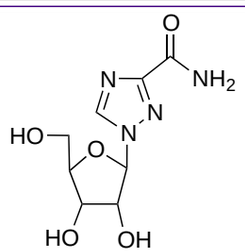
Cidofovir





Foscarnet
Phosphonoformate

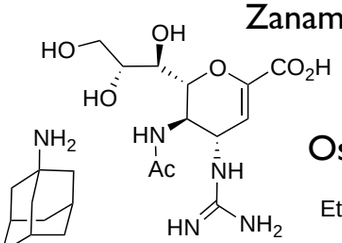
Herpes infections



RSV

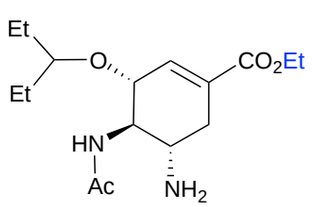
Ribavirin
(also used for HCV)

Zanamivir (Relenza)



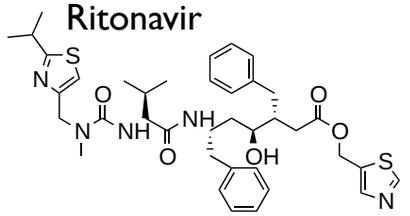
Amantadine

Oseltamivir (Tamiflu)

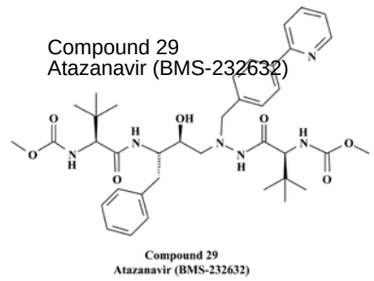


Influenza

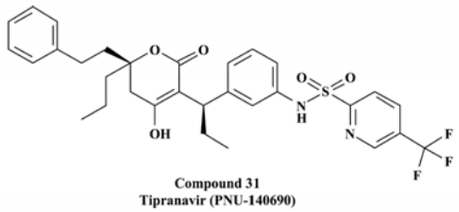
Ritonavir



Compound 29
Atazanavir (BMS-232632)

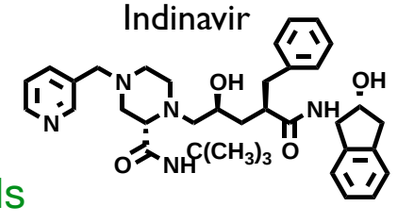


Compound 29
Atazanavir (BMS-232632)



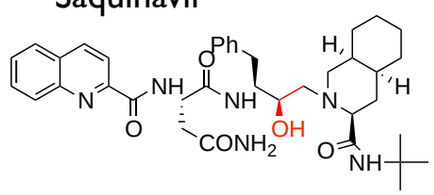
Compound 31
Tipranavir (PNU-140690)

Indinavir

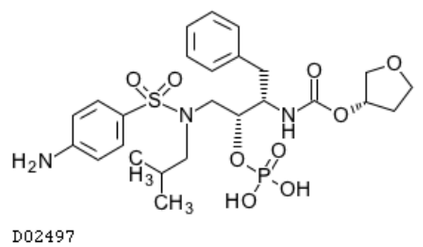


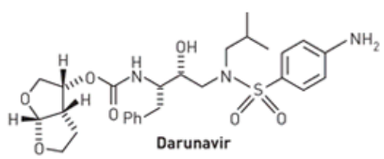
HIV PIs

Saquinavir



Fosamprenavir

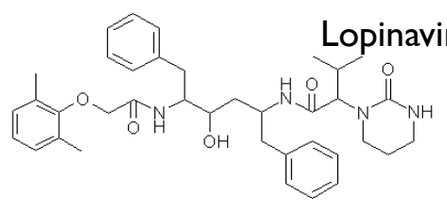




Darunavir

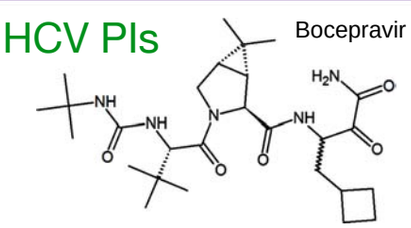
D02497

Lopinavir

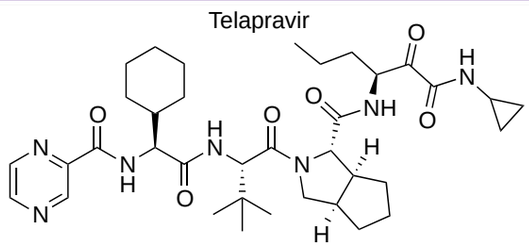


HCV PIs

Boceprevir

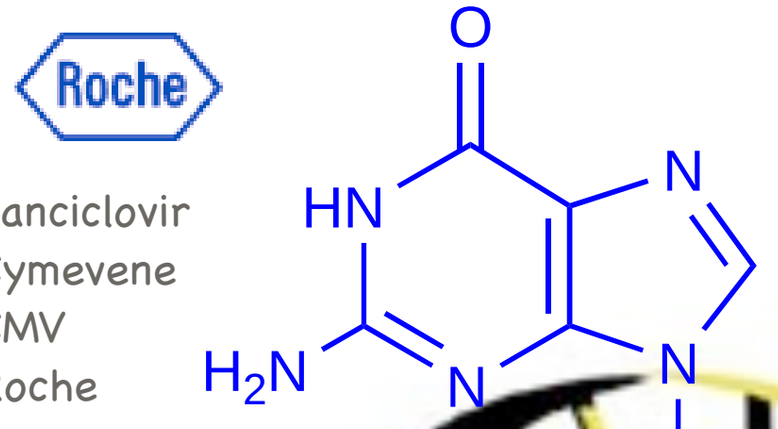


Telapravir

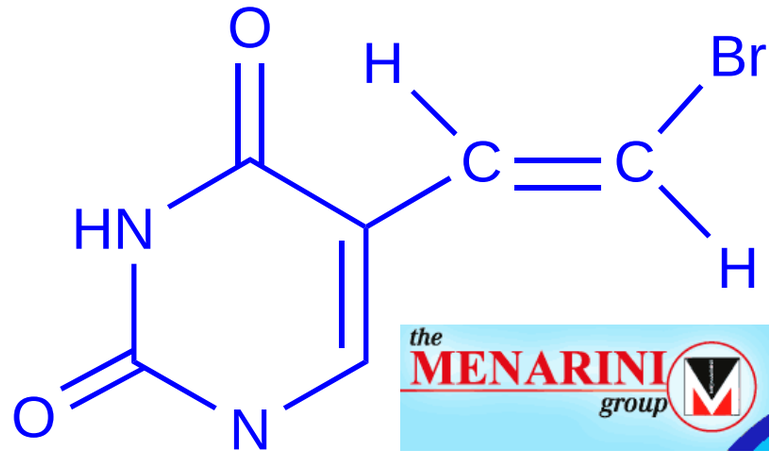


Half of them are nucleosides.

acyclovir
Zovirax
herpes
GSK

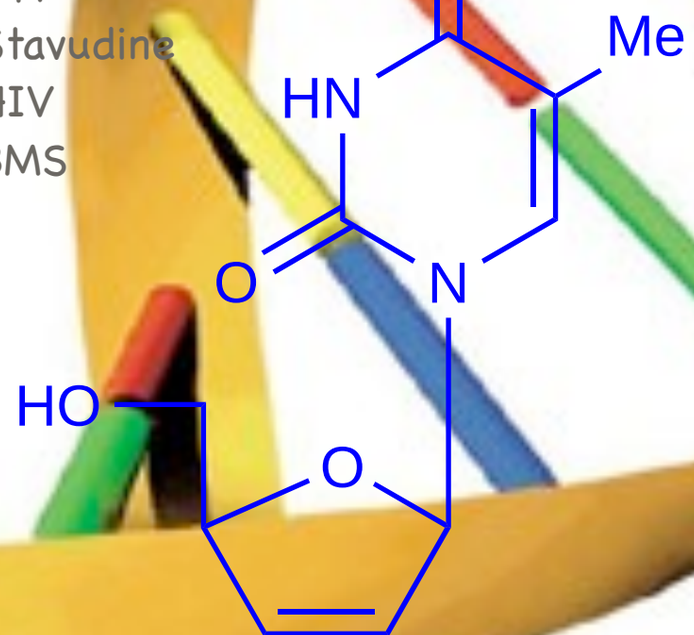


ganciclovir
Cymevene
CMV
Roche

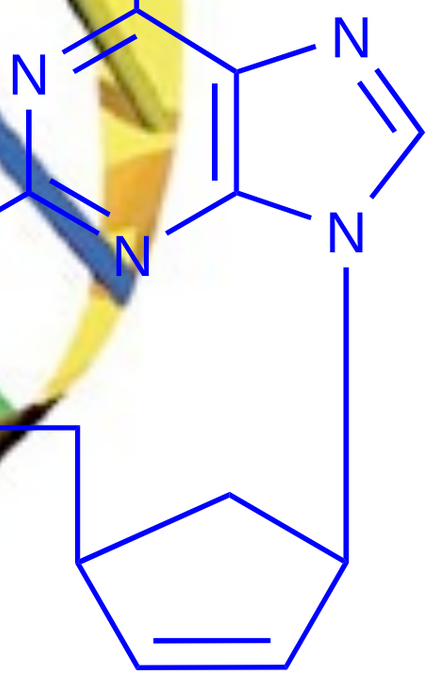


BVDU
Brivudin
VZV
Menarini

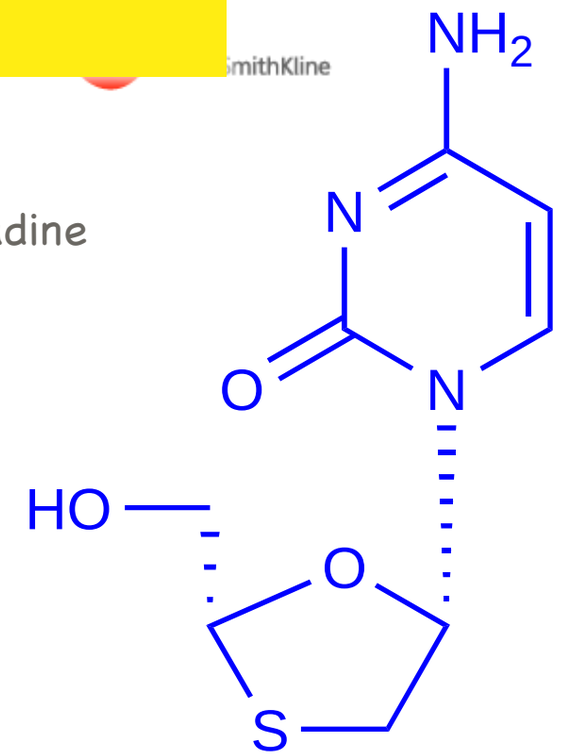
20/41 approved antivirals are nucleoside analogues.



d4T
Stavudine
HIV
BMS

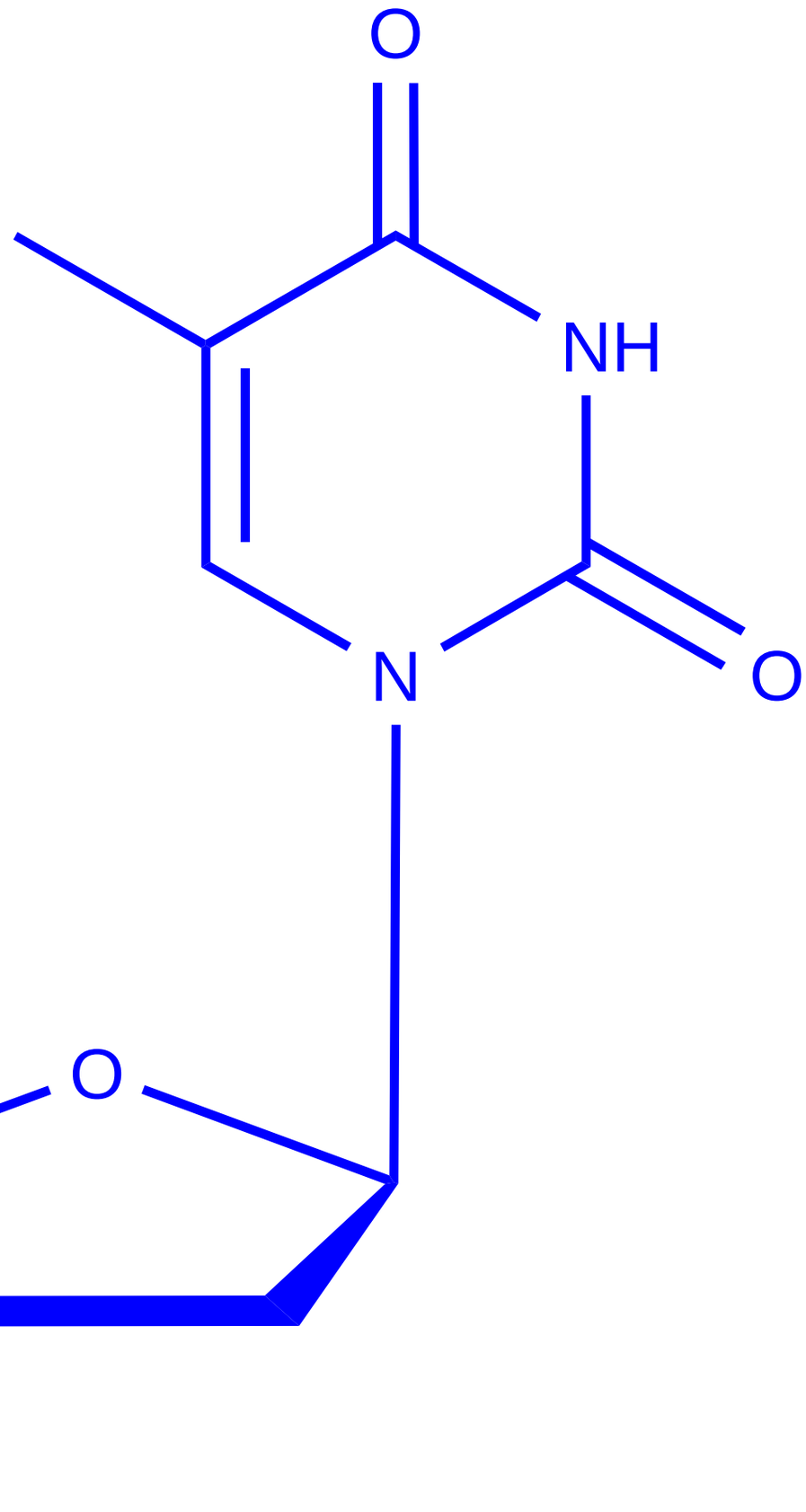


abacavir
Ziagen
HIV
GSK

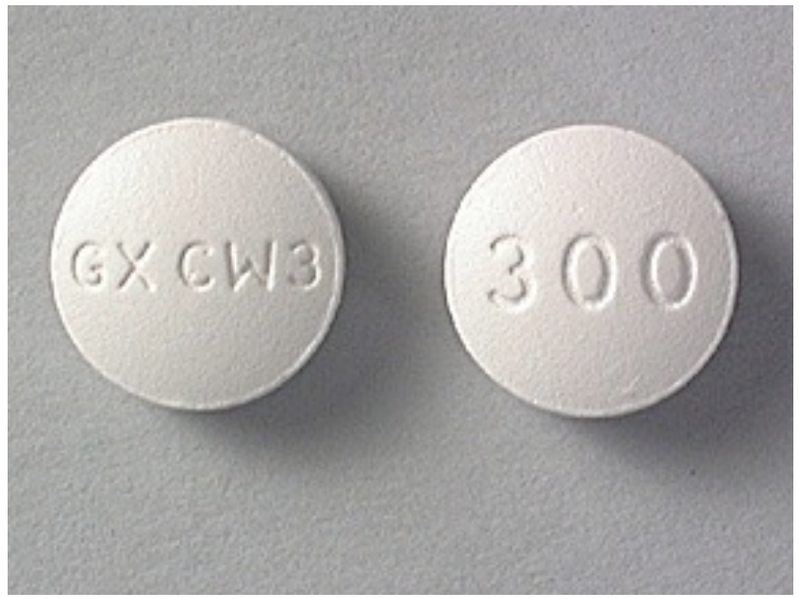


3TC
lamivudine
HepB
GSK

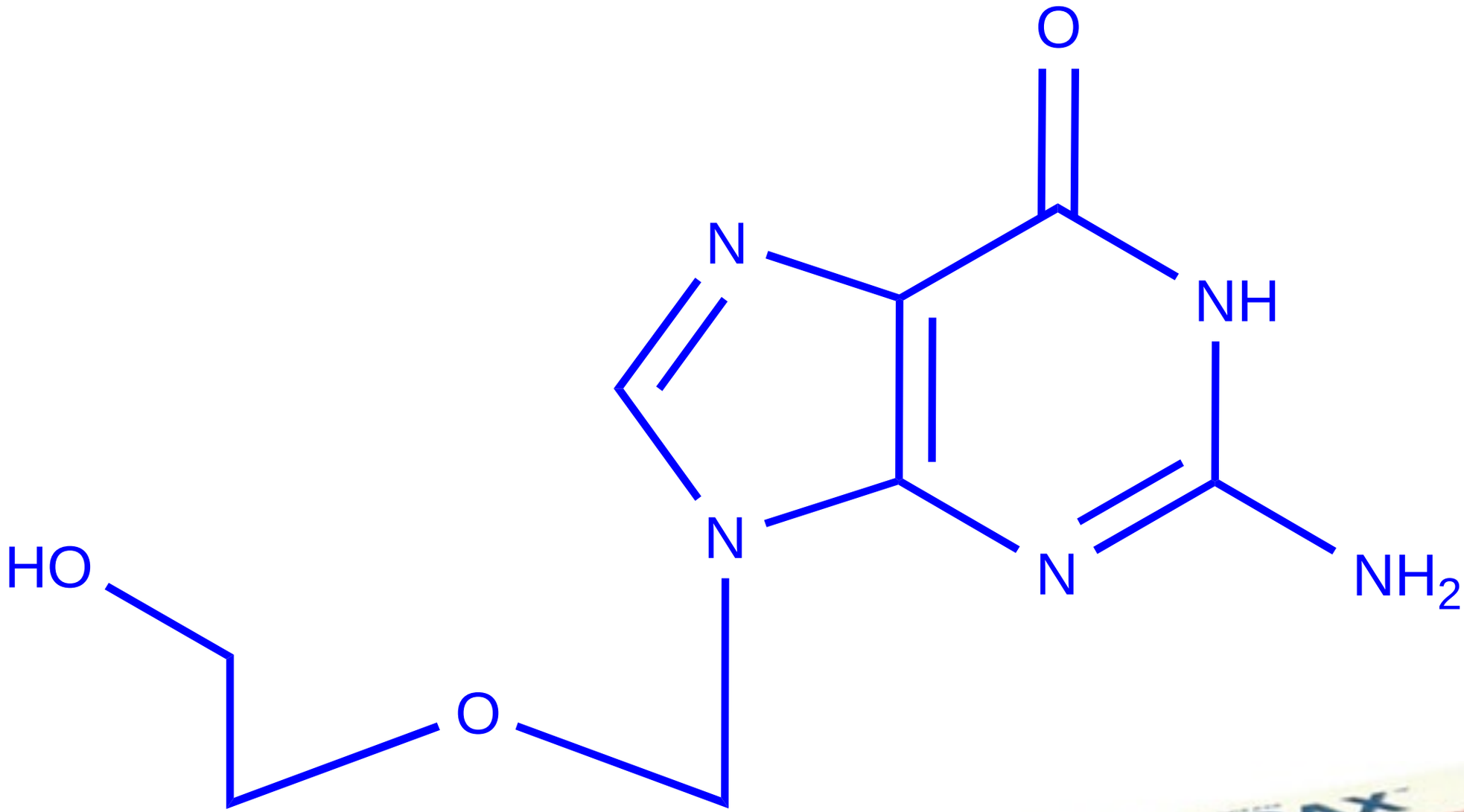
Nucleoside Drugs



AZT



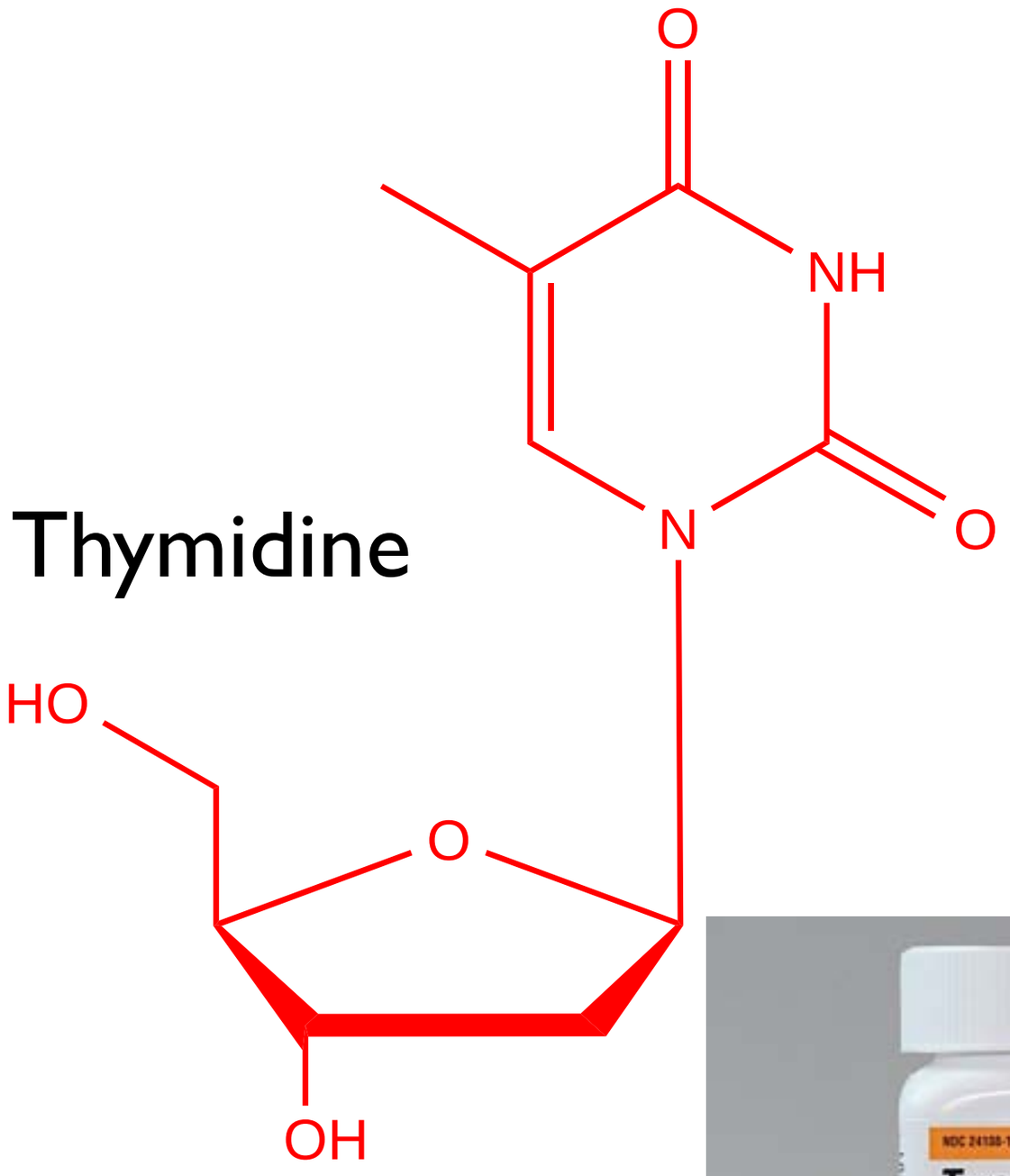
Nucleoside Drugs



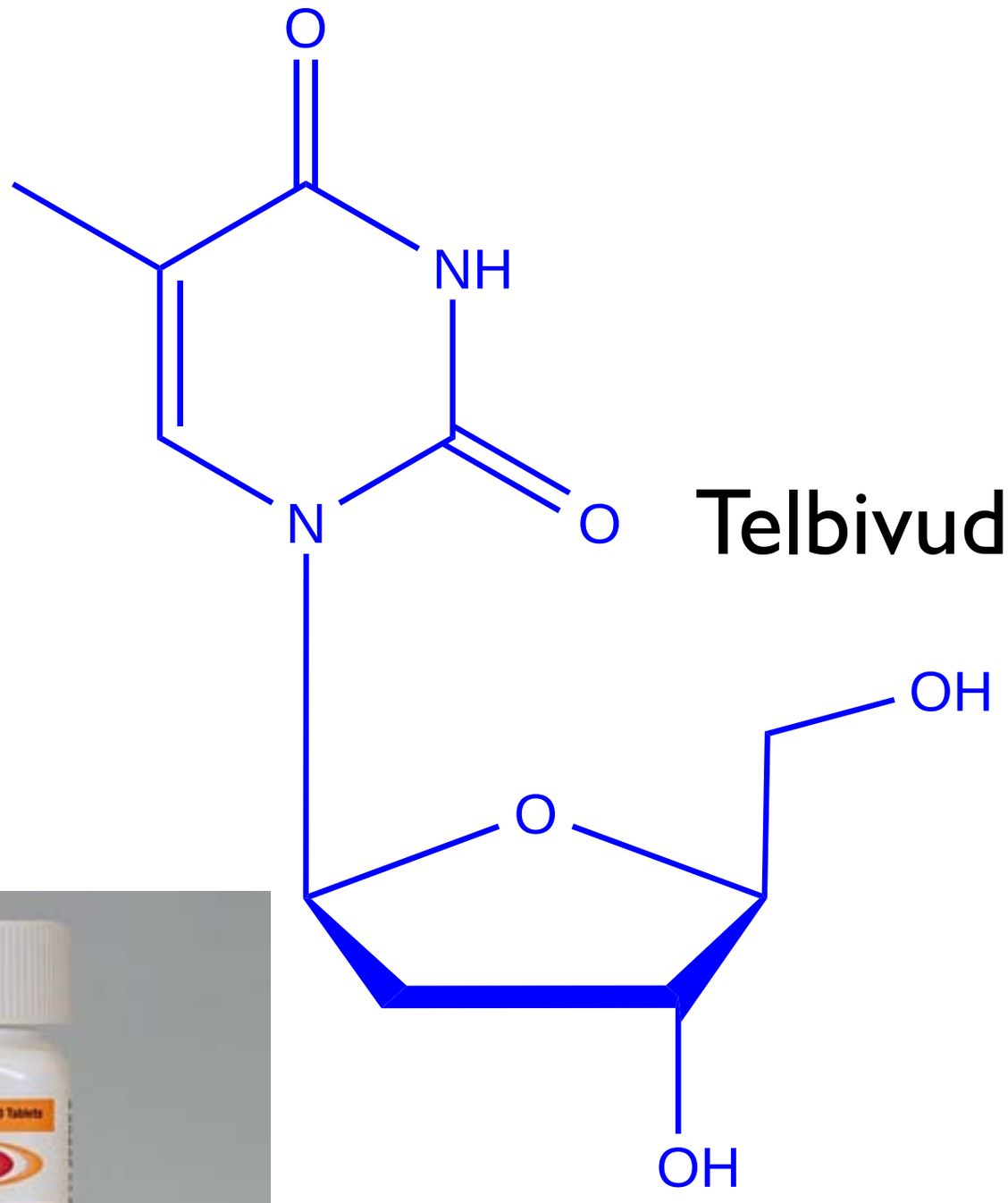
acyclovir

Nucleoside Drugs

Thymidine

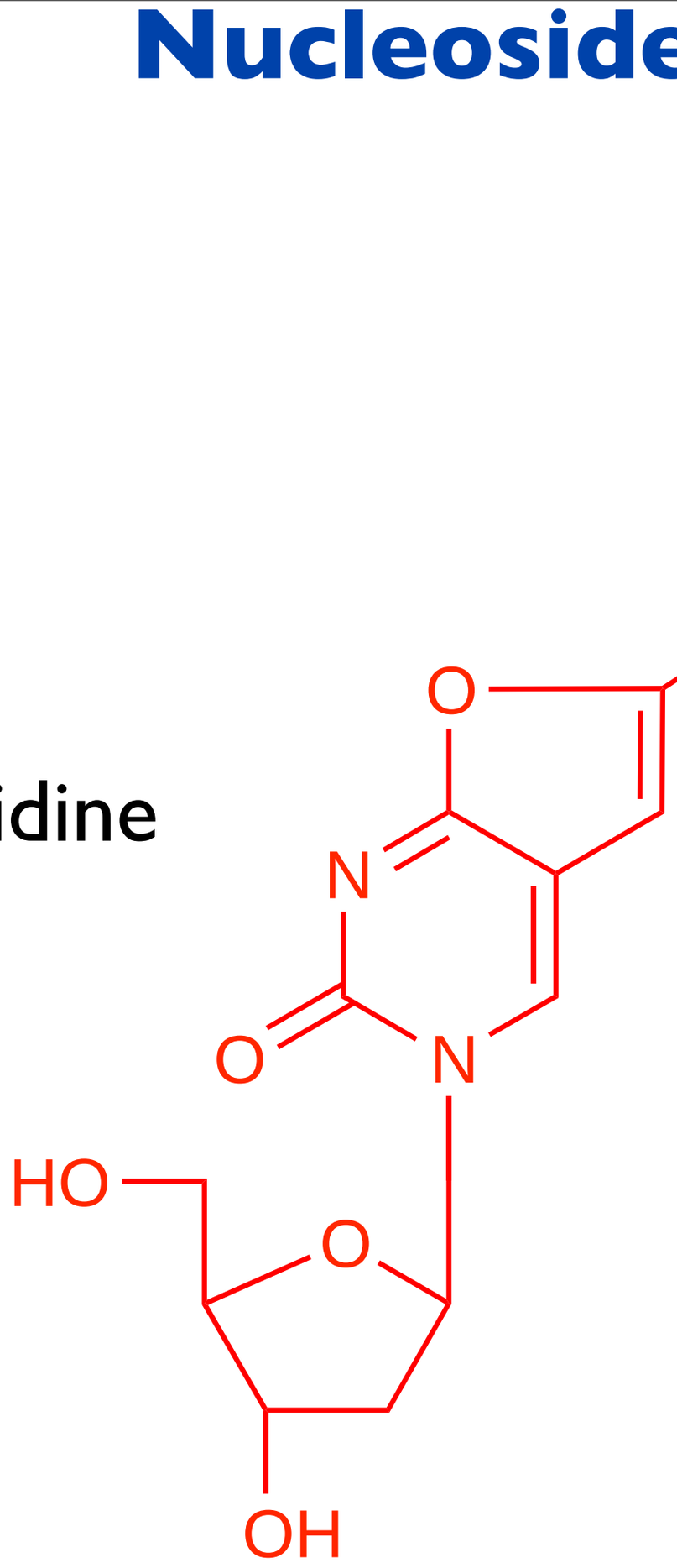


Telbivudine



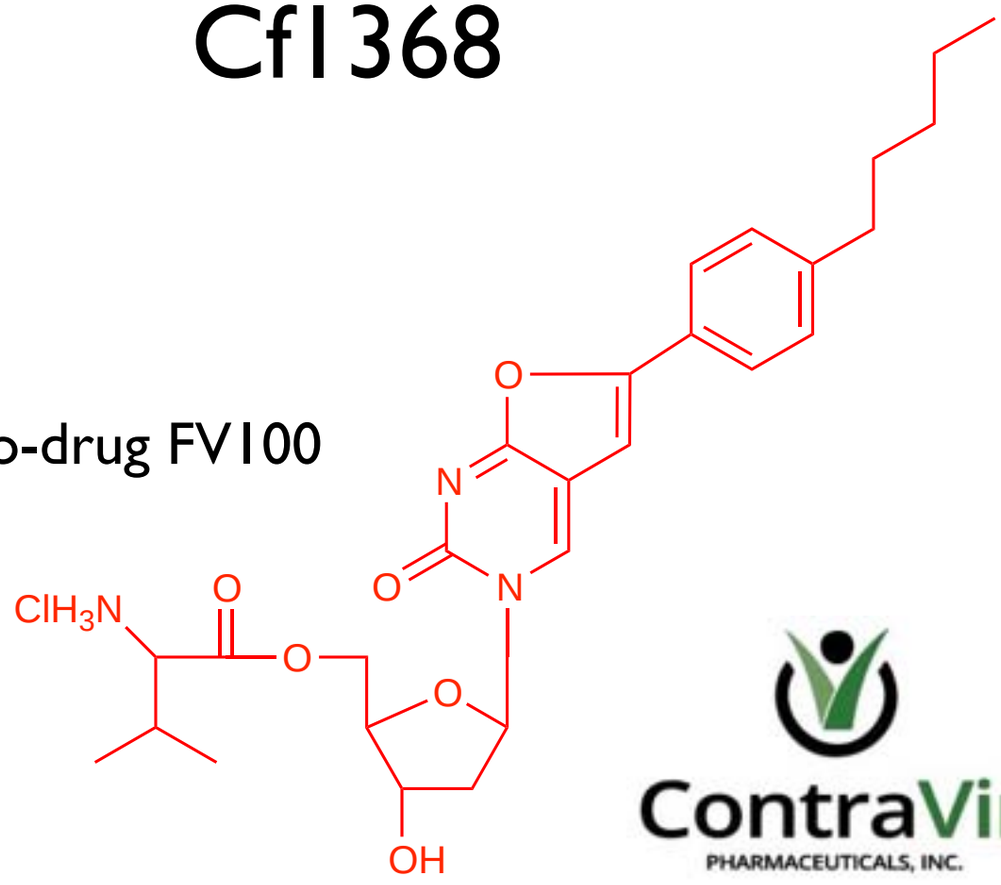
Nucleoside Drugs

Thymidine



Cf1368

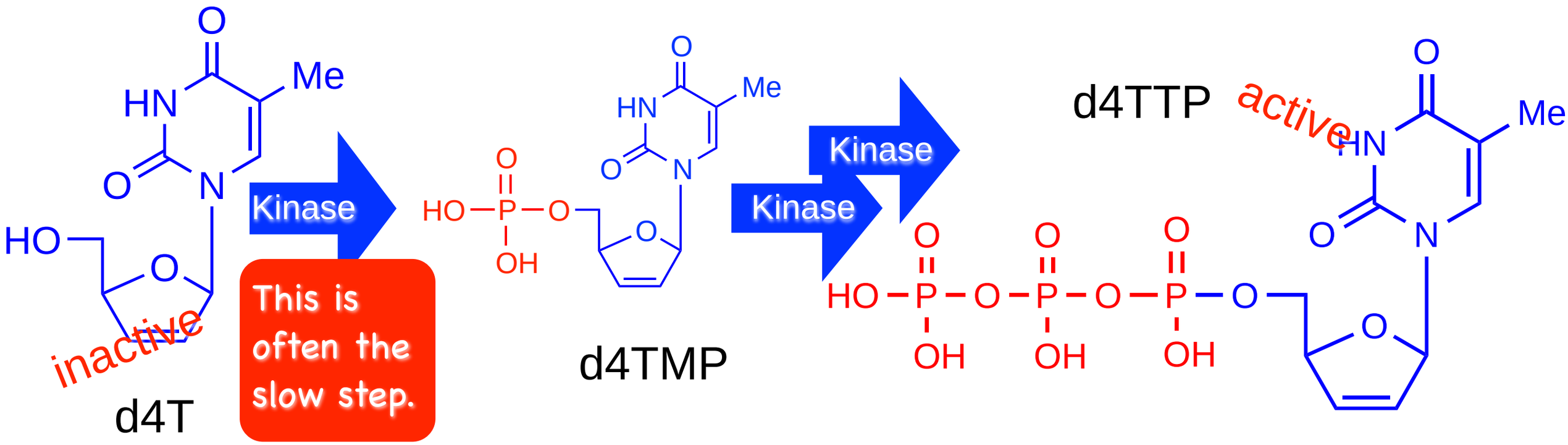
Pro-drug FV100



ContraVir
PHARMACEUTICALS, INC.

Nucs: Mechanism of Action

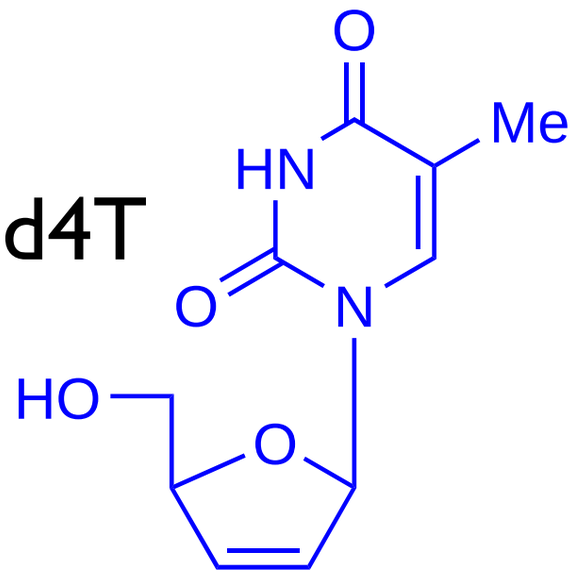
All nucleoside drugs require metabolic activation in their target cell to the bio-active phosphate forms:



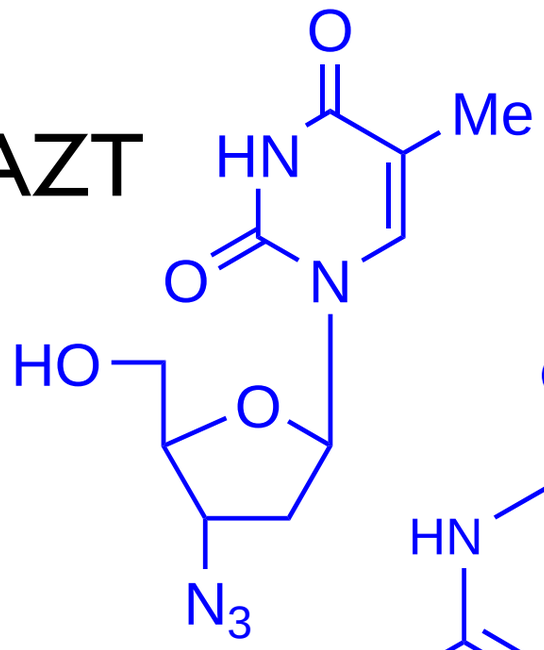
In general - this requirement is a disadvantage.

Problems of Nucleoside Drugs

d4T



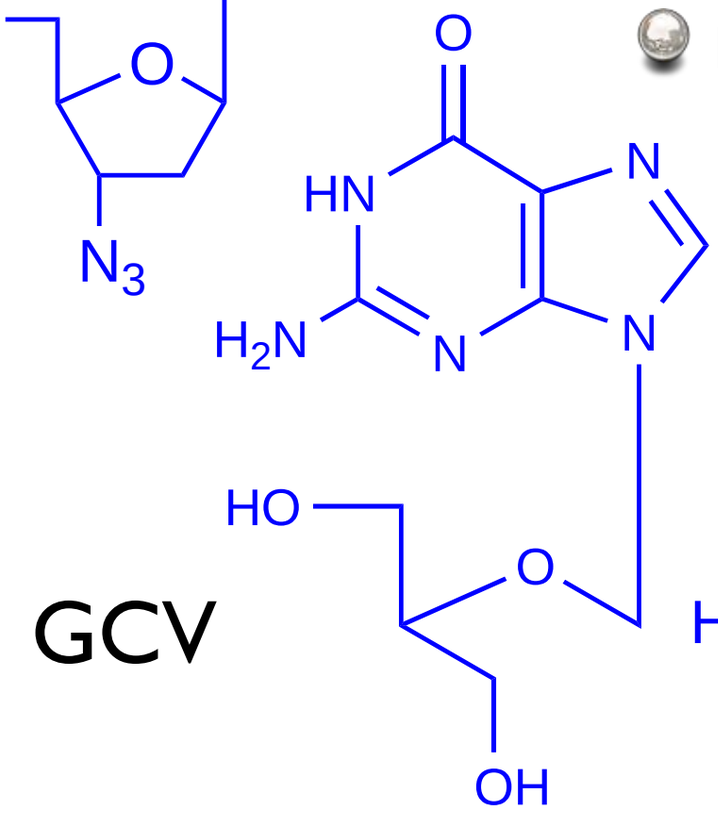
AZT



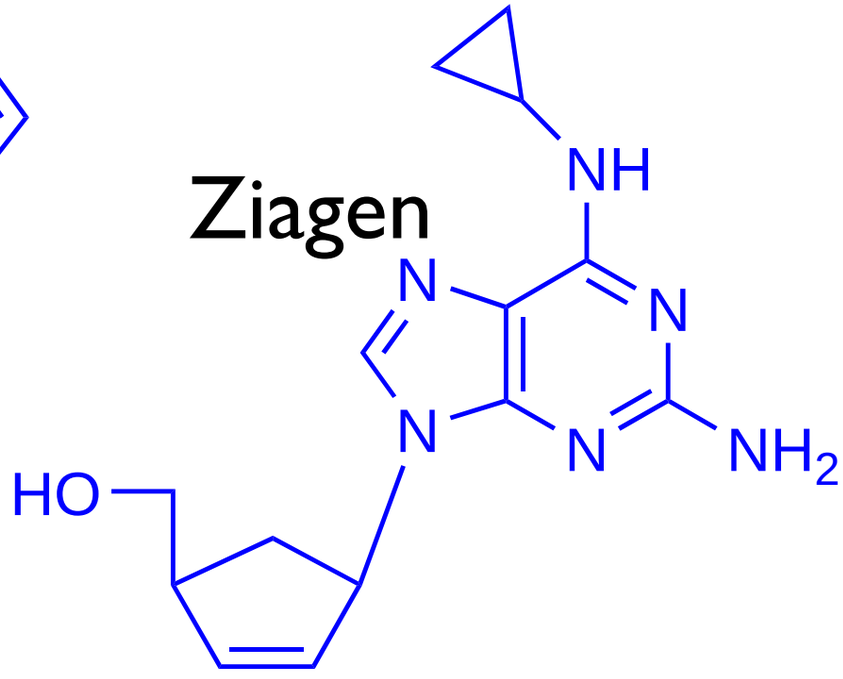
- (Often) poor metabolism to the active triphosphates
- Rapid deactivation
- Active transport needed
- Toxicity common
- Structure based / RDD 'difficult'
- Emergence of resistant virus (tumour)
  - transporter
  - kinase
  - polymerase

Often linked to poor clinical responses to therapy.

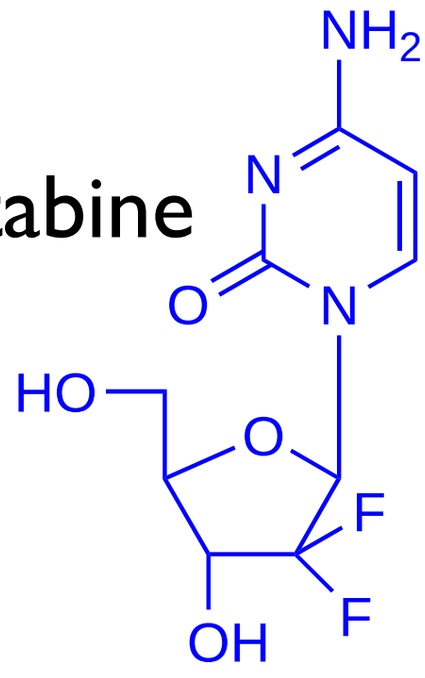
GCV



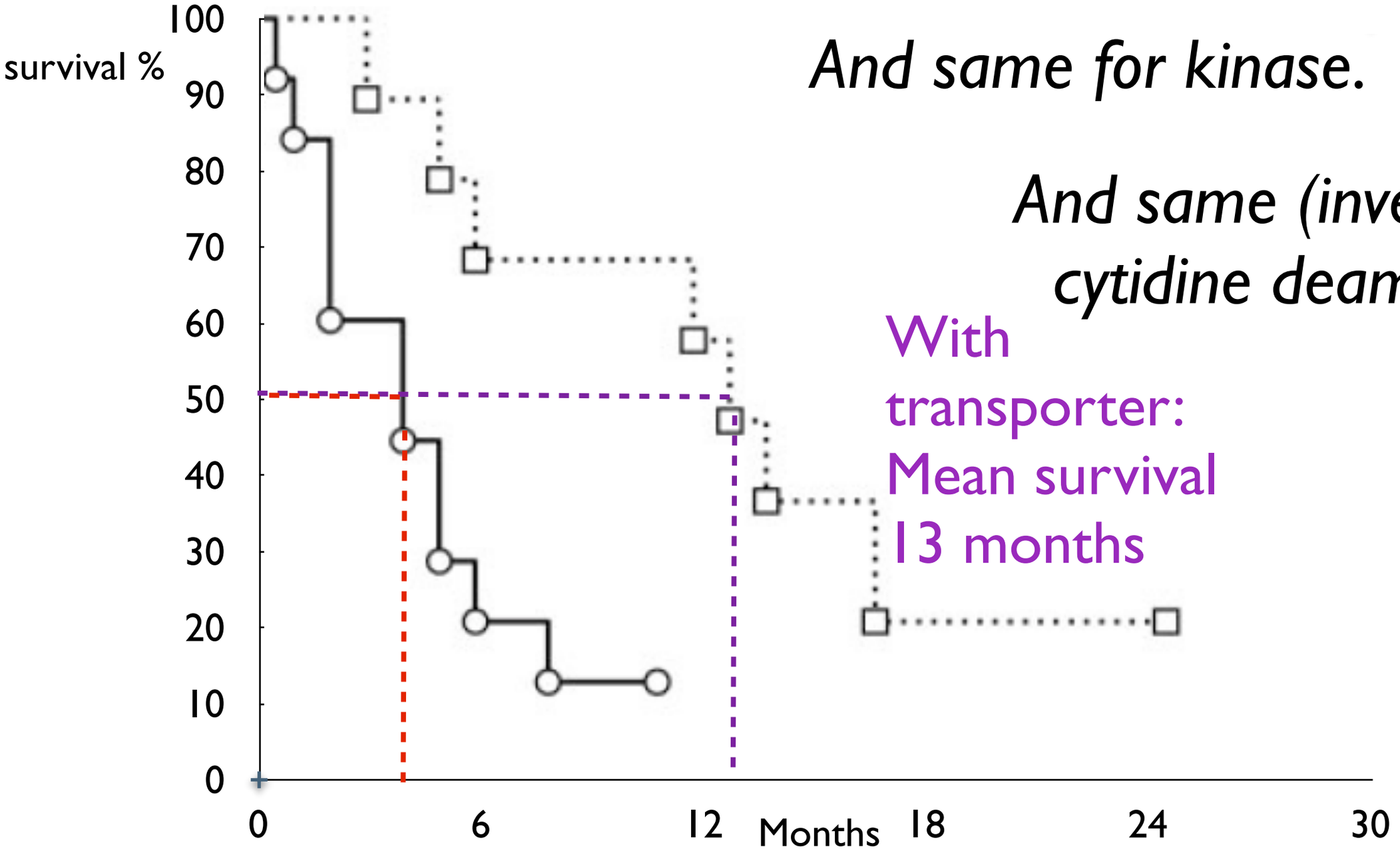
Ziagen



Gemcitabine



The Absence of Human Equilibrative Nucleoside Transporter 1 Is Associated with Reduced Survival in Patients With Gemcitabine-Treated Pancreas Adenocarcinoma



And same for kinase.

And same (inverse) for cytidine deaminase.

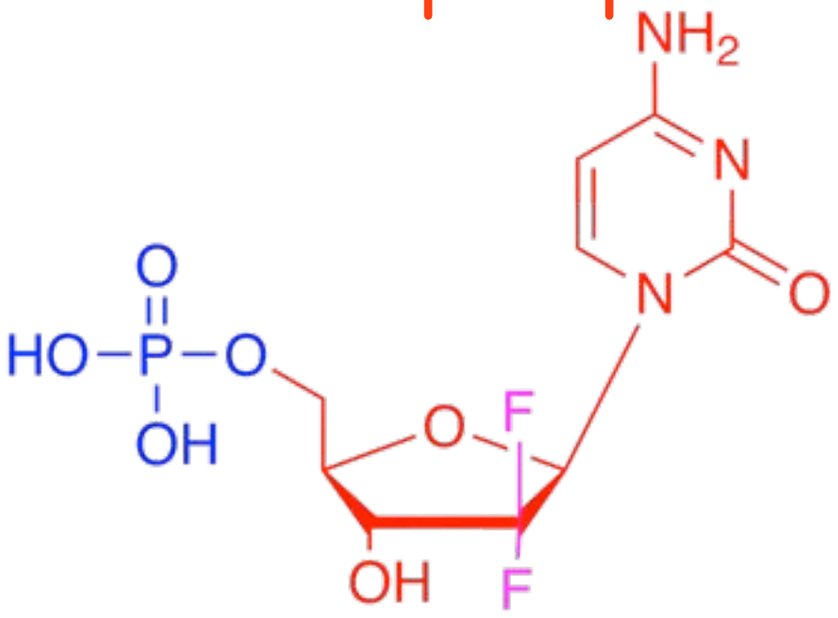
With transporter:
Mean survival 13 months

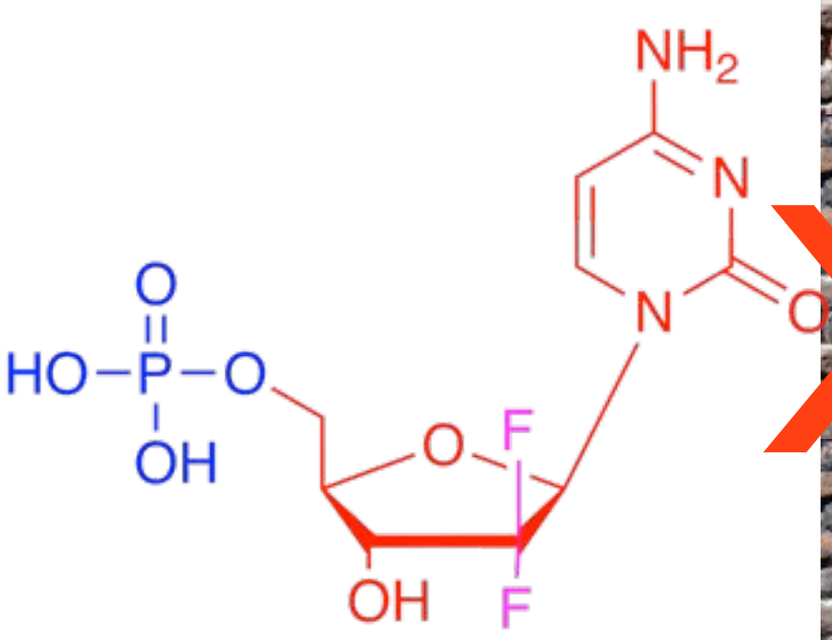
Without transporter:
Mean survival 4 months

Clin Cancer Res 2004;10: 6956-6961.

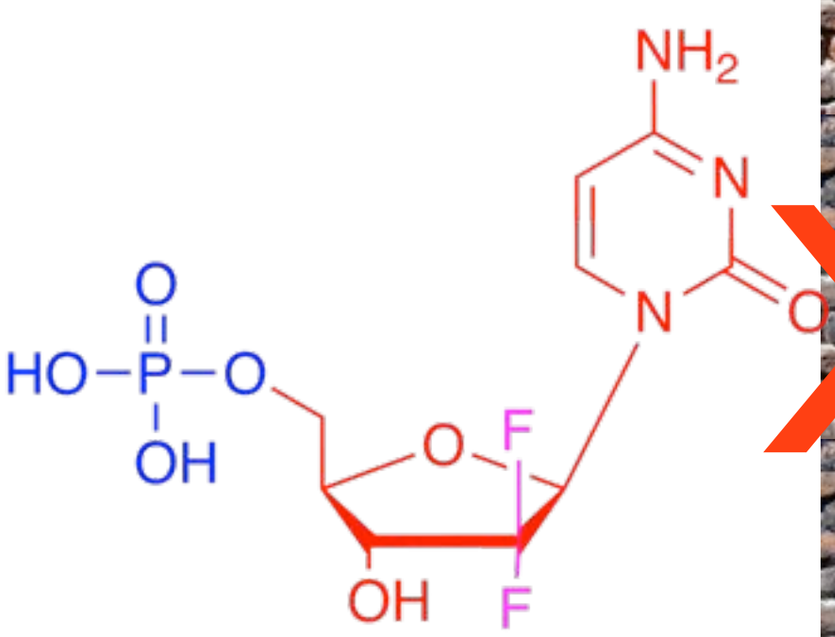
Jennifer Spratlin, Randeep Sangha, Darryl Glubrecht, et al.

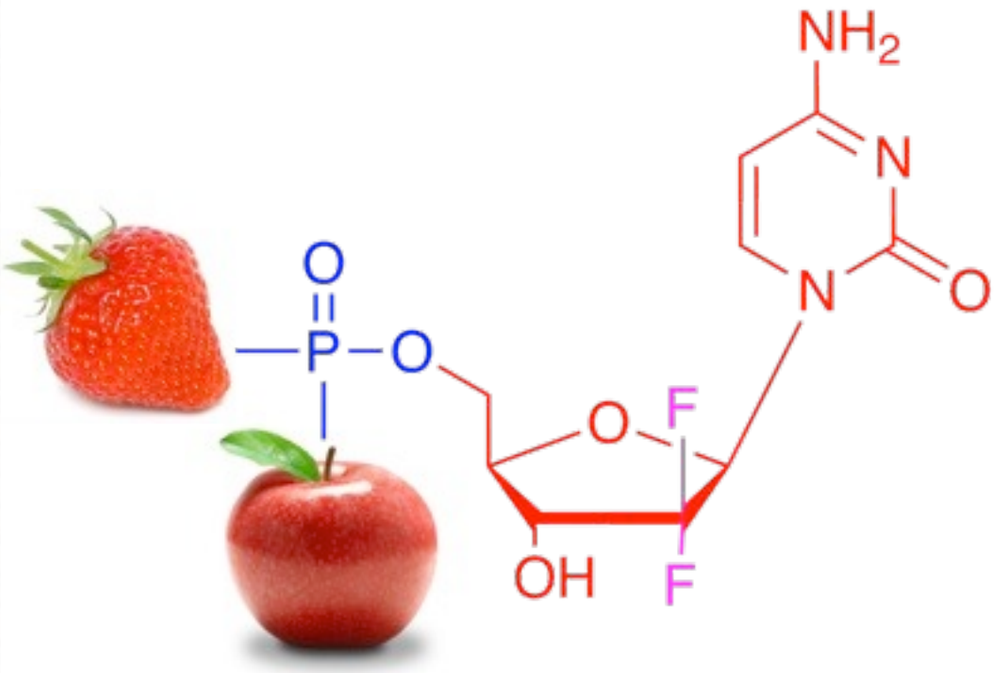
Why not use the pre-formed phosphate?

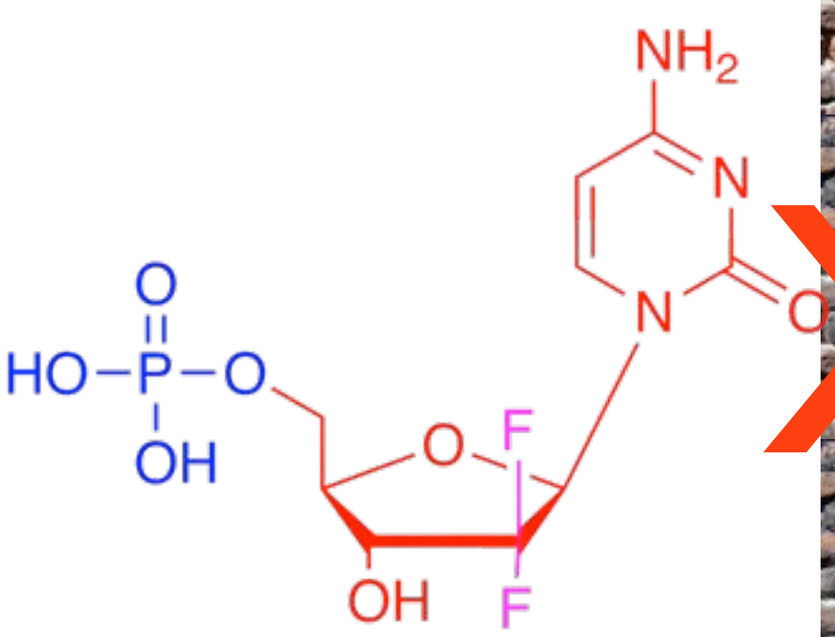


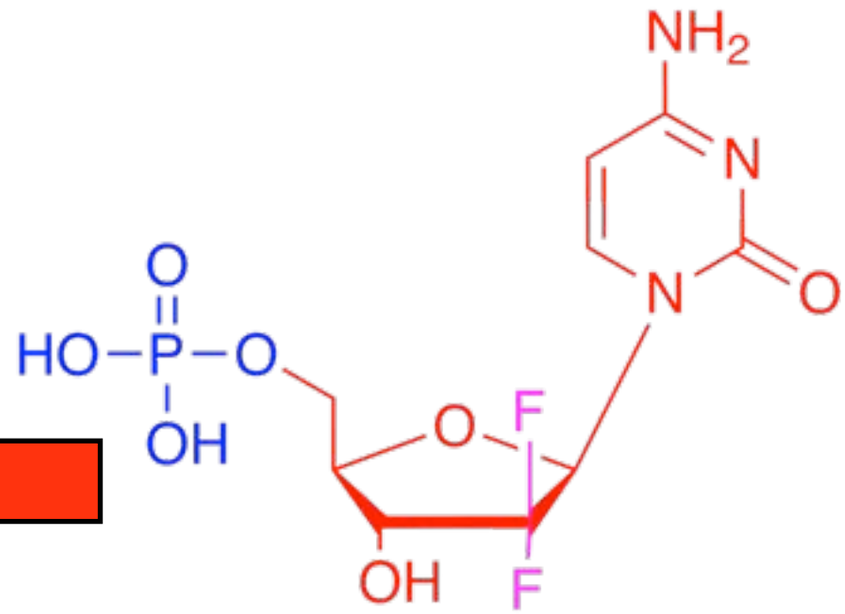


Lets try masking the charges?


NH2
N
N
O
O
HO
P
O
OH
O
F
OH
F


NH2
N
N
O
O
P
O
O
F
OH
F


NH2
N
N
O
HO
P
O
OH
O
F
OH
F


NH2
N
N
O
HO
P
O
OH
O
F
OH
F

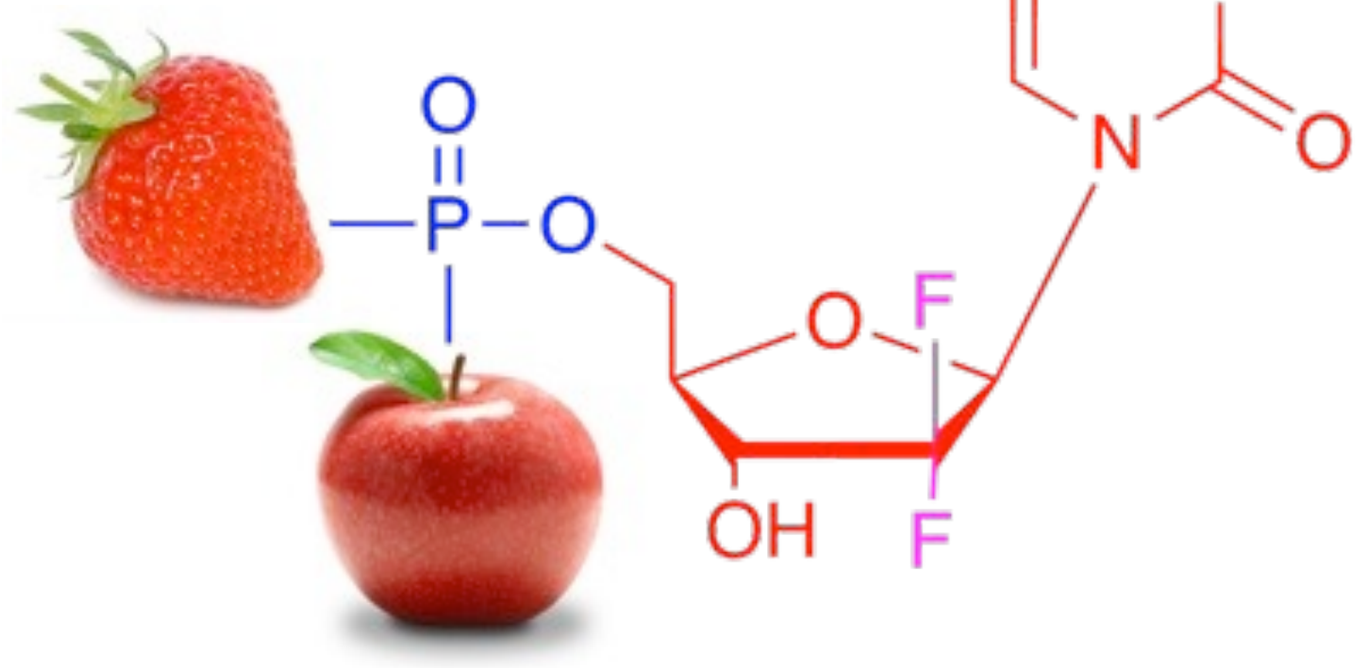
NH2
N
N
O
O
P
O
O
F
OH
F

"ProTides"

Properties of the blocking groups?

Requirements:

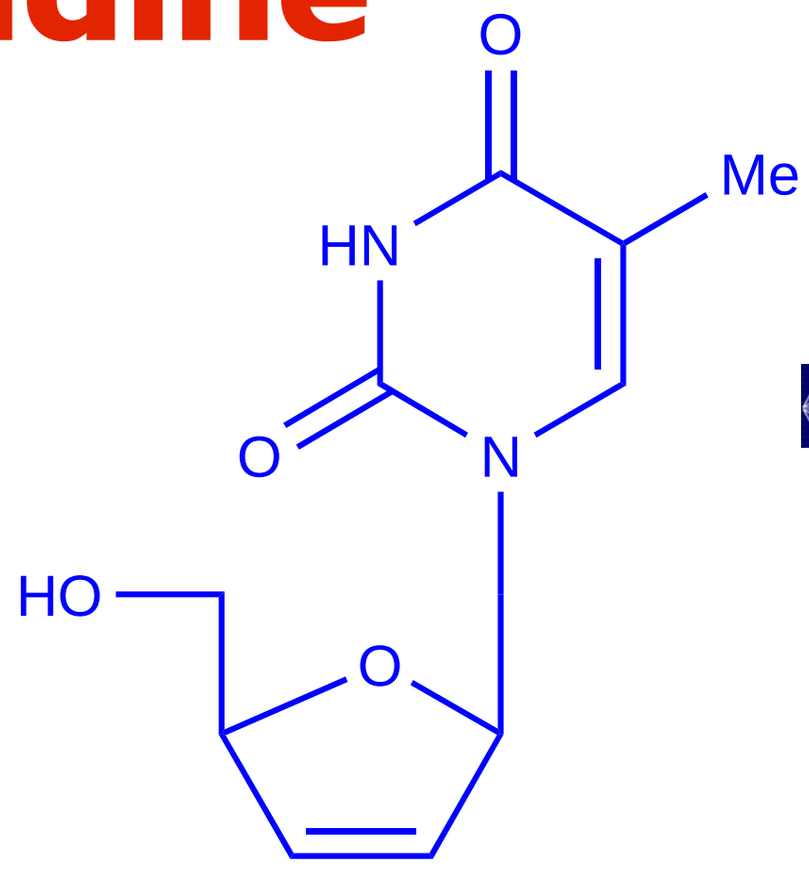
- Lipophilic ✓
- Stable in plasma ✓
- Hydrolyse in cells ✓
- Byproducts non-toxic ✓



Desirable:

- *More rapid hydrolysis in target cells.* ?

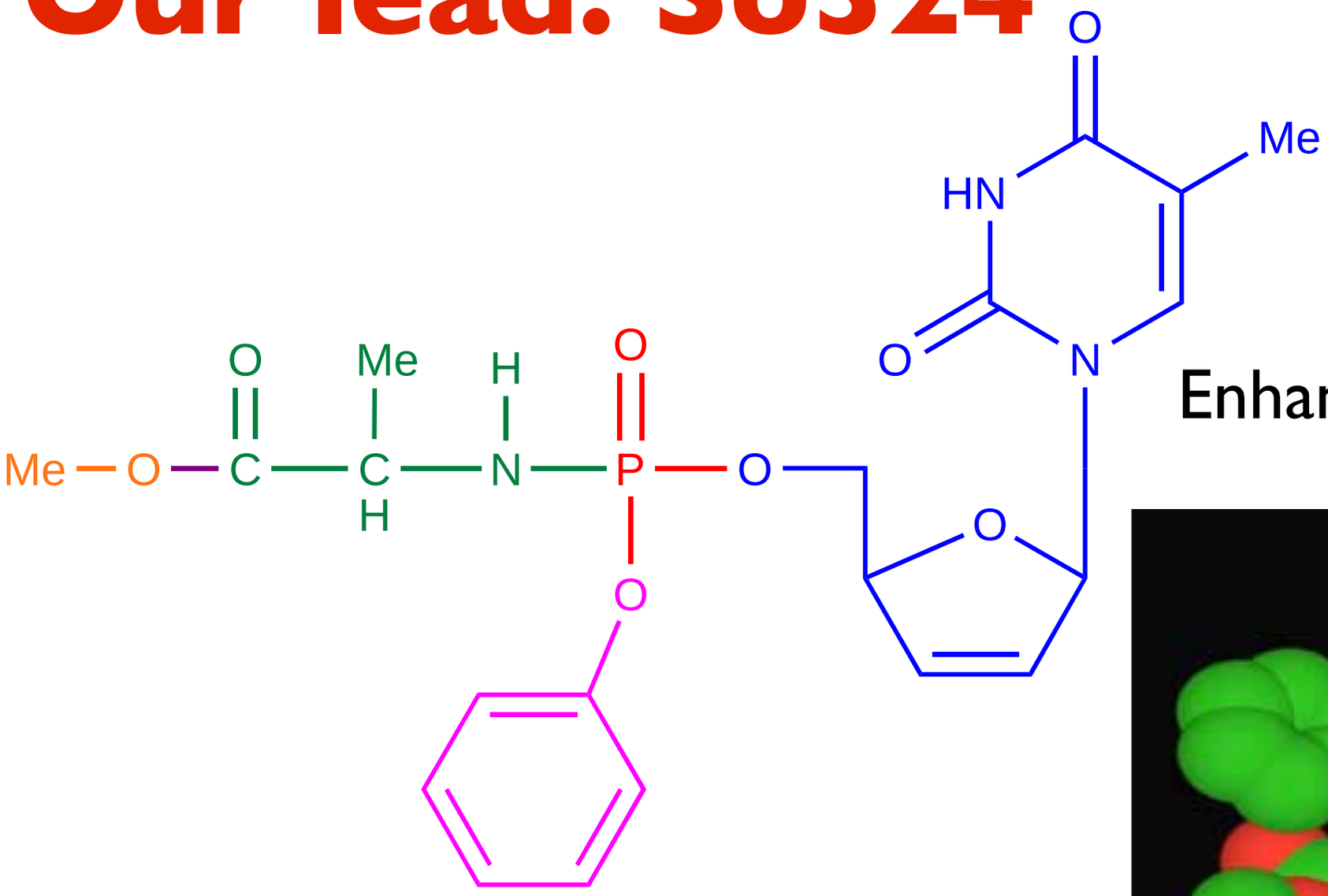
d4T: Stavudine



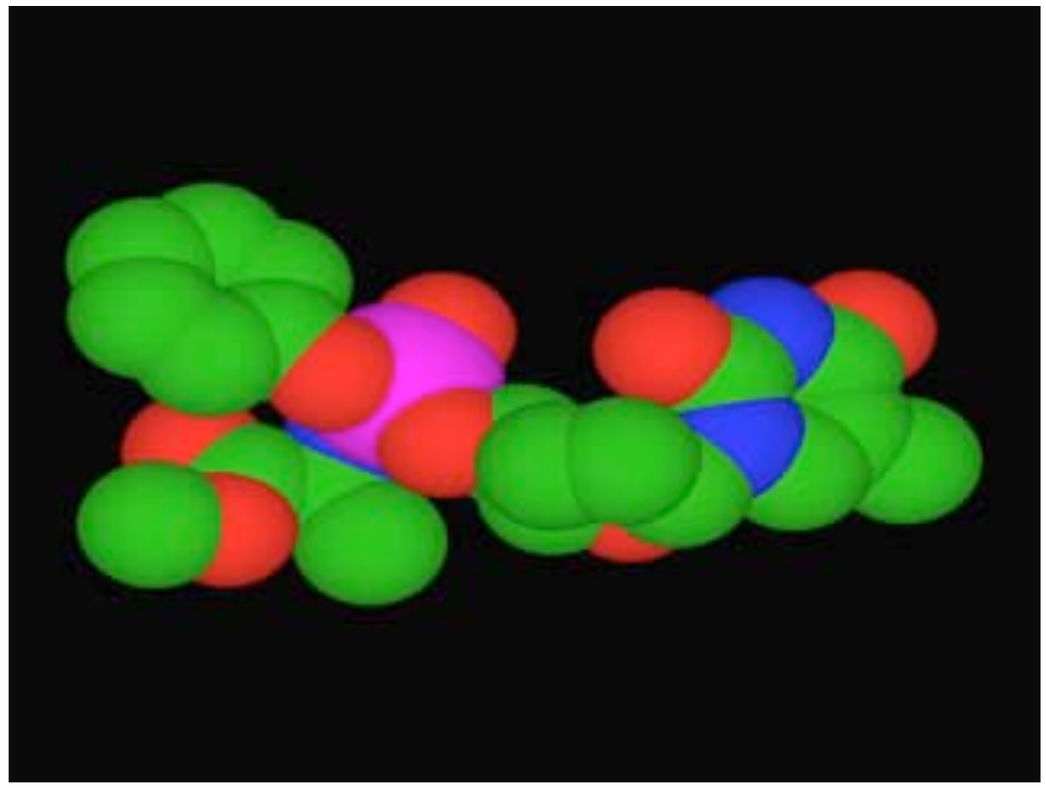
Bristol-Myers Squibb Company

anti-HIV

Our lead: So324



Enhanced anti-HIV?



GB Patent appl. 9505025, Mar 13 1995
McGuigan, J Med Chem, 1996, 39, 1748

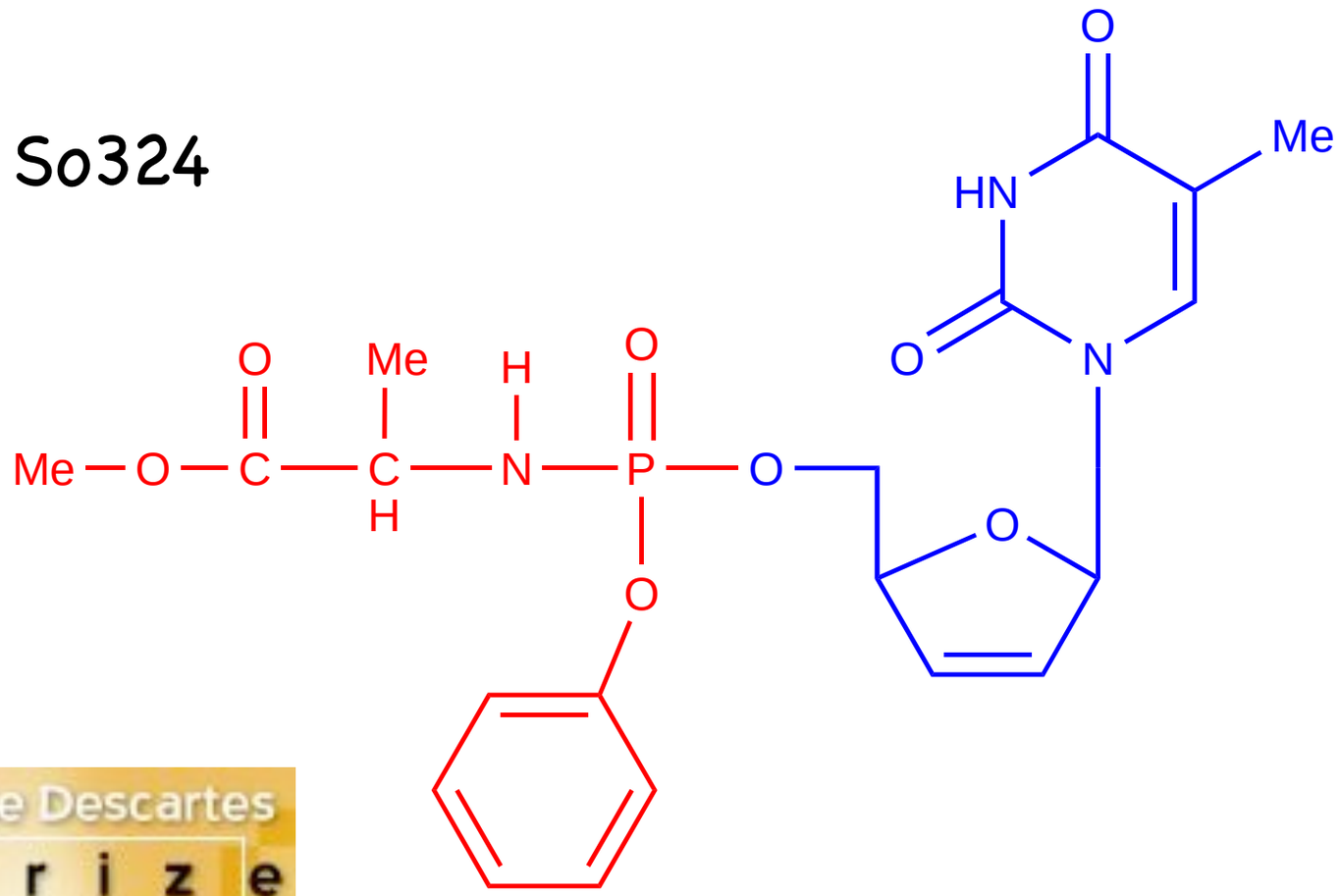
US006455513B1

(12) **United States Patent**
McGuigan et al.

(10) **Patent No.: US 6,455,513 B1**
(45) **Date of Patent: *Sep. 24, 2002**

Anti-HIV Activity in Cells:

So324

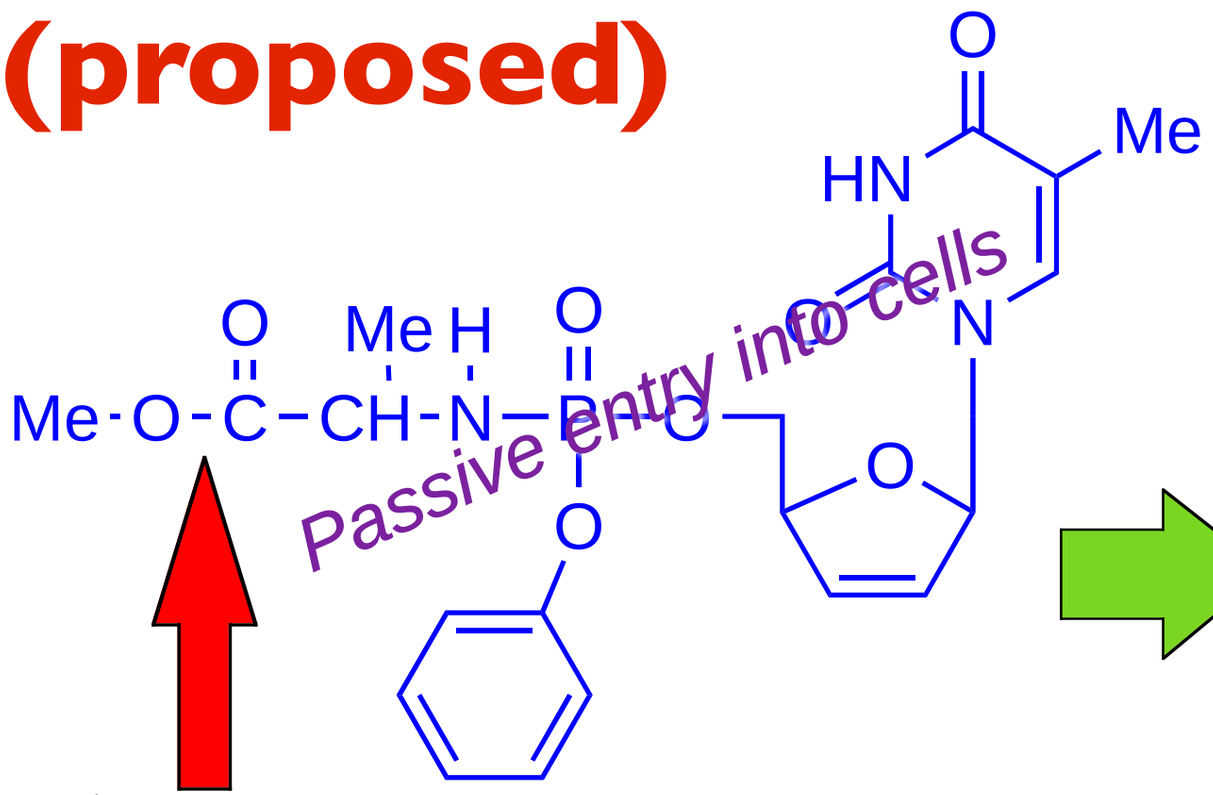


So324 became an important lead for us. The EU Descartes Prize 2001 was awarded in part for this collaboration.

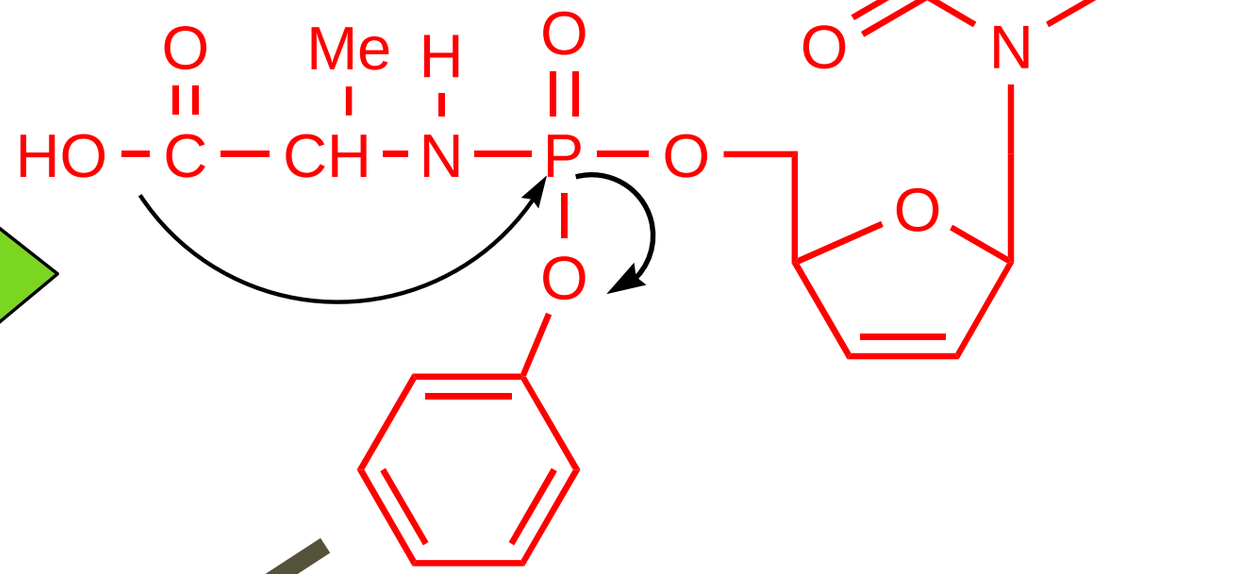
Cpd	EC_{50} µM HIV2/TK$^+$	EC_{50} µM HIV2/TK$^-$
d4T	0.8	25
So324	0.075	0.075
		333

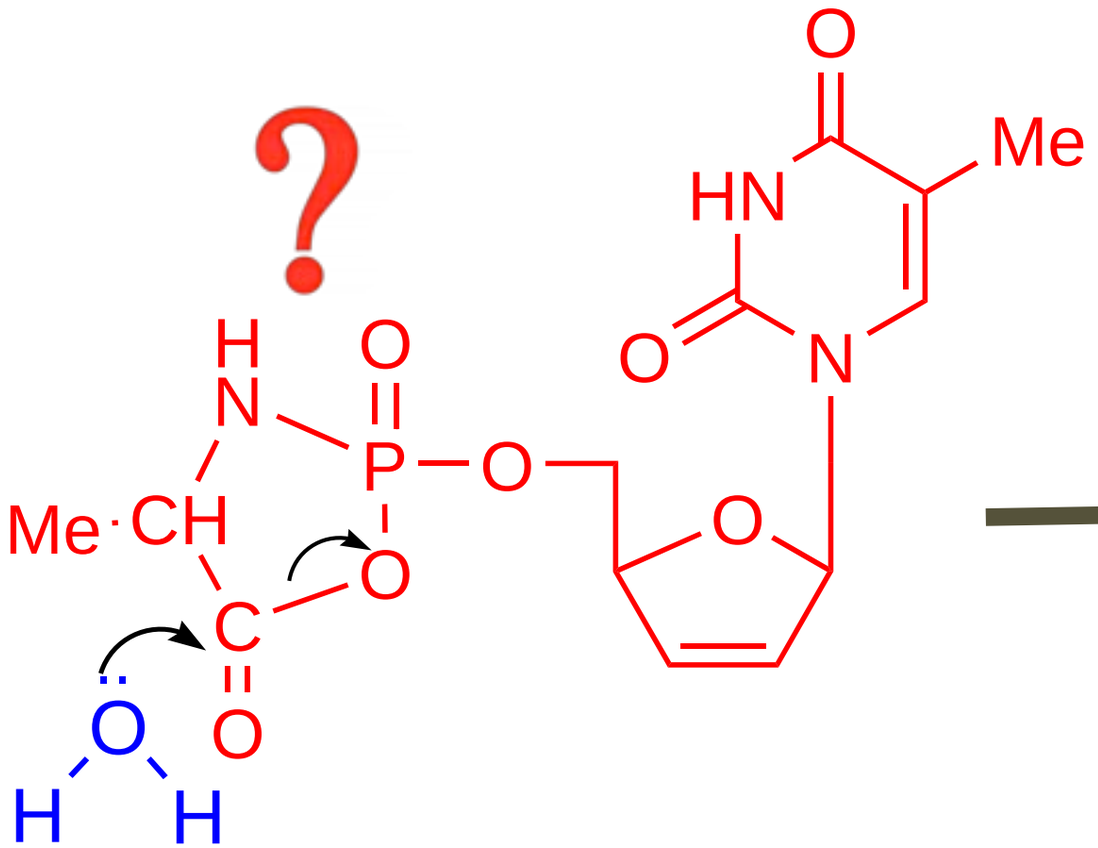
But - does it work by phosphate delivery into cells?

Mechanism of Action (proposed)



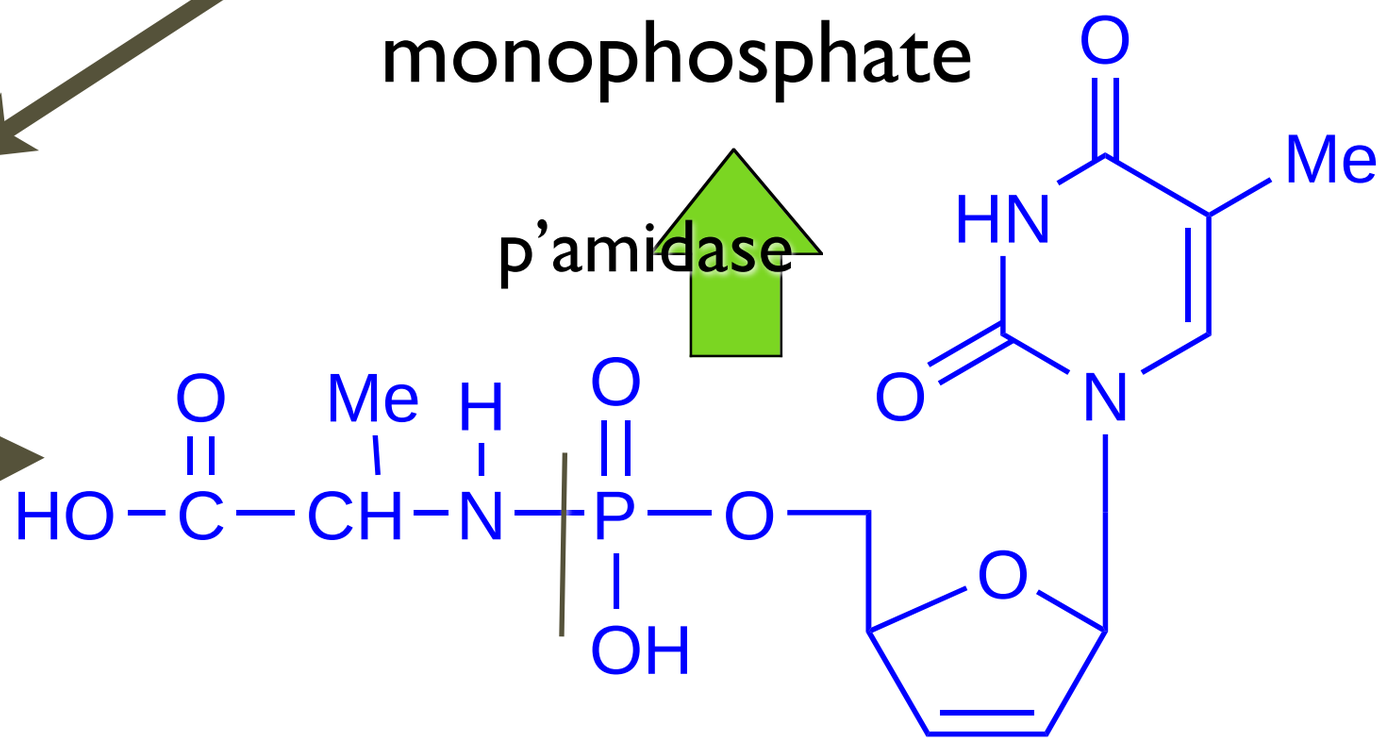
esterase or peptidase





monophosphate

p'amidase

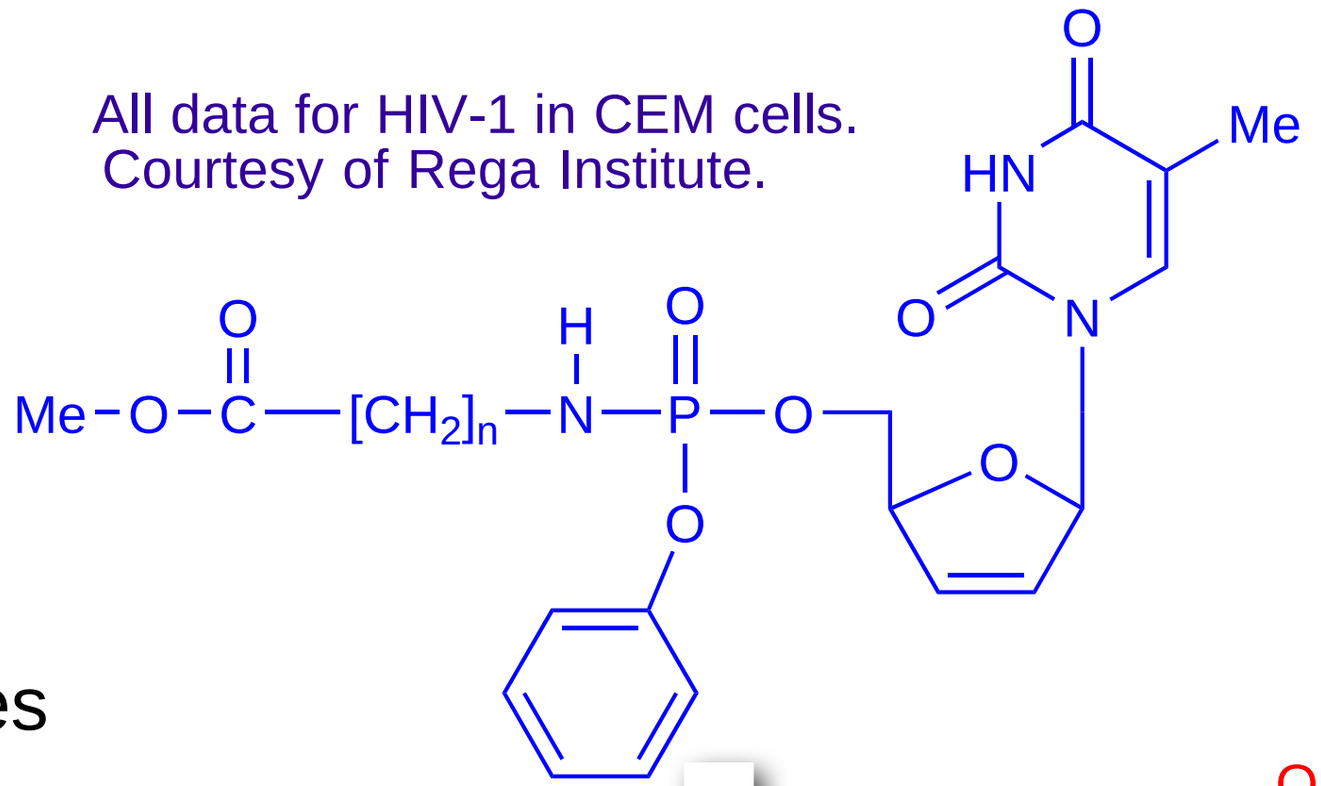


Some Evidence for This Mechanism

80-fold worse than Ala!

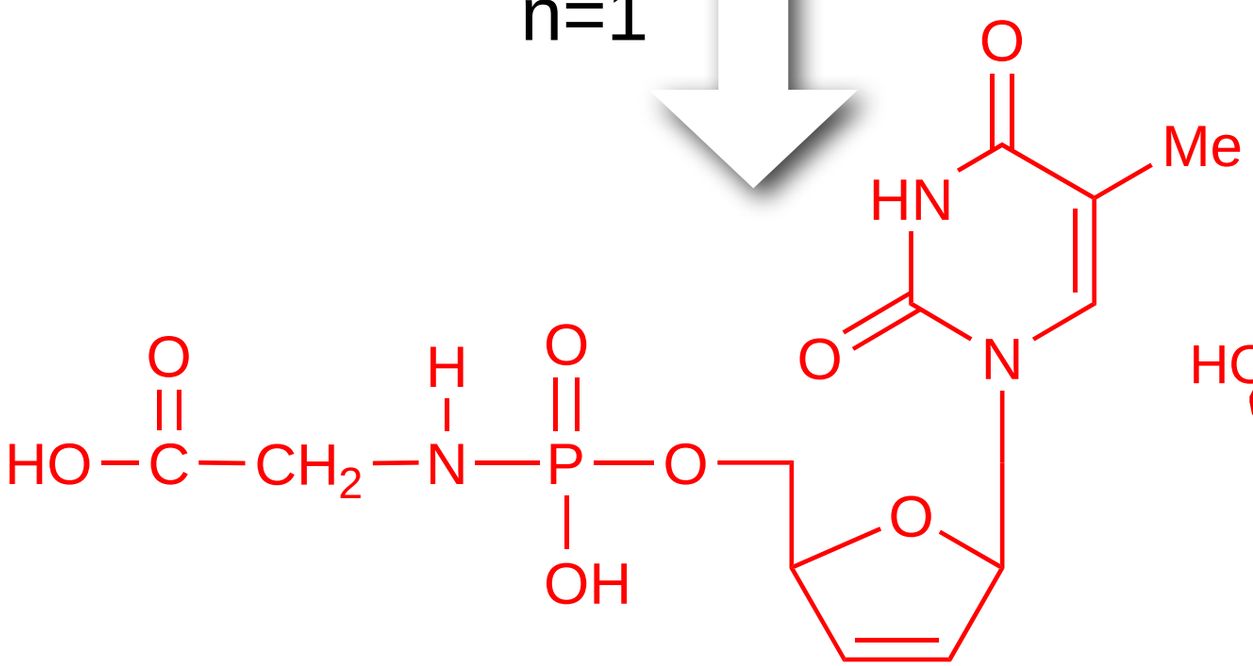
n	Cpd	EC_{50}
1	Cf866	6
2	Cf1197	>250

All data for HIV-1 in CEM cells.
Courtesy of Rega Institute.

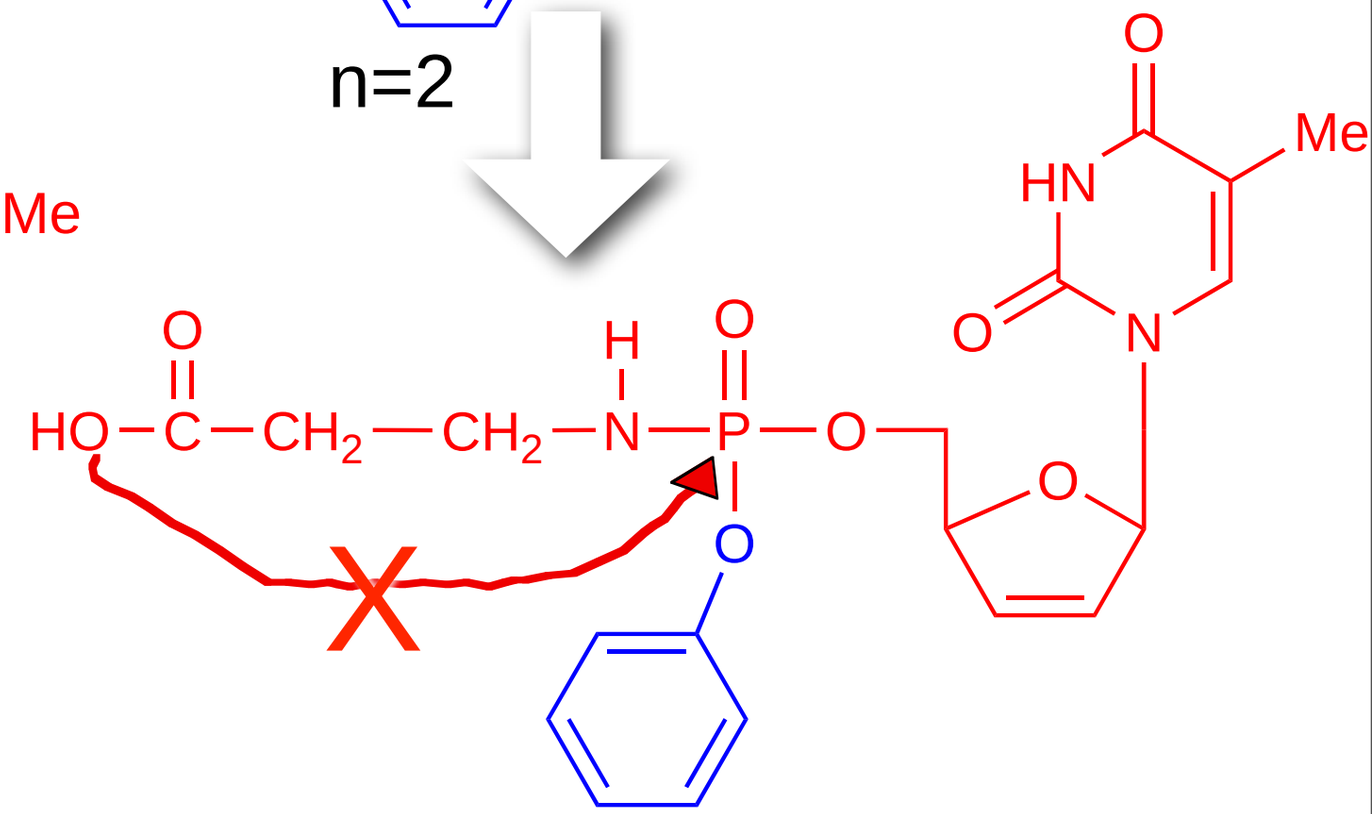


esterases

n=1



n=2



Acid stability

SGF
pH 1.2
37 C

2h:
ca 90-95%

4936266
4930518
4932279
4936265

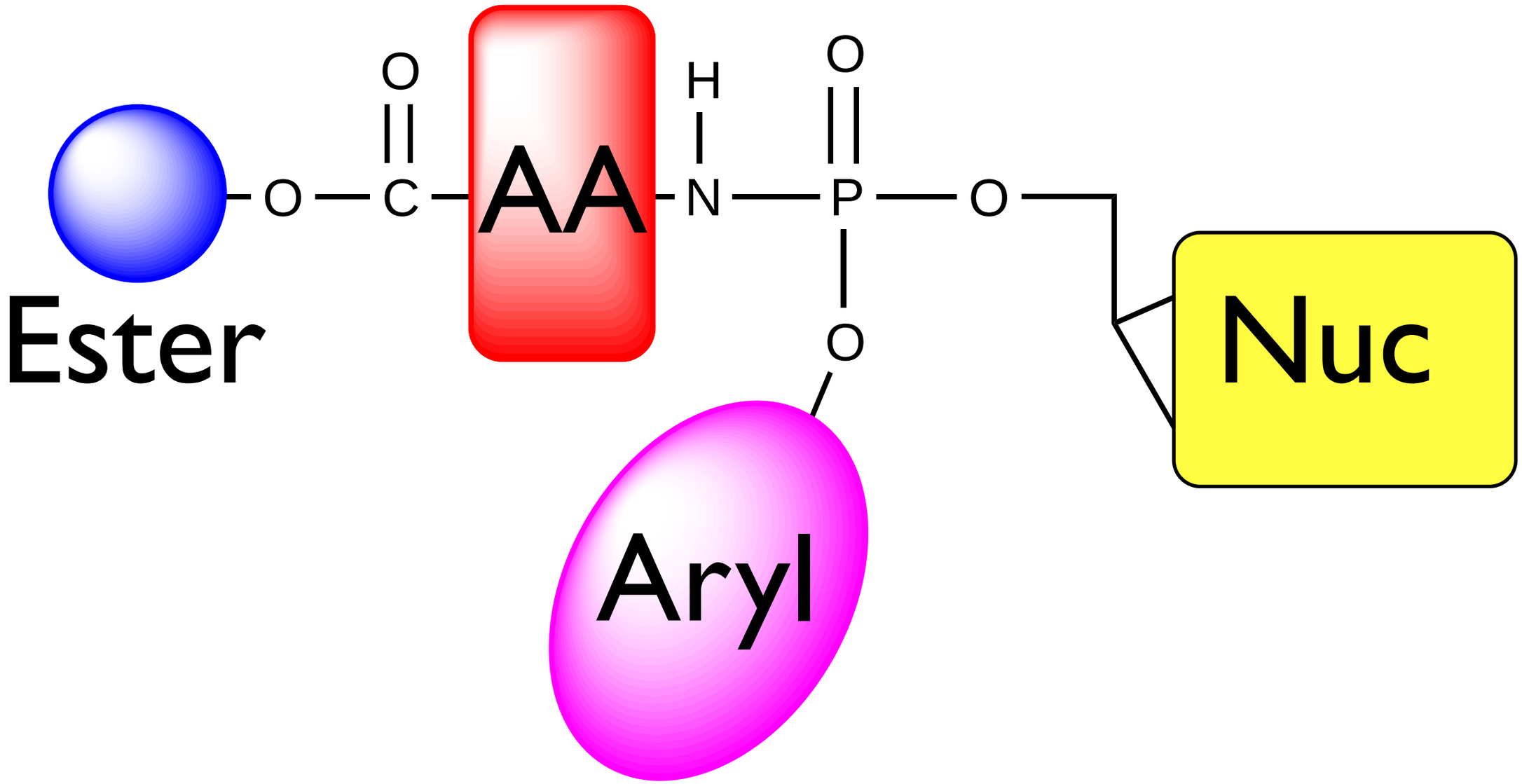
%Remaining by Peak Area

120
100
80
60
40
20

-5
0
5
10
15
20
25

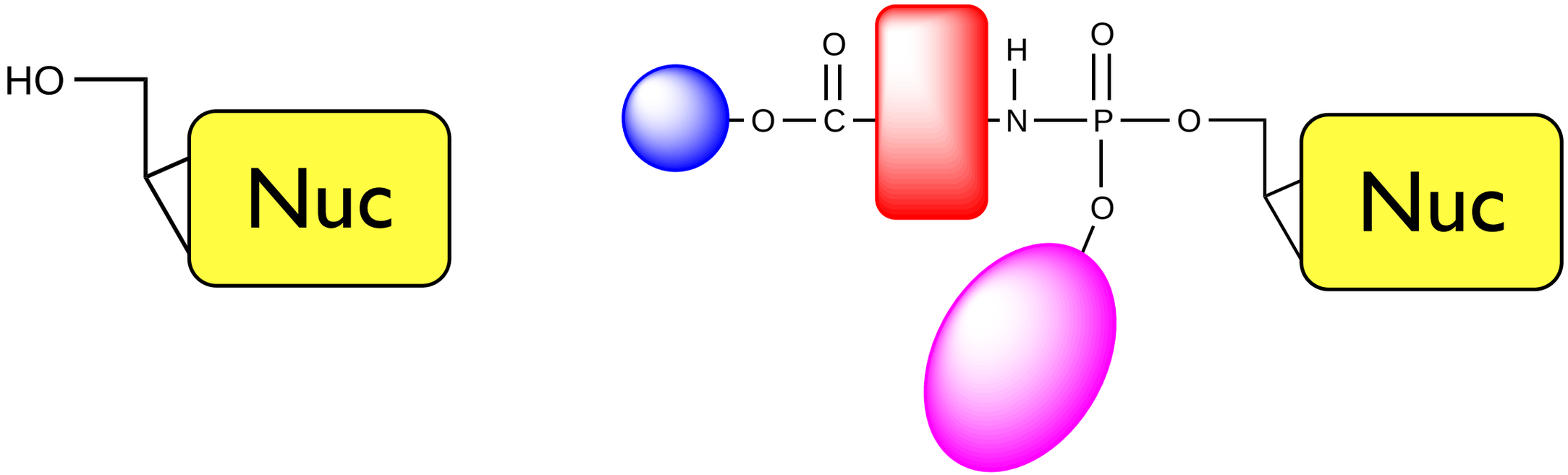
Time (hr)

Elements of a ProTide



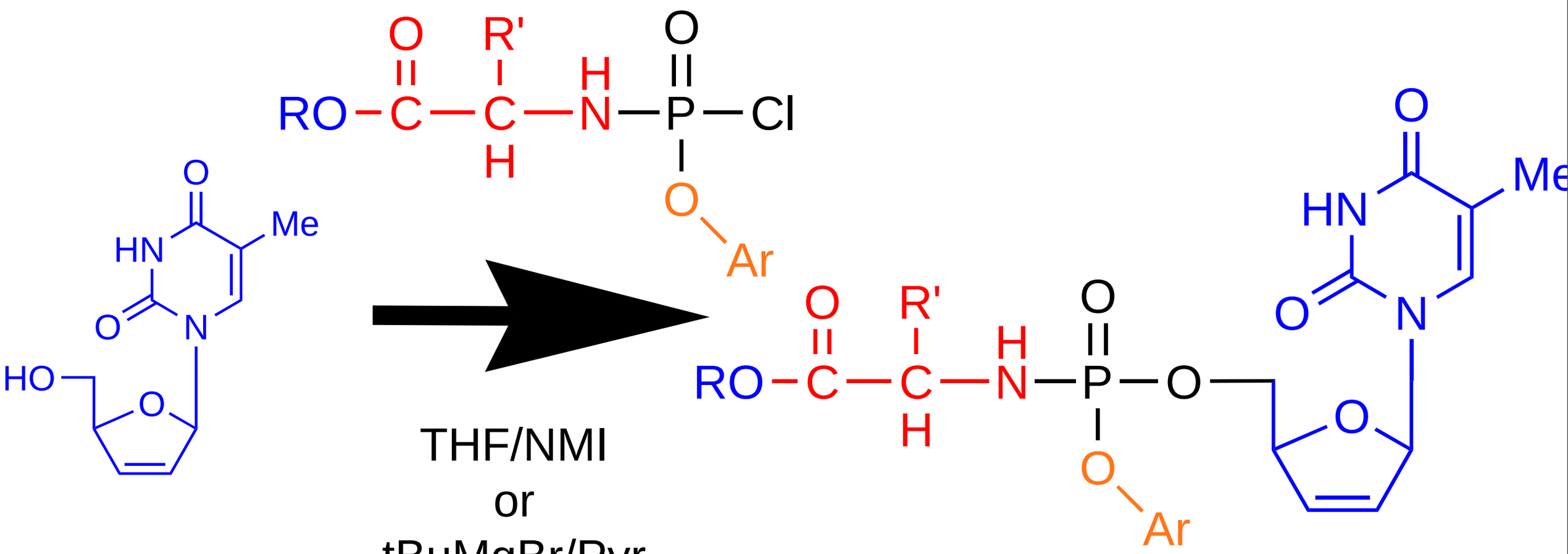
- A tunable delivery motif for any bio-active nucleoside.

Nucs and ProTides



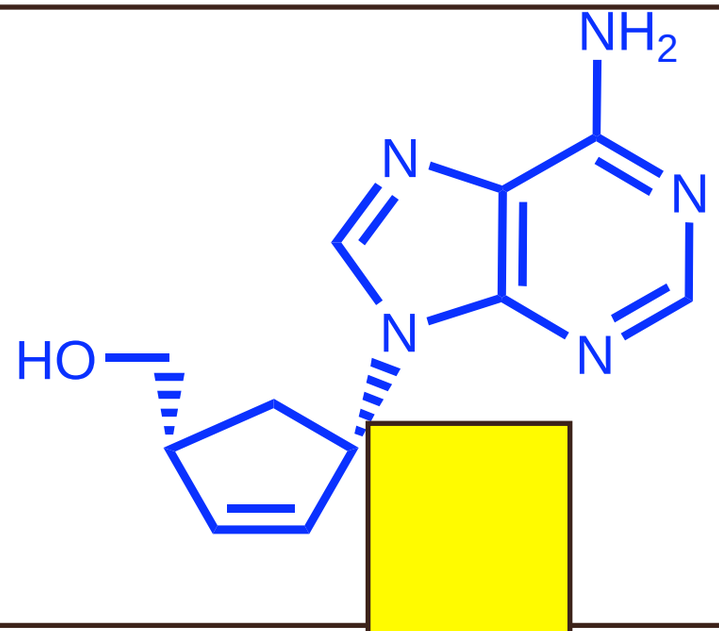
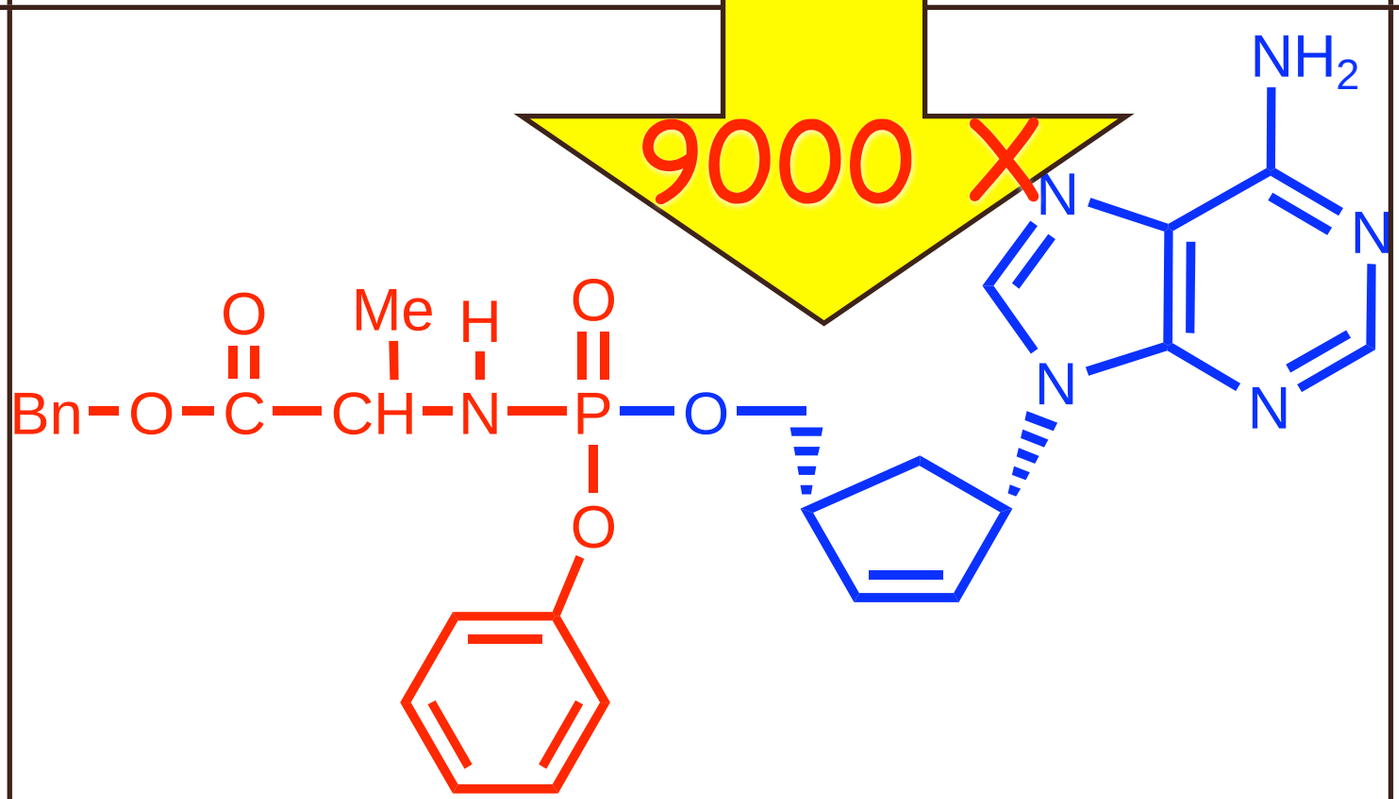
Nuc	ProTide
Transporter dependent	Transporter independent
Kinase dependent	Kinase independent
Subject to degradation	Resistant to degradation

Synthesis



- >250,000 analogues possible per nucleoside with proven variations; we have ppd ca. 5000 to date.
  - Works on free deoxy and ribo purines and pyrimidines.
  - Purification can be lengthy.
  - Sometimes Nuc protection useful.

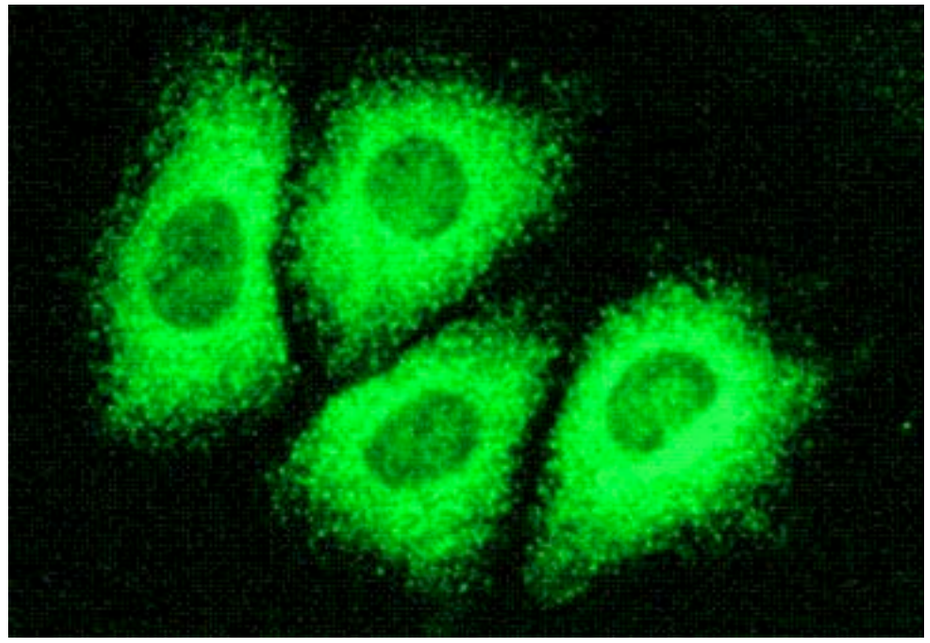
Application to LCd4A

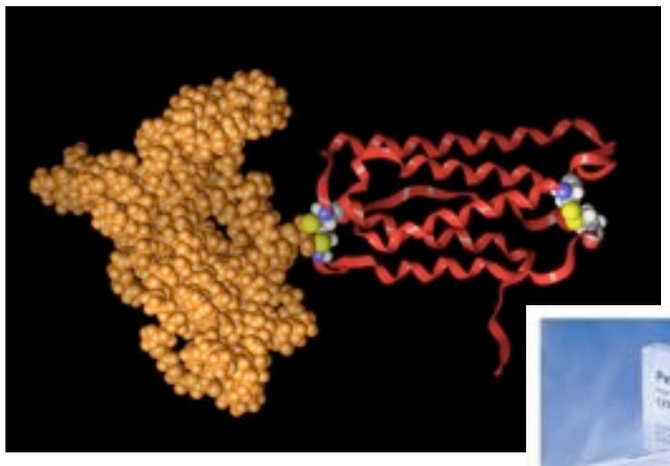
		EC50/μM HIV-1
LCd4A 		80
583004X		0.009

McGuigan et al, J. Med. Chem., 2006, 49, 7215.

Hepatitis C virus HCV

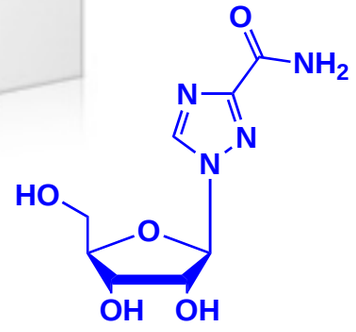
- ca 170M infections worldwide: ca 3% of the World's population.
- ca 3-4M in USA, 250K in UK.
- Standard therapy Rbv / peg-INF plus PIs





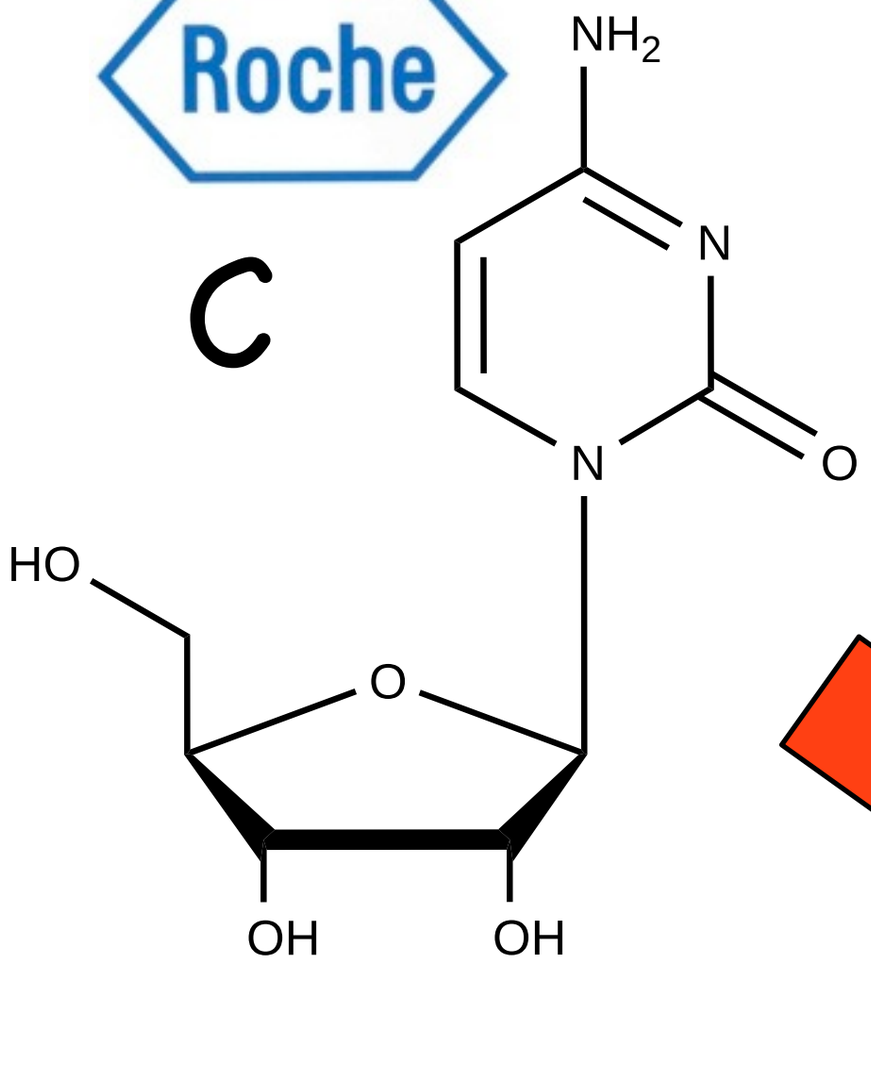
PEG-INF

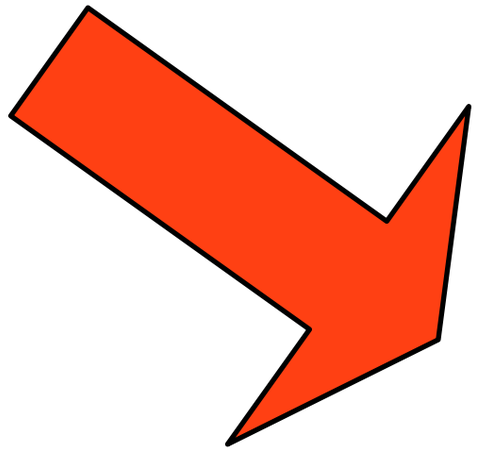
Ribavirin

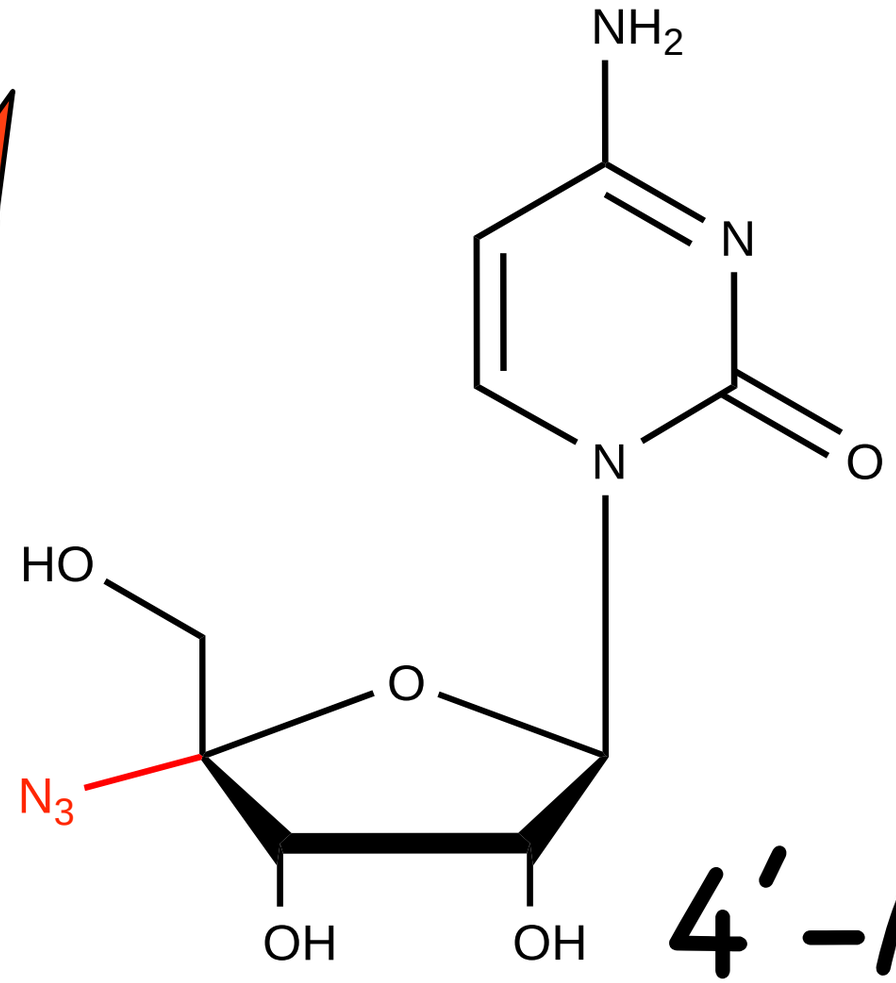


Roche

C





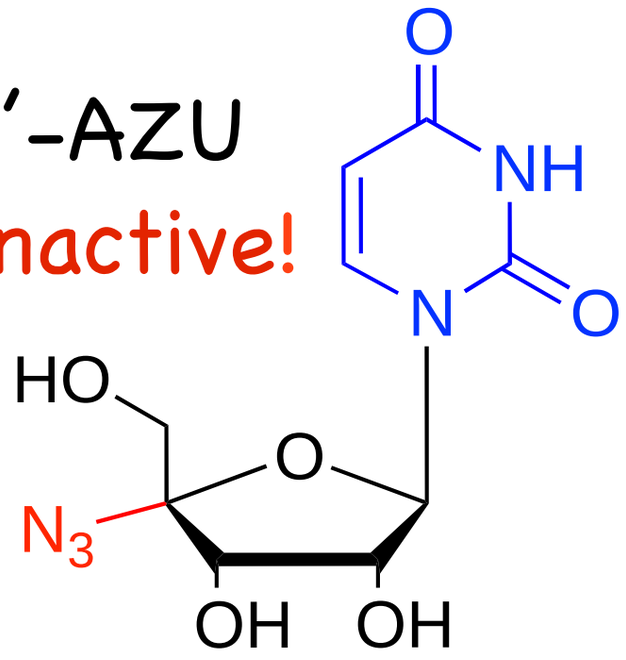


4′-AZC

Roche Palo Alto / Cardiff Collaboration

4′-AZU

Inactive!



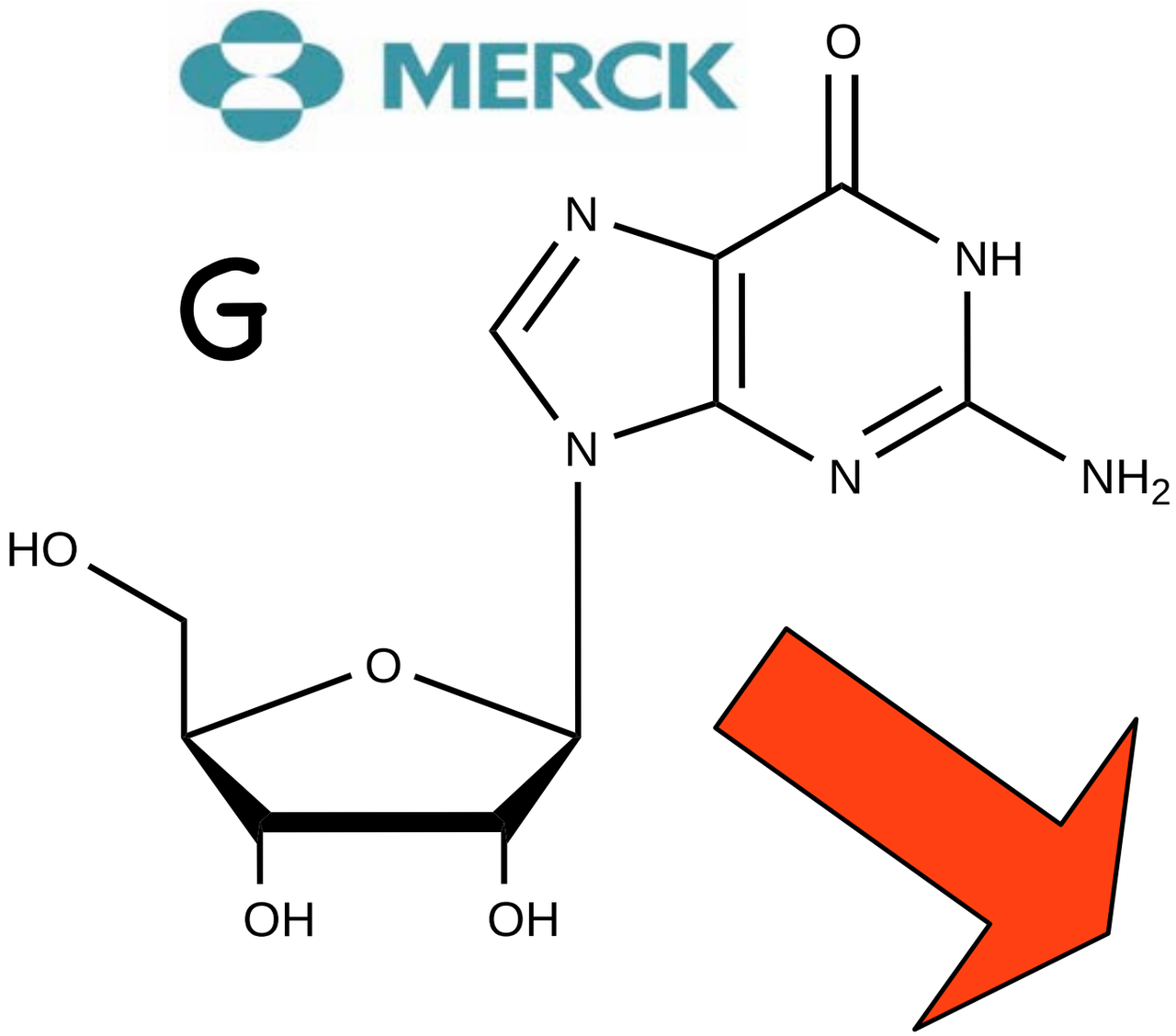
J. Med. Chem. **2007,** *50,* 1840−1849

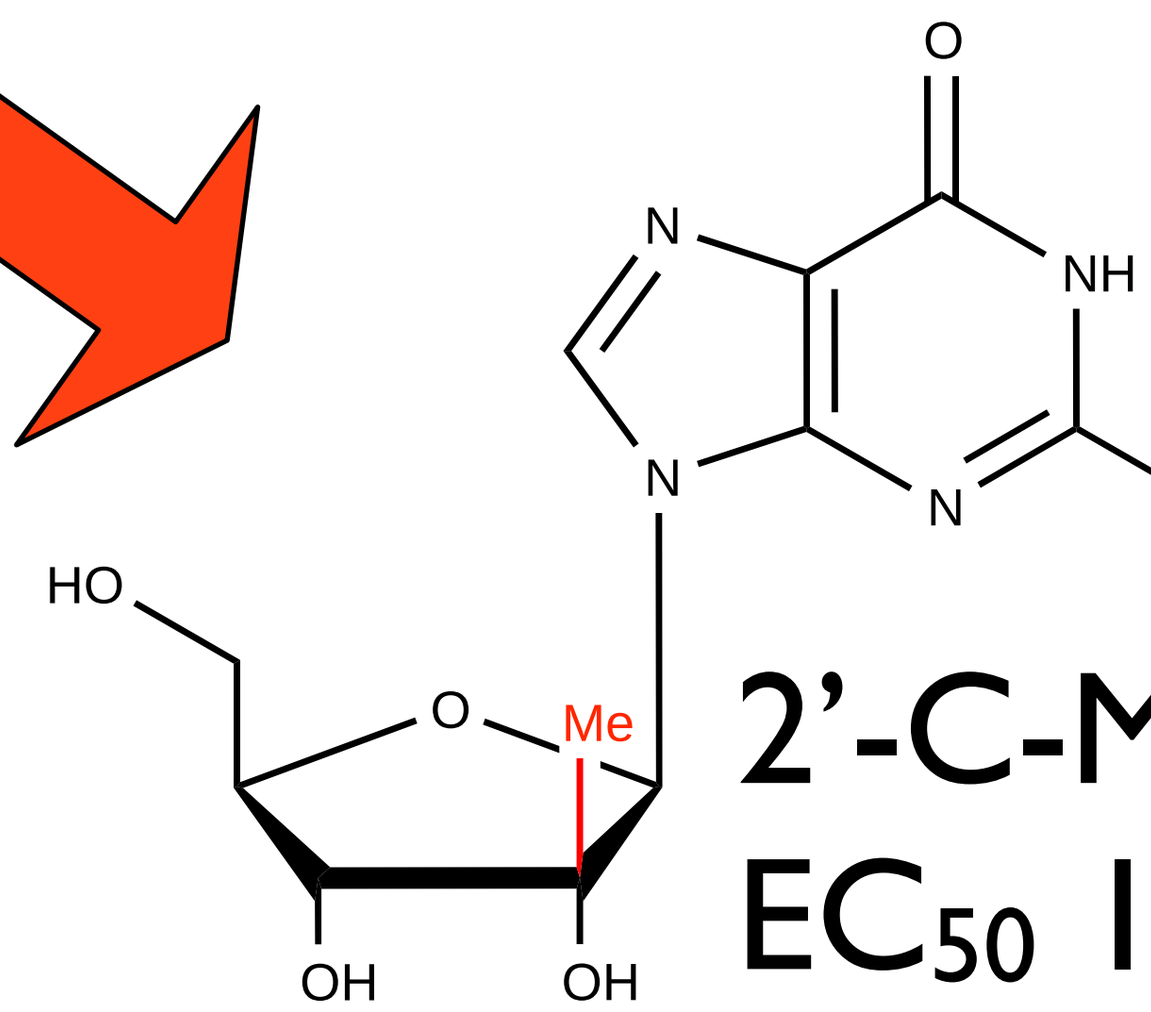
Application of the Phosphoramidate ProTide Approach to 4′-Azidouridine Confers Sub-micromolar Potency versus Hepatitis C Virus on an Inactive Nucleoside

Plinio Perrone,[†] Giovanna M. Luoni,[†] Mary Rose Kelleher,[†] Felice Daverio,[†] Annette Angell,[†] Sinead Mulready,[†] Costantino Congiatu,[†] Sonal Rajyaguru,[‡] Joseph A. Martin,[‡] Vincent Levêque,[‡] Sophie Le Pogam,[‡] Isabel Najera,[‡] Klaus Klumpp,[‡] David B. Smith,[‡] and Christopher McGuigan*,[†]

Welsh School of Pharmacy, Cardiff University, King Edward VII Avenue, Cardiff CF10 3XF, UK, and Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, California 94304

Received November 17, 2006





2’-C-MeG

EC_{50} 10μM

G family

Time h

13

8

1

0.25

0.2

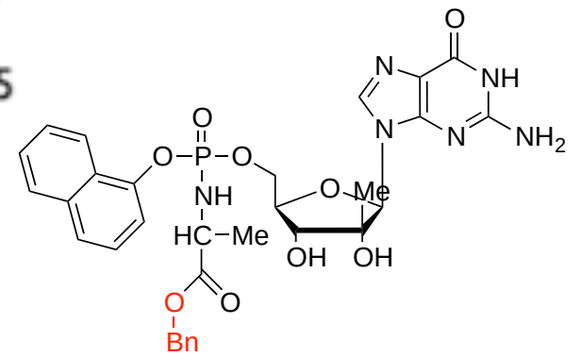
0.15

0

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

Bn ester

EC_{50} 0.1μM



2′-C-MeG 10μM

Time h

13

11

8

2.5

1.5

0.5

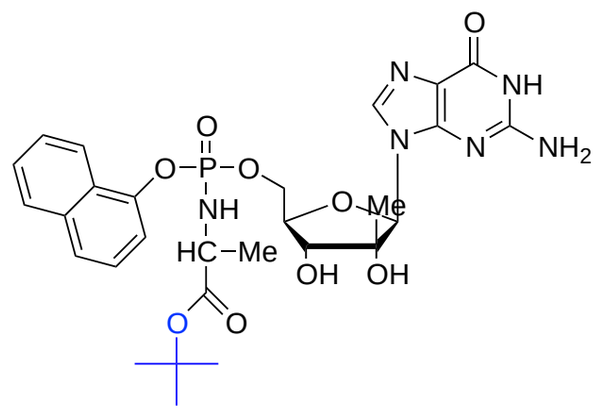
0

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

MERCK

tBu ester

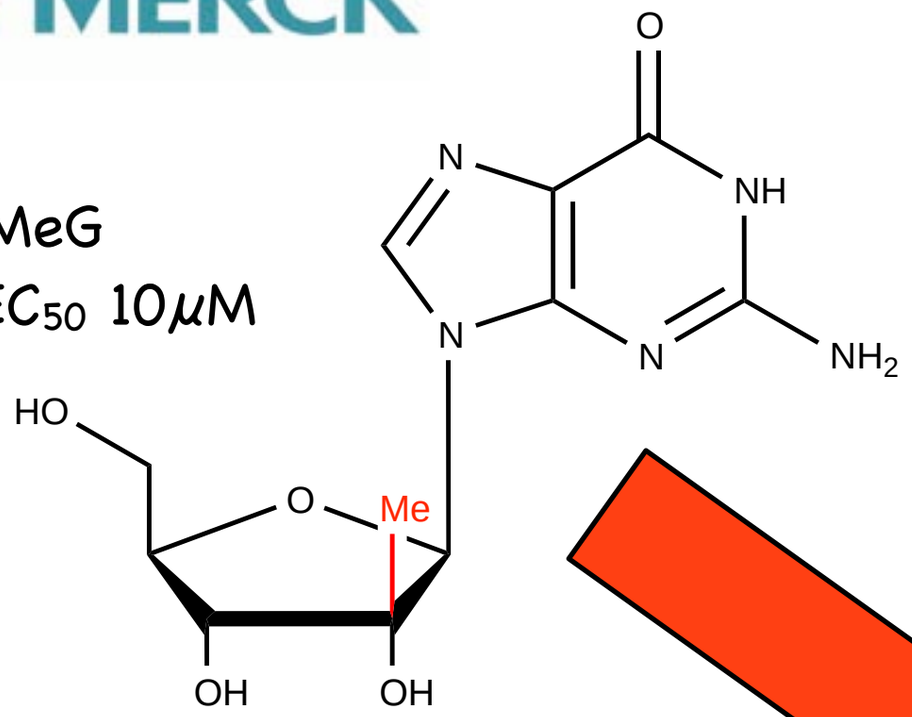
EC_{50} 27μM



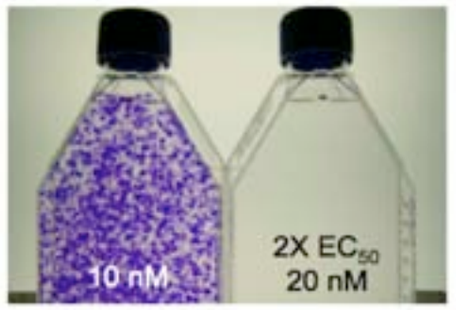
MERCK

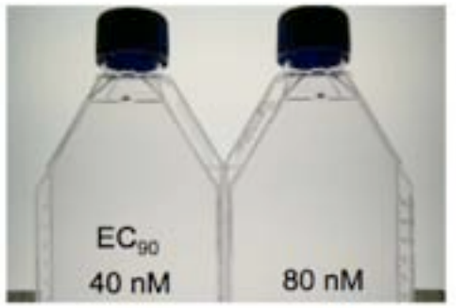
2′-C-MeG

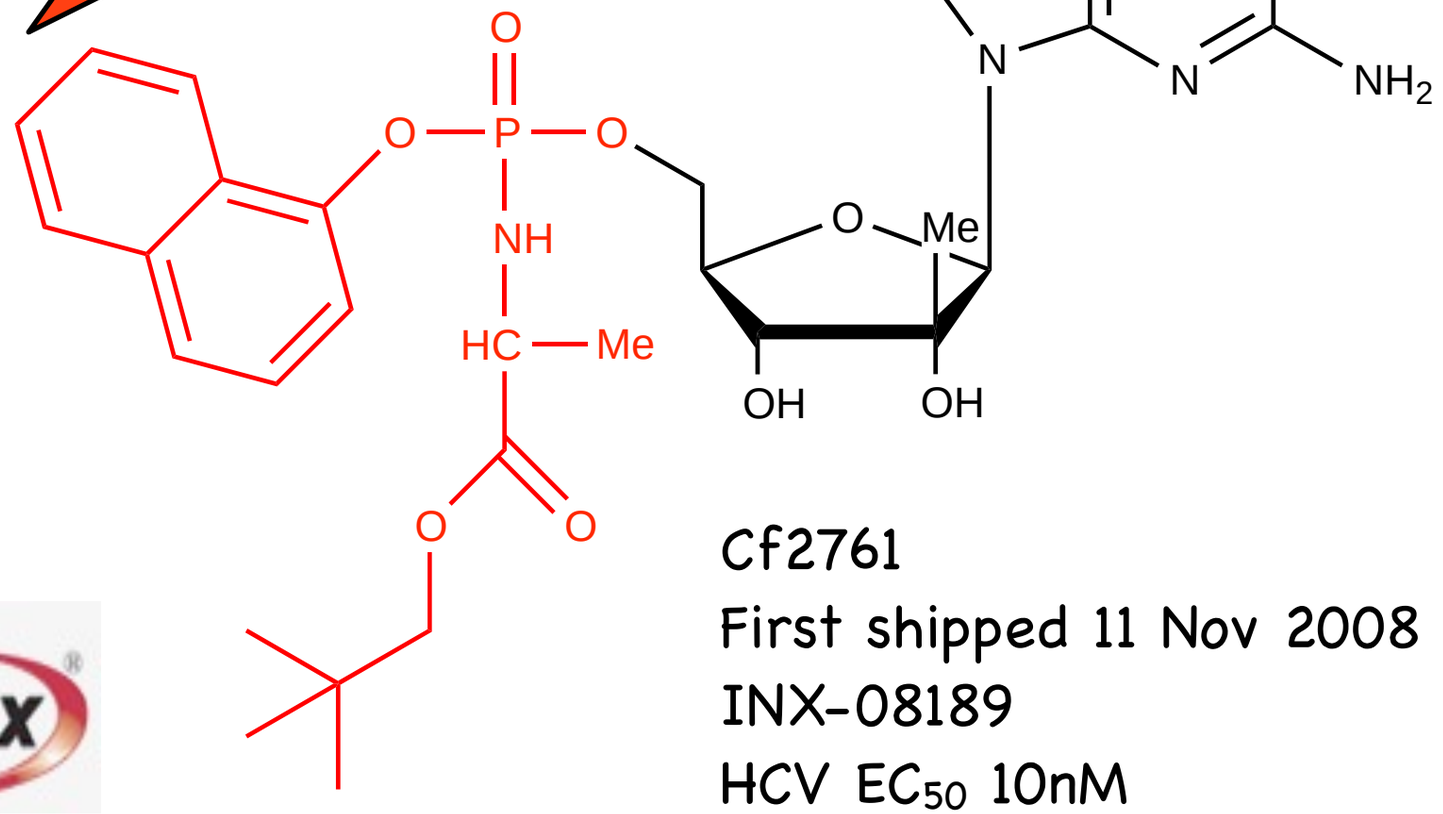
HCV EC_{50} 10μM



1000x in vitro







CARDIFF UNIVERSITY

inhibitex

Cf2761

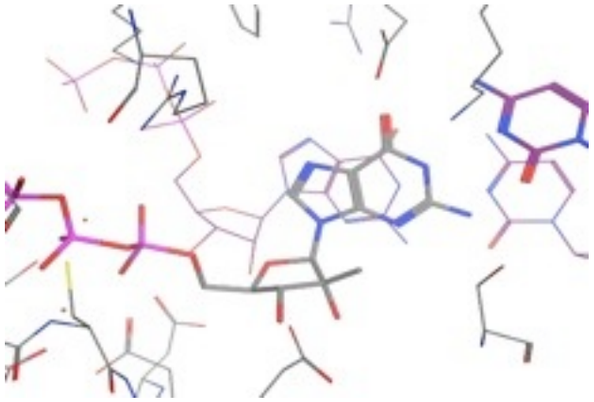
First shipped 11 Nov 2008

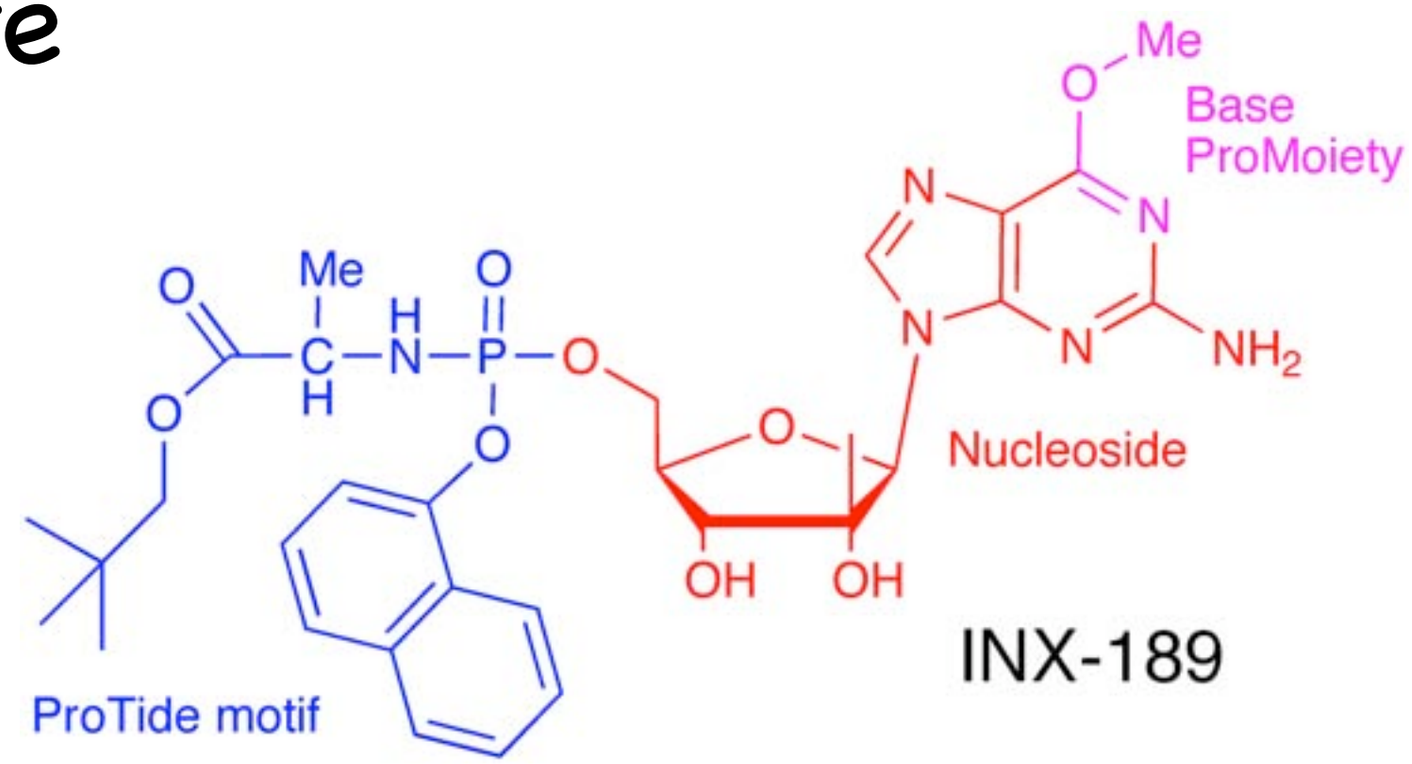
INX-08189

HCV EC_{50} 10nM

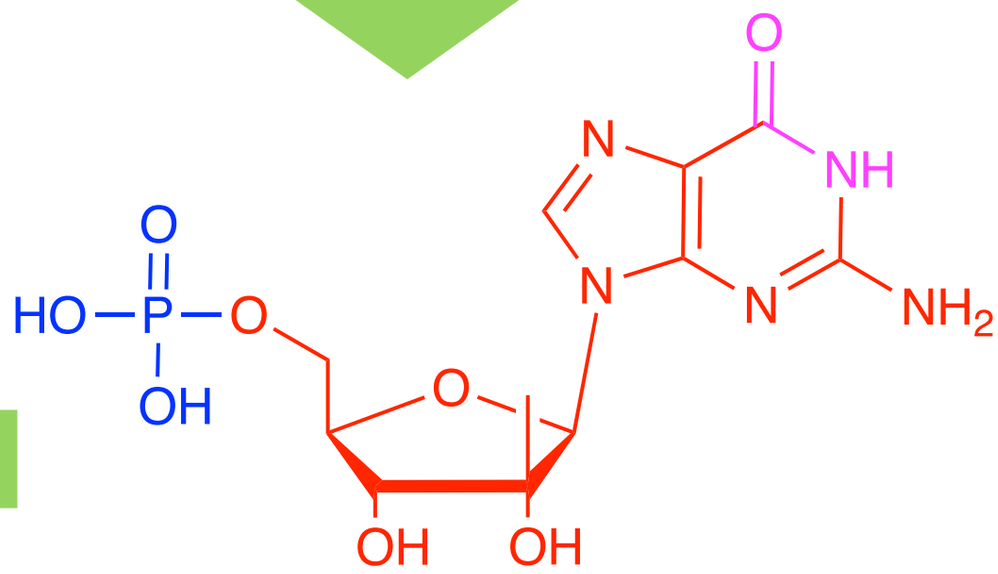
Clinical candidate INX-189

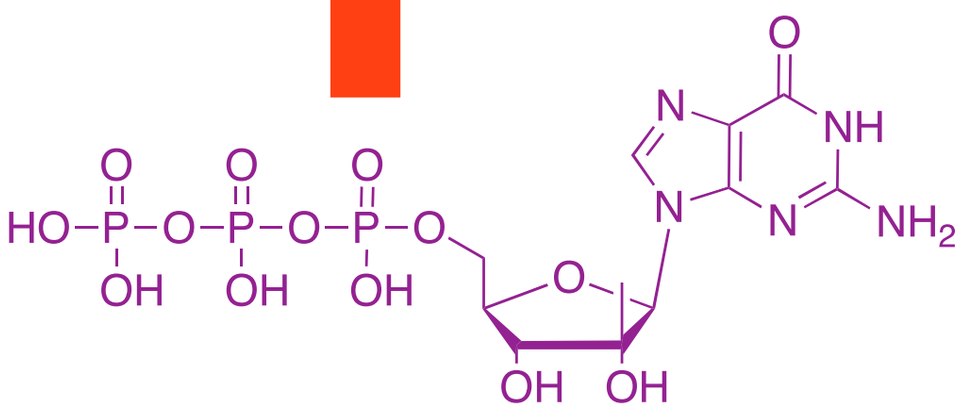
INX-189 was a novel dual pro-drug.





in vivo





Collaboration

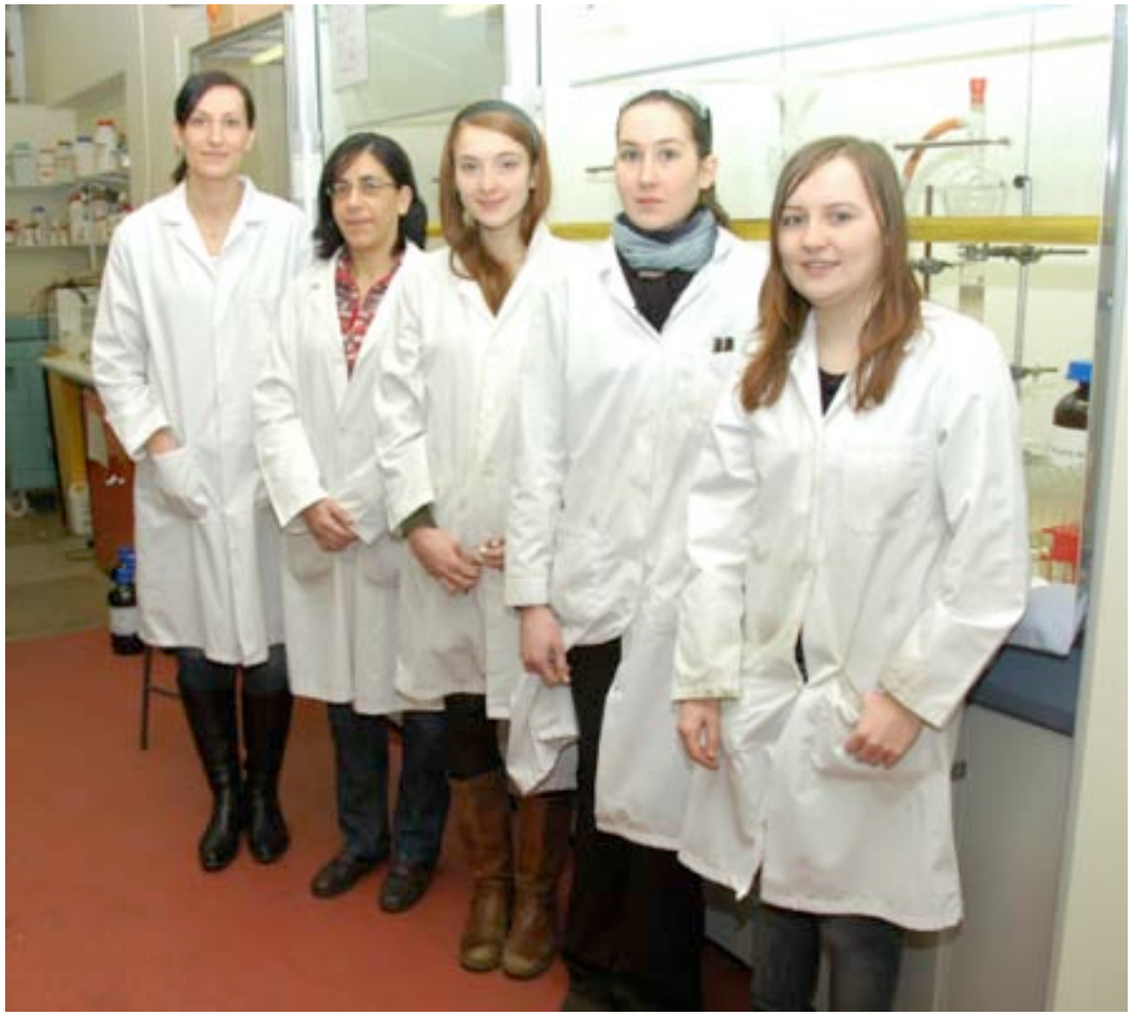
Agreement signed - 2007

INX-189 first prepared - Nov 2008

First into man - May 2010

Efficacy in patients - Mar 2011

POC in 2.5yrs



18 mos from synthesis to first in man

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inhibitex

Clinical Trial

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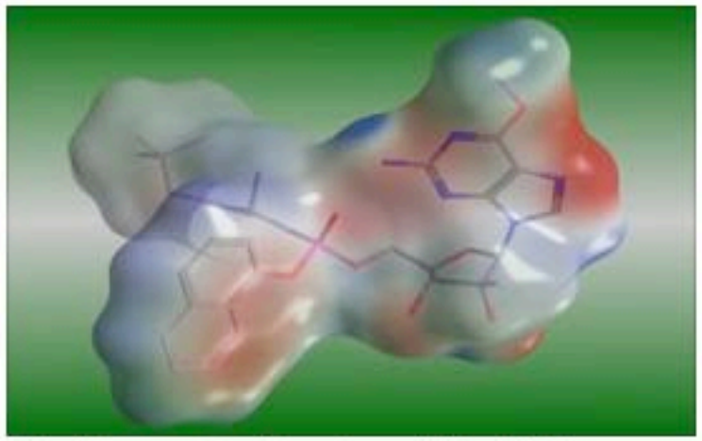
Wales Politics

2 September 2010 Last updated at 15:52

Cardiff trial for new hepatitis C drug 'successful'

Scientists say the first human clinical trials on a new drug to treat infections caused by the Hepatitis C virus have been successfully completed.



The licence for the drug, INX-189, is owned by a US firm

Monday 09 January 2012

The Telegraph

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Bristol-Myers Squibb targets hepatitis C with $2.5bn deal to buy Inhibitex

American pharmaceutical giant Bristol-Myers Squibb is set to buy US biotech company Inhibitex in a $2.5bn (£1.6bn) deal, bolstering its portfolio of drugs targeting the burgeoning hepatitis C market.

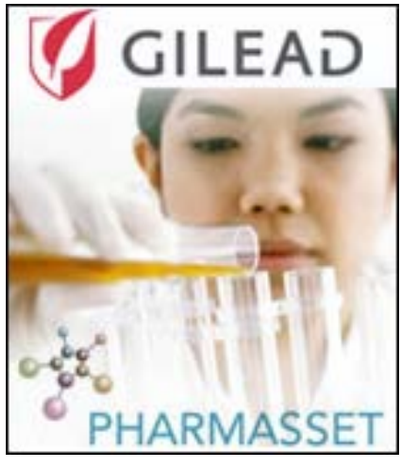
Currently, the hepatitis C market is thought to be worth around $3bn globally, but estimates suggest that it could be worth $20bn by 2020 Photo: Alamy

Summer 2012
Major phase 2b combination study.
Probability of success ca 50%.

Abandoned due to serious cardiotox in a combination study with another experimental agent.

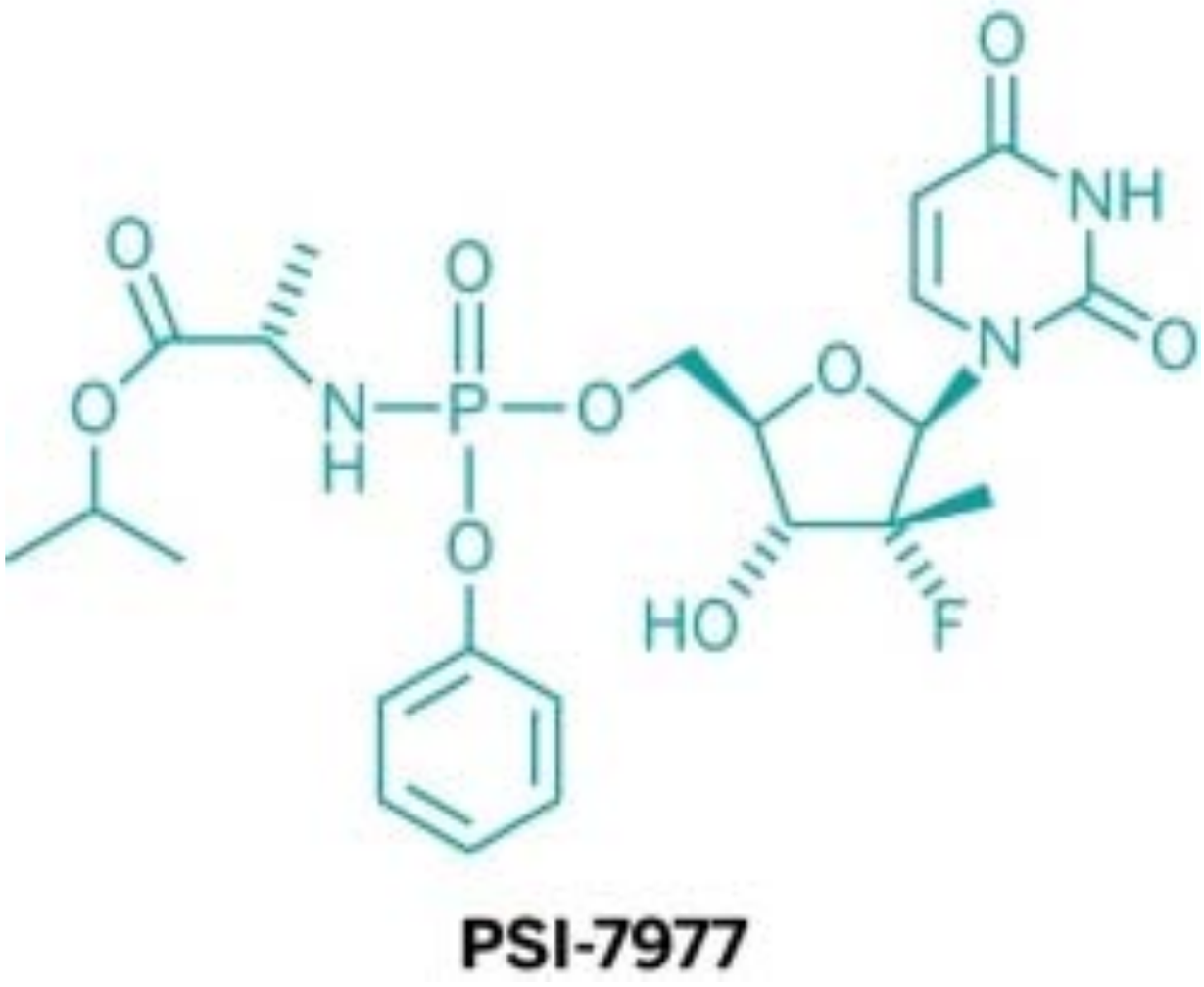
Technology Adoption

GILEAD



ProTide PSI 7977

- Pharmasset Primary Asset – Phase II
- $11.2 billion cash acquisition – Jan 2012



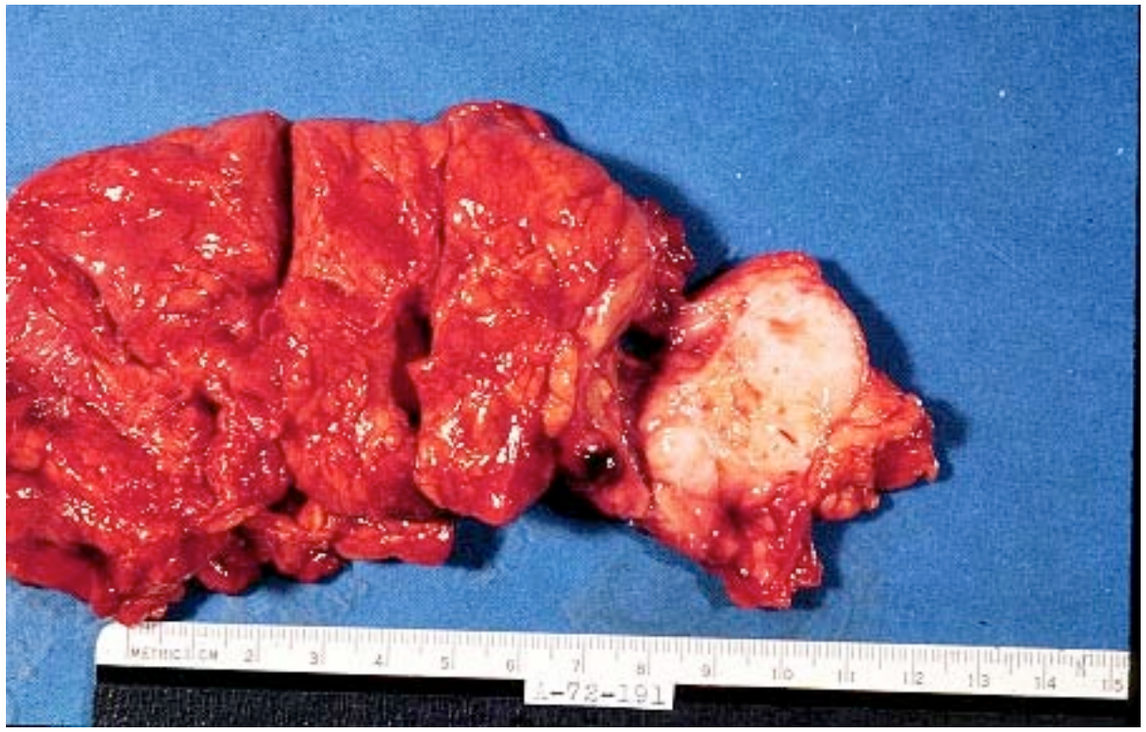
PSI-7977

FDA approval 6th Dec 2013.

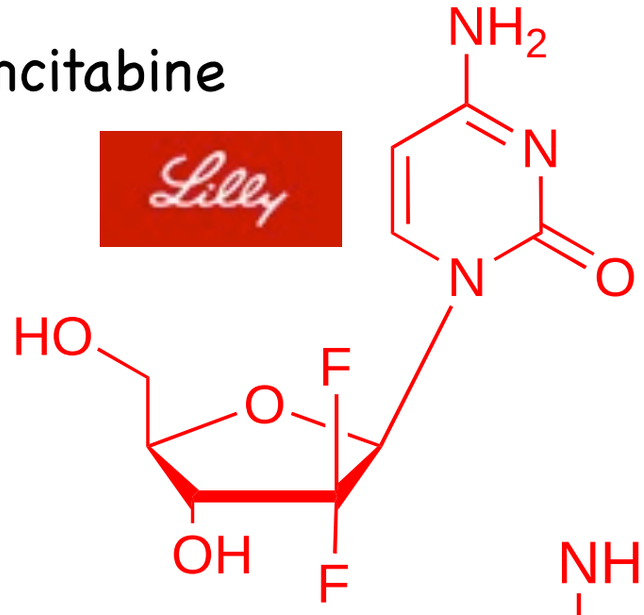
Predicted sales: $40Bn Sofosbuvir (‘Sovaldi’).

1st year sales $10Bn

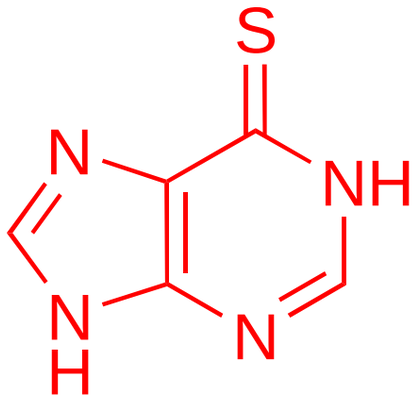
Anti-cancer ProTides



gemcitabine

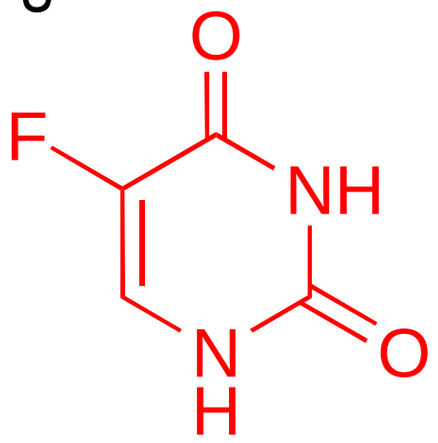


MP
(also TG)

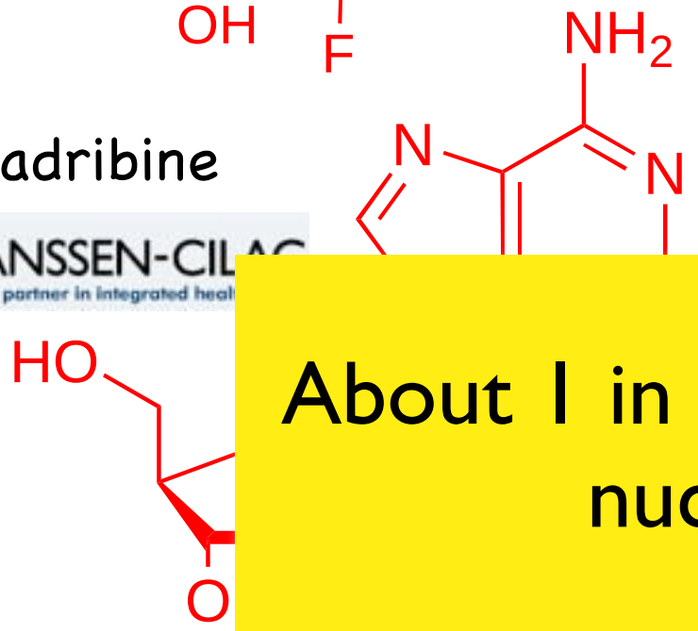


FU

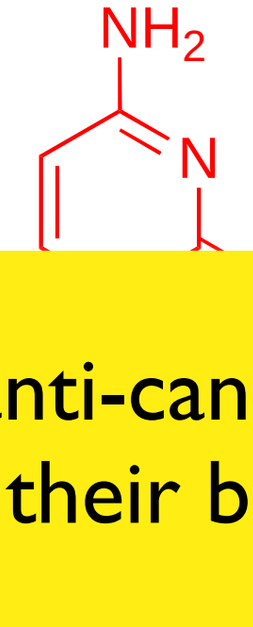
also capecitabine



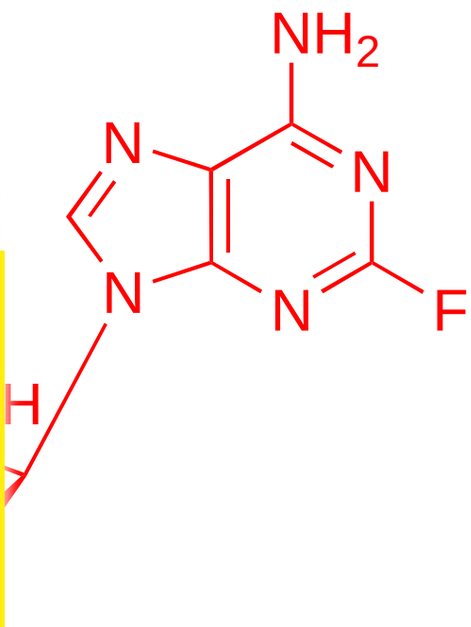
cladribine



cytarabine

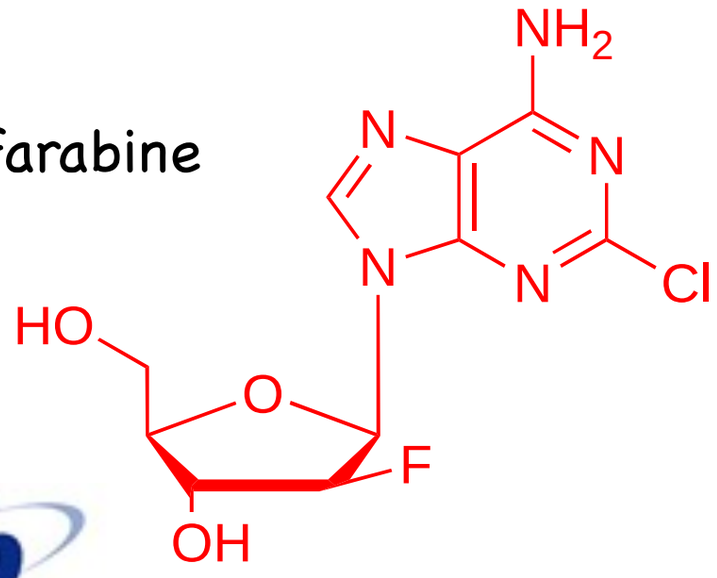


fludarabine

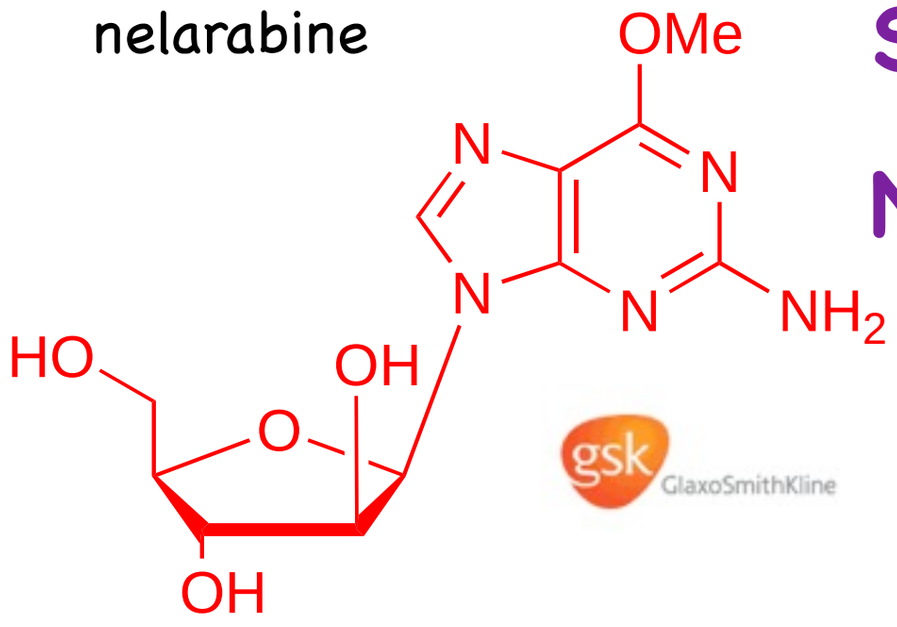


About 1 in 5 approved anti-cancer drugs are nucleosides (or their bases)

clofarabine



nelarabine

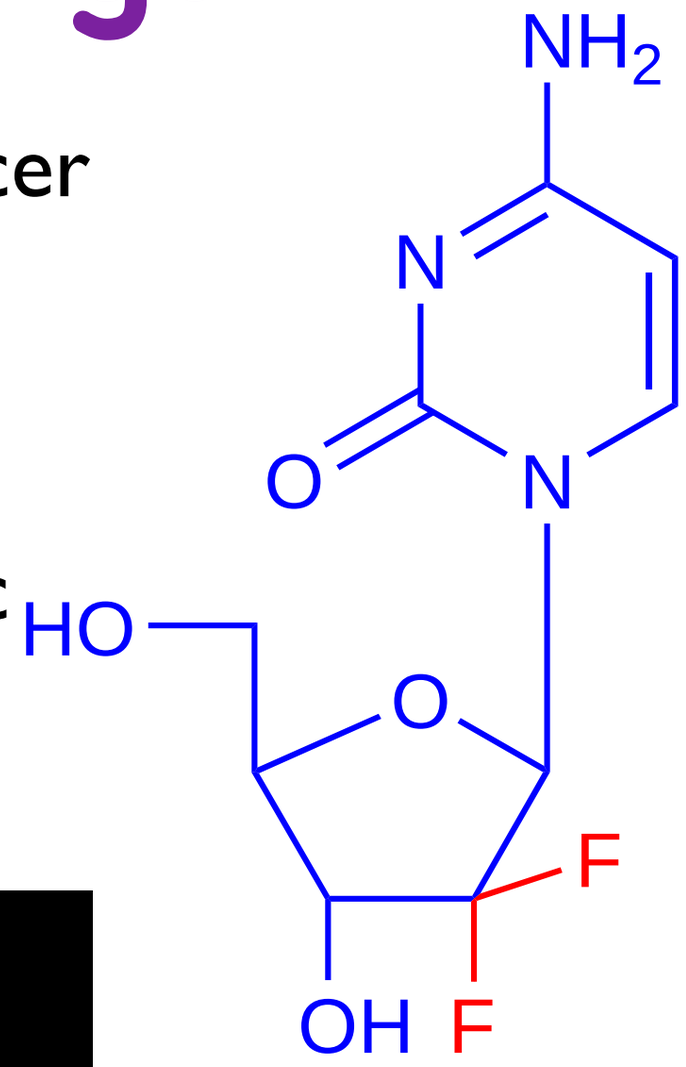


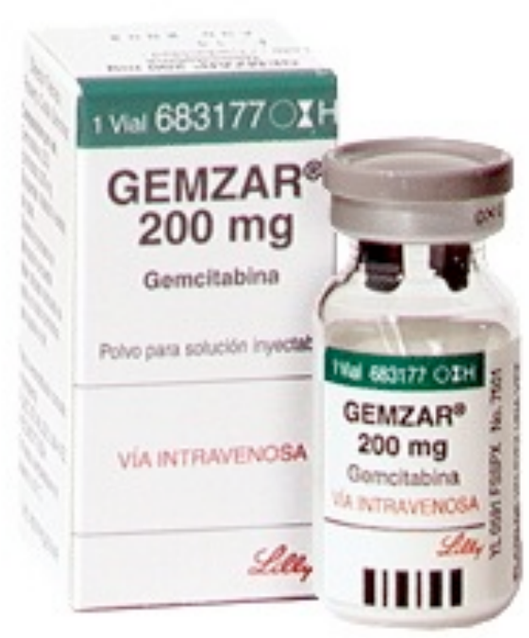
Some Anticancer Nucleosides

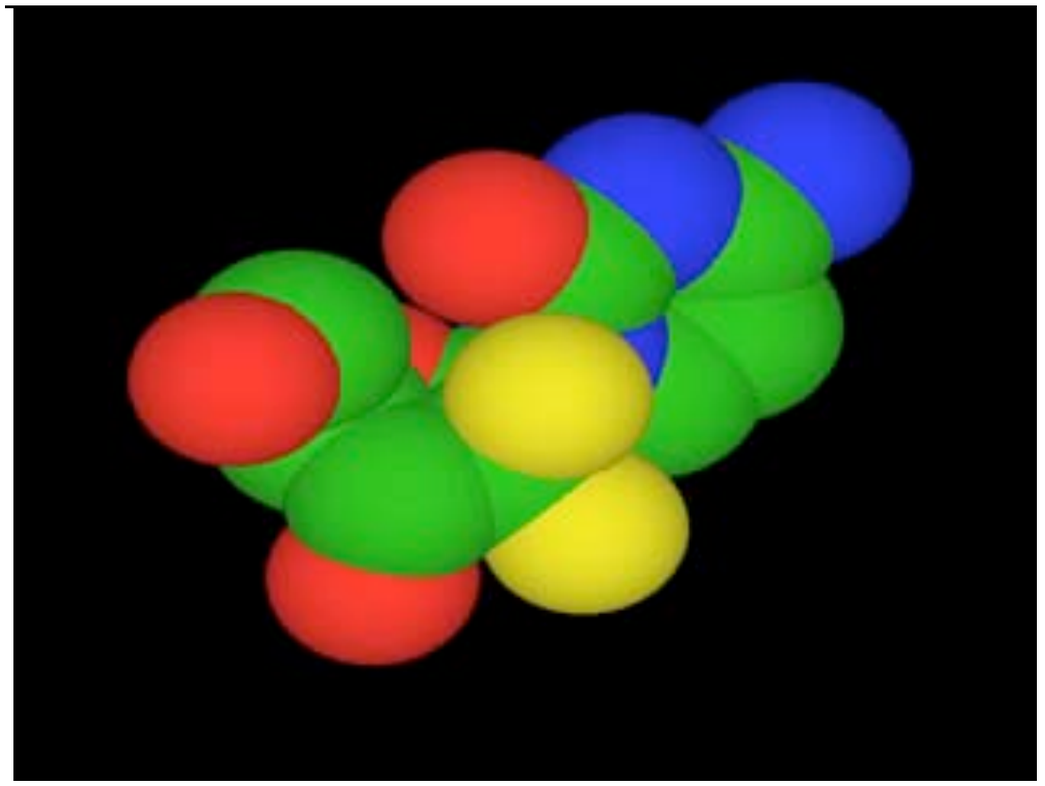
Nucleoside Drugs

- Gemzar (Gemcitabine) $2Bn anti-cancer drug from Lilly.

- Used in therapy of lung and pancreatic cancer, also for bladder cancer.







Cancer ProTides

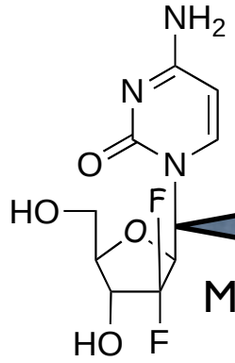
CARDIFF UNIVERSITY

Cardiff ProTides Ltd

morvus

NUCANA BIOMED

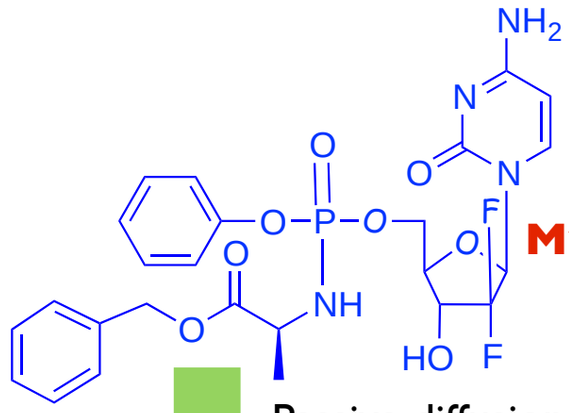
Gem



1

Mycoplasma sensitive

Active transport



Mycoplasma insensitive

>1,000 times more lipophilic

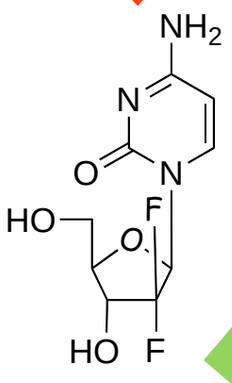
Passive diffusion

2

4

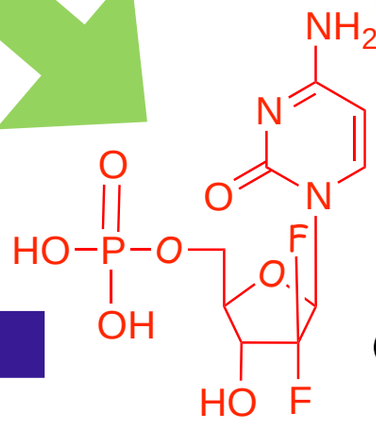
Deactivation

CDA



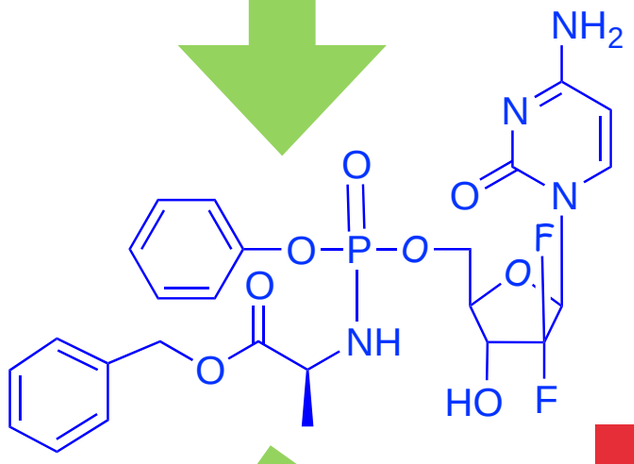
dCK needed

3



DNA

GemMP



ProTide Phase I/II Study

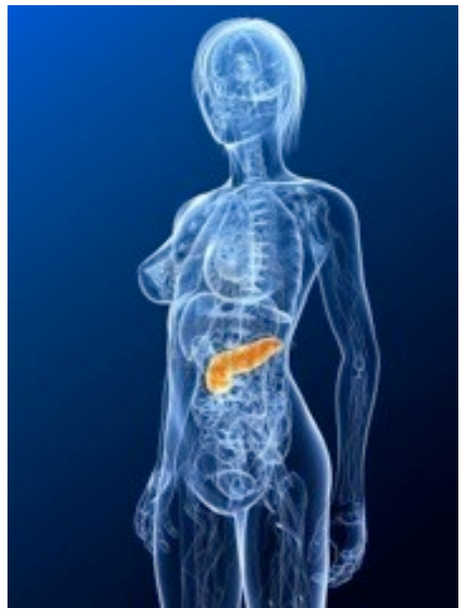
PROGEM1

- Hammersmith Hospital, London
- Advanced Solid Tumours
- Two Parts:
  - Dose Escalation
  - Expansion Cohort – Safety & Efficacy
- Opened Oct 2012

ACELARIN NUC-1031

NUCANA BIOMED

- Patients treated to date include:
  - Pancreatic, ovarian, colorectal, breast...
- No unexpected adverse events
- PK data confirm ProTide significant advantage over parent nucleoside: enhanced NTP release.



PROGEM1

Strong efficacy signals

* ≥2 cycles

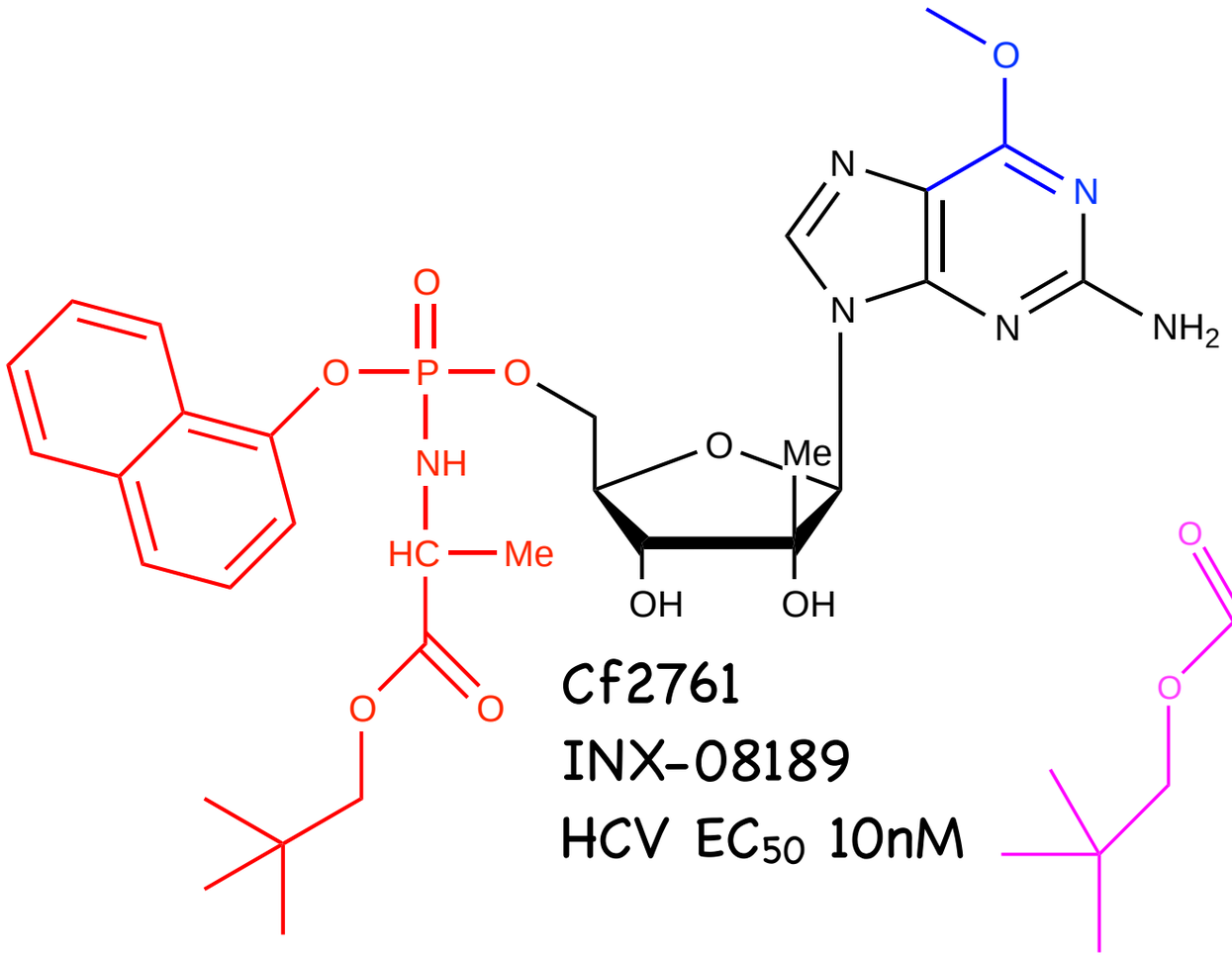
	All patients		Evaluable patients*	
	n	%	n	%
Total	36	100	25	100
Partial response	5	14	5	20
Stable disease	17	47	17	68
Disease control	22	**61**	22	**88**

Trial now closed with 37 patients treated and strong efficacy signals. Data to be presented at ASCO this Spring. Phase 2 trials now started.

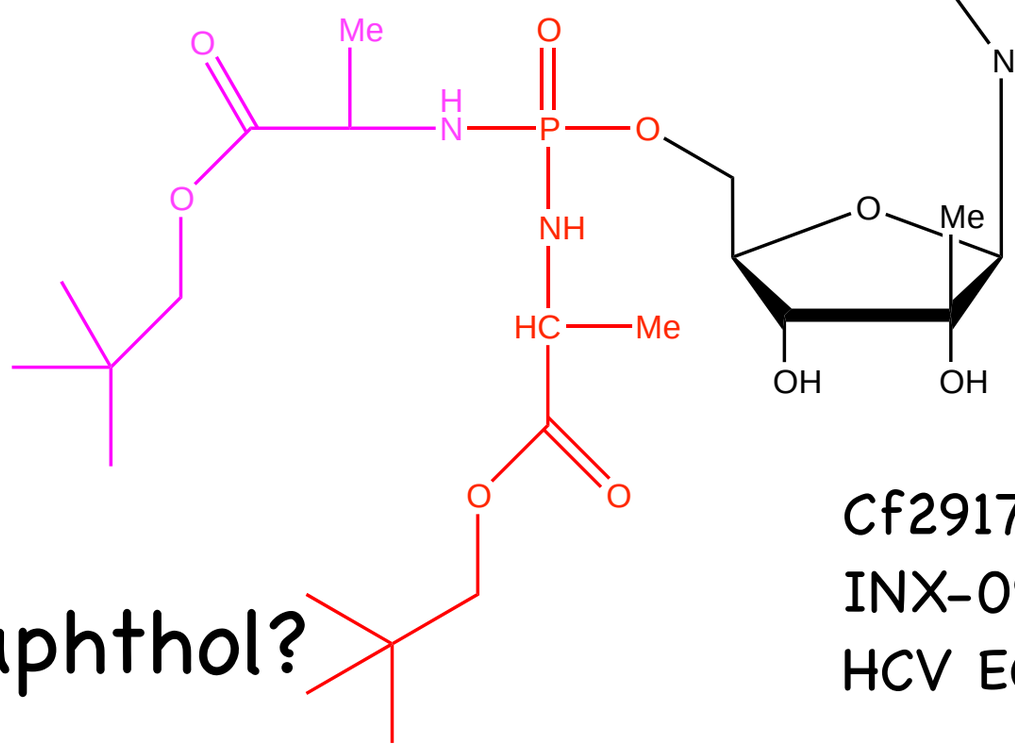
NUCANA BIOMED

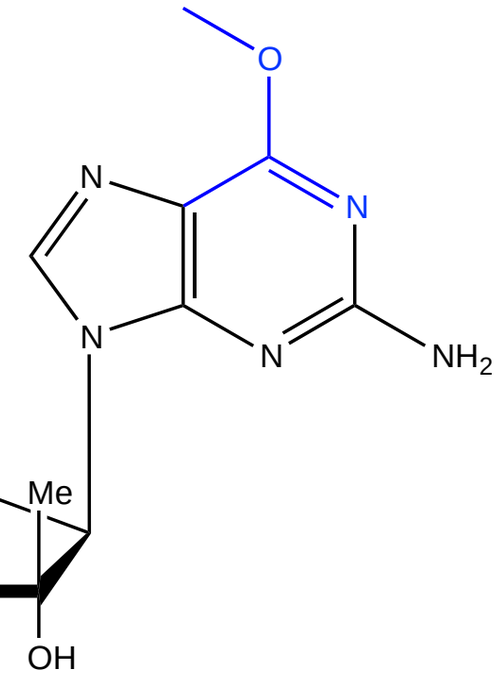
NEW:

Phosphorodiamidates:
A new motif.



Cf2761
INX-08189
HCV EC_{50} 10nM



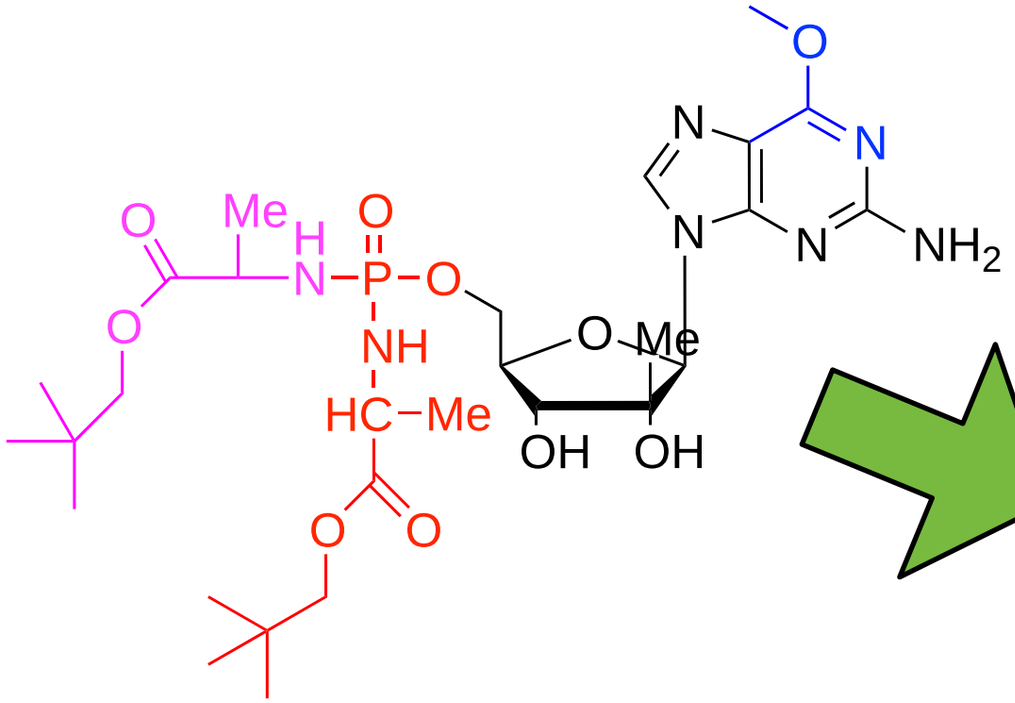


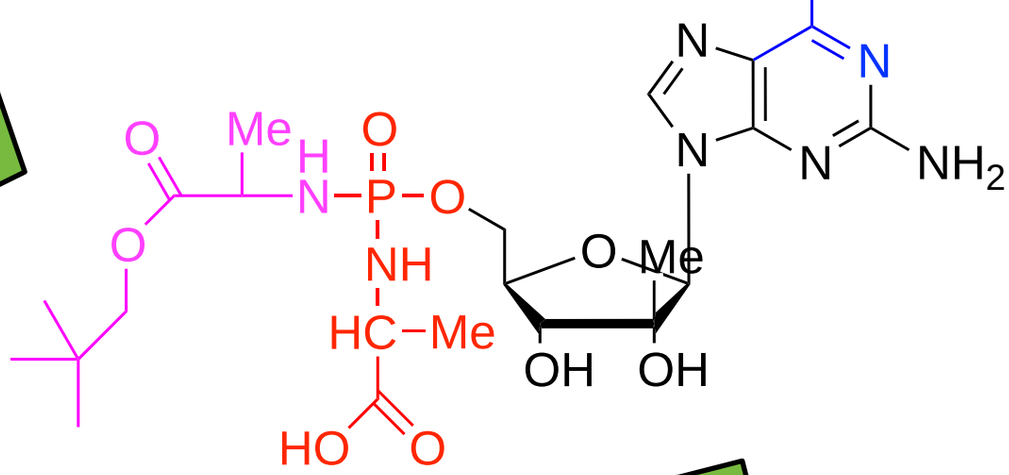
Cf2917
INX-09134
HCV EC_{50} 30nM

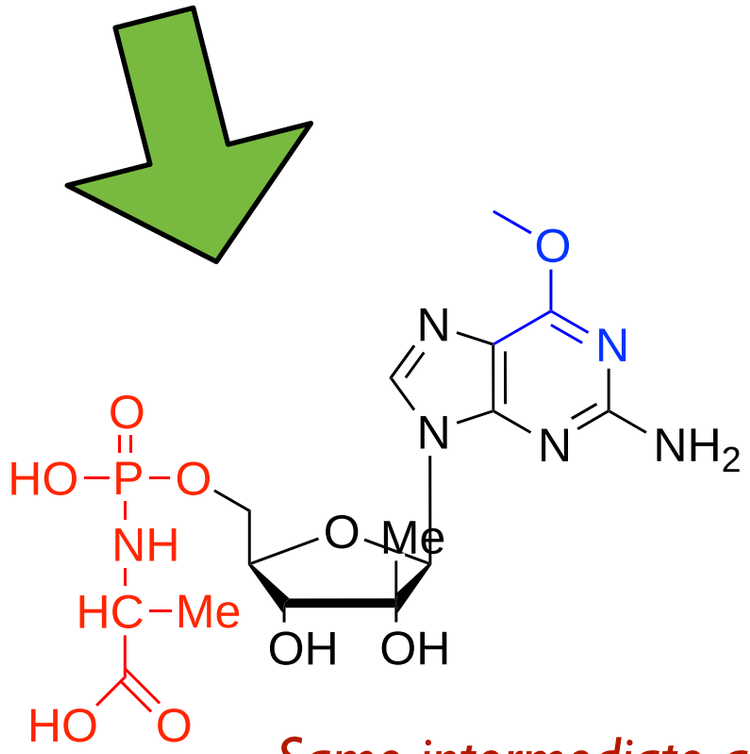
Issues??? Chirality? Naphthol?

The next generation of ProTides

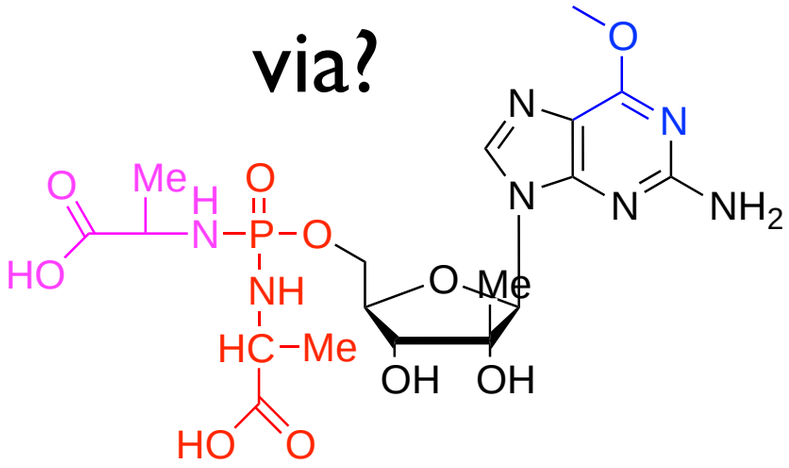
MoA







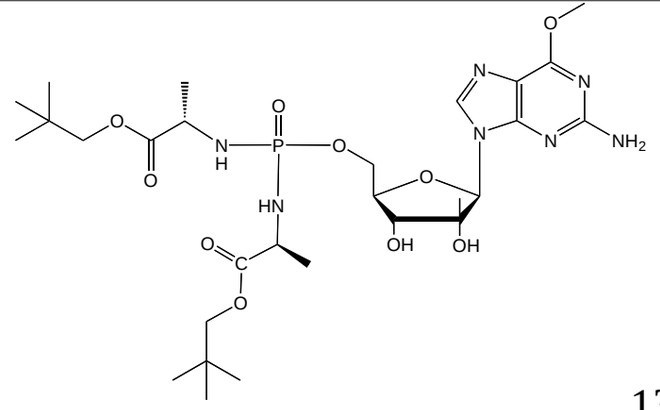
via?



One amino acid (ester) is important for activity.

Same intermediate as regular ProTide

identical chemical shift as for ProTide



13h

111’

104’

97’

90’

73’

52’

diester

45’

38’

-ester

6.95

10’

14.91

blank

14.24

Diam

15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

Conditions: 5.0 mg of diamidate in 200µl of Acetone-d_6 + 400µl of Trizma buffer (pH 7.4), 0.3- 0.5 mg of Carboxypeptidase Y in 200µl of Trizma buffer (pH 7.4)

McGuigan Labs Pipeline: April 2015

Project	Hit finding	Hit to lead	Candidate selection	pre-clin workup	Phase 1	Phase 2	Phase 3	Sponsor
shingles FV100							ContraVir PHARMACEUTICALS, INC.	inhibitex
HCV INX-189						X	Bristol-Myers Squibb	inhibitex
Cancer NUC1031								NUCANA BIOMED
Cancer 2nd in class								NUCANA BIOMED
Osteoarthritis								
Pox / measles							MRC Medical Research Council	SARTRE
HIV								NATIONAL INSTITUTES OF HEALTH
Flu								fusion IP
MS								LIFE SCIENCES RESEARCH NETWORK WALES RHWYDWAITH GWYDDORAU BYWYD CYMRU

Key collaborators

<u>Cardiff University</u>
Andrea Brancale, Andy Westwell, Joachim Bugert, Malcolm Mason, Wen Jiang, Rob Nicholson, Huw Mottram, Arwyn Jones, Alan Clarke and team, Tim Maughan, Alan Burnett, Beth Walsby, Ned Powell, Amanda Tristram, Bruce Caterson and team, Yves Barde, Ken Broadley.

<u>Rega Institute, Leuven</u>
Jan Balzarini, Johan Neyts, Lieve Naesens.

<u>GSK, RTP</u>
Susan Daluge and Co-workers

<u>Roche Pala Alto</u>
Dave Smith, Klaus Klumpp

<u>Inhibitex GA</u>
Geoff Henson and team.

<u>Nucana UK</u>
Chris Wood, Hugh Griffith & Morvus team.
Plus Sarah Blagden and Hammersmith team

McGuigan Group, 2014-15

and ca 100 former PhDs and researchers

mcguigan@cardiff.ac.uk

Life Sciences Bridging Fund

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RHWYDWAITH GWYDDORAU BYWYD CYMRU

£15M. 100 new drug discovery projects

ARTHURIAN LIFE SCIENCES

£100M. So far 7 deals incl UKs 1st proton beam unit.

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