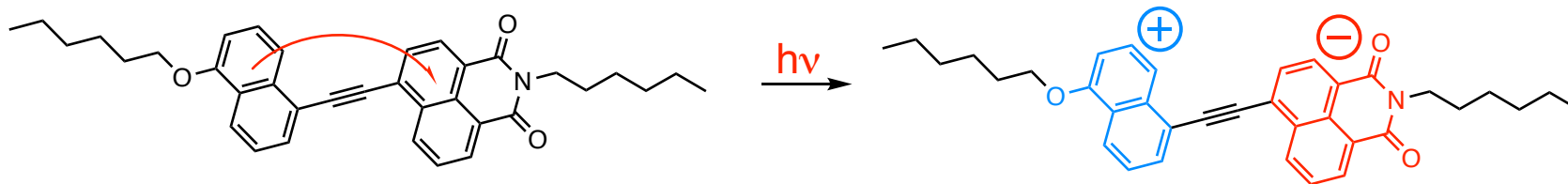
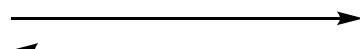


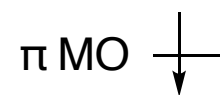
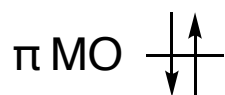
Blue Light = higher energy  
Orange light = lower energy

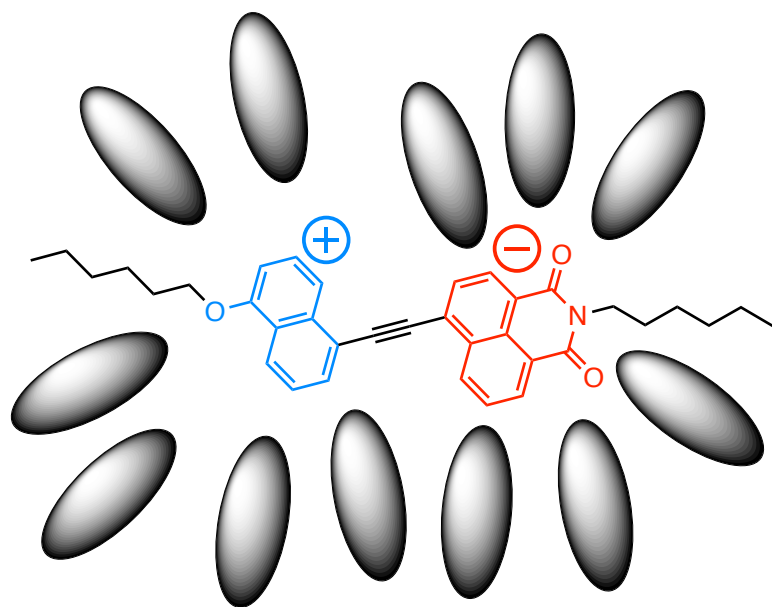


$h\nu$  absorb (UV)



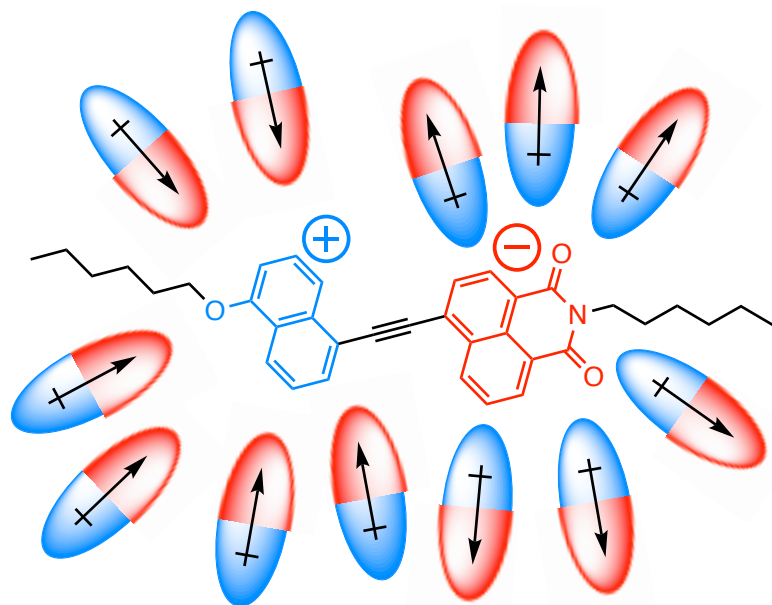
$h\nu$  fluorescence  
(visible)





Non-polar Solvent Molecule

No stabilization of the  
charged excited state

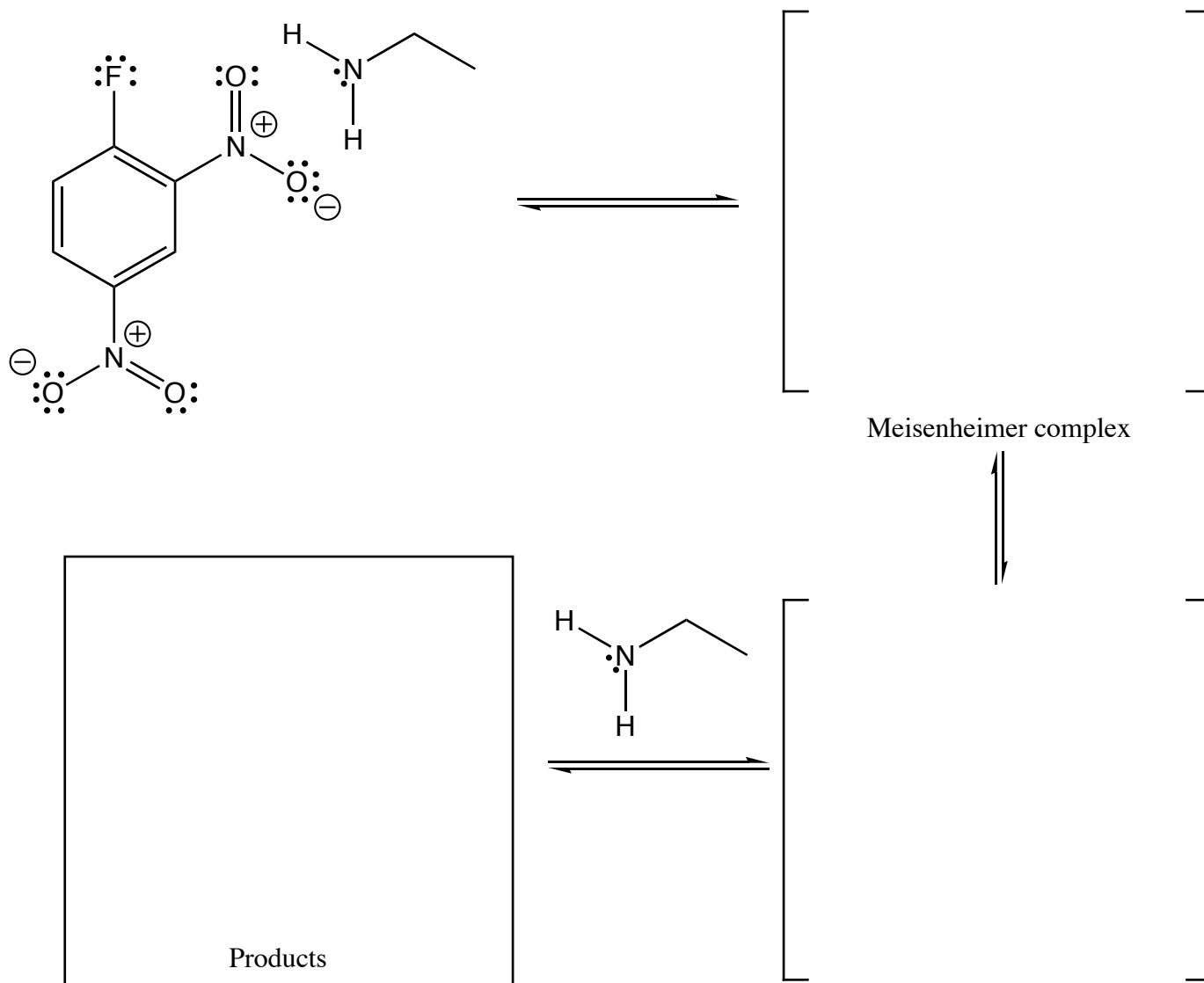


Polar Solvent Molecule

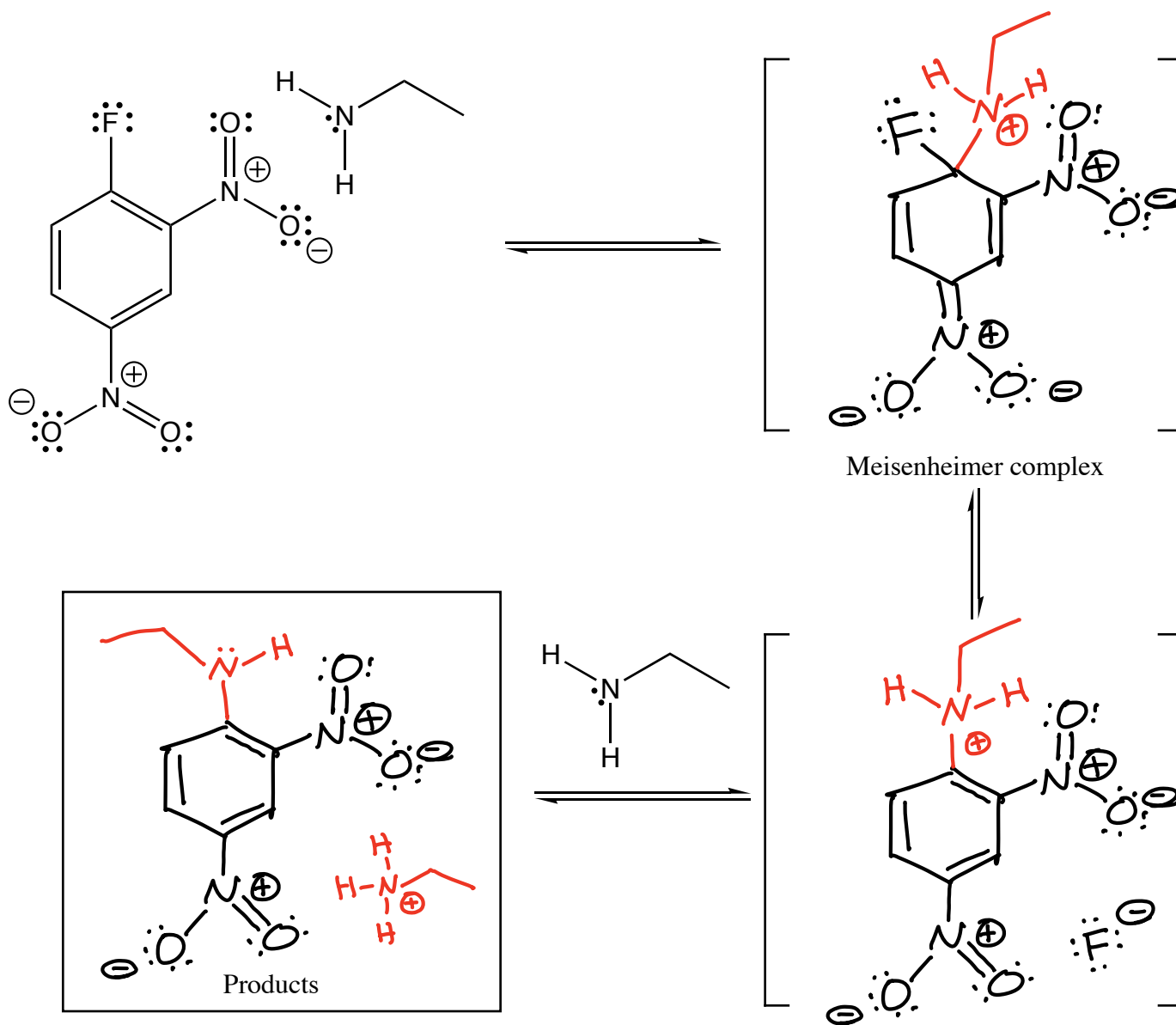
Stabilization of the  
charged excited state



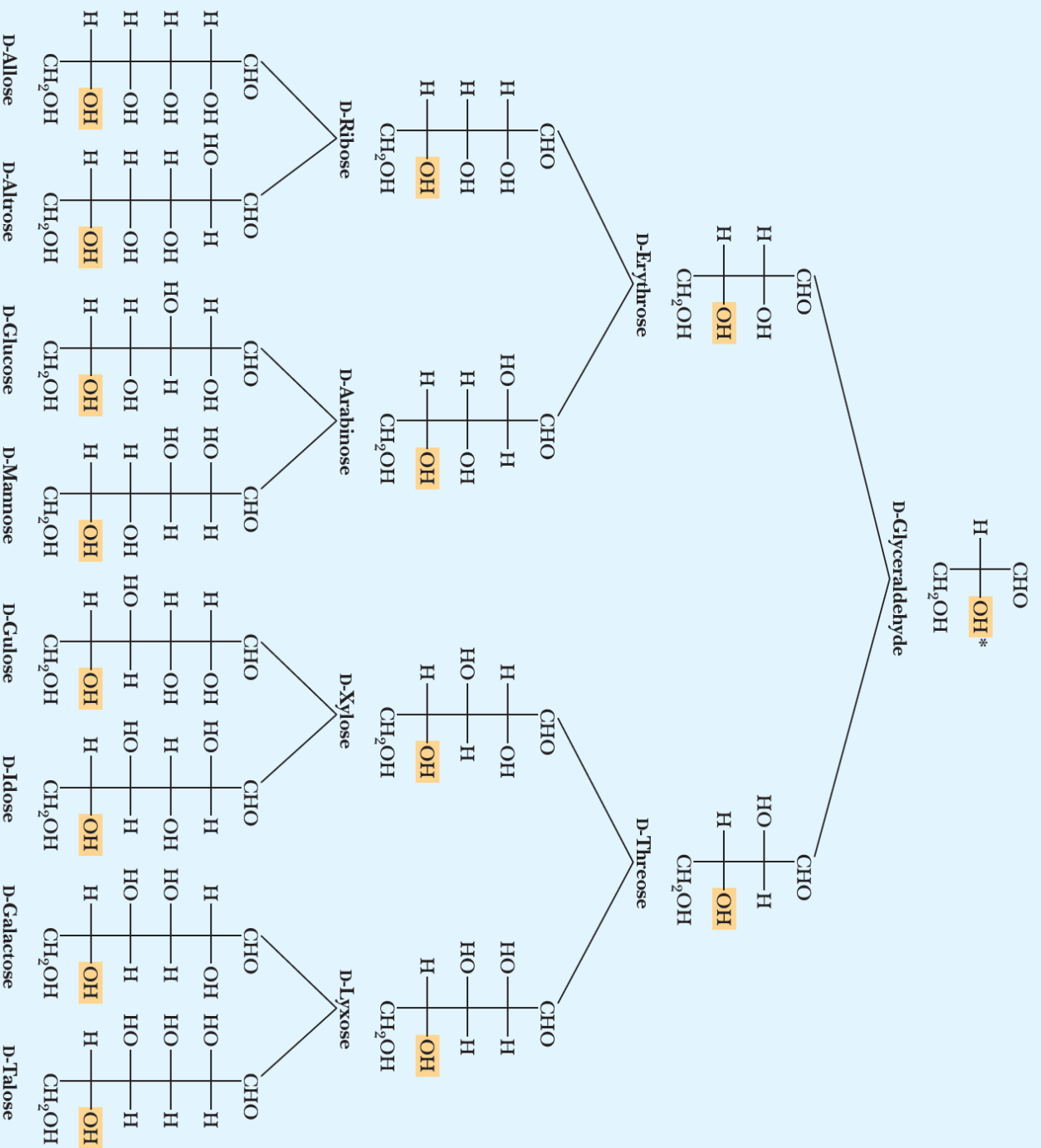
# Nucleophilic Aromatic Substitution

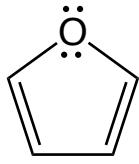


## Nucleophilic Aromatic Substitution

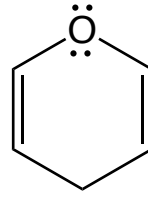


**Table 25.1** Configurational Relationships Among the Isomeric D-Aldotetroses, D-Aldopentoses, and D-Aldohexoses

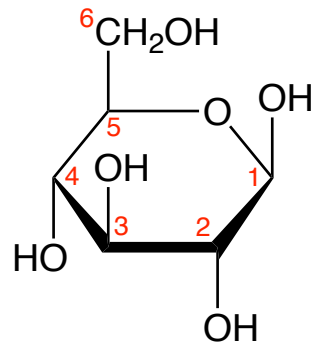
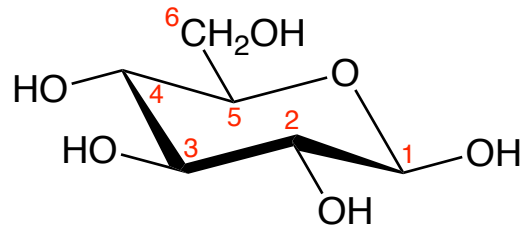
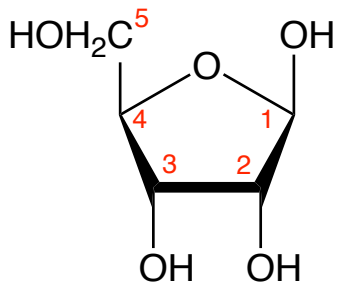


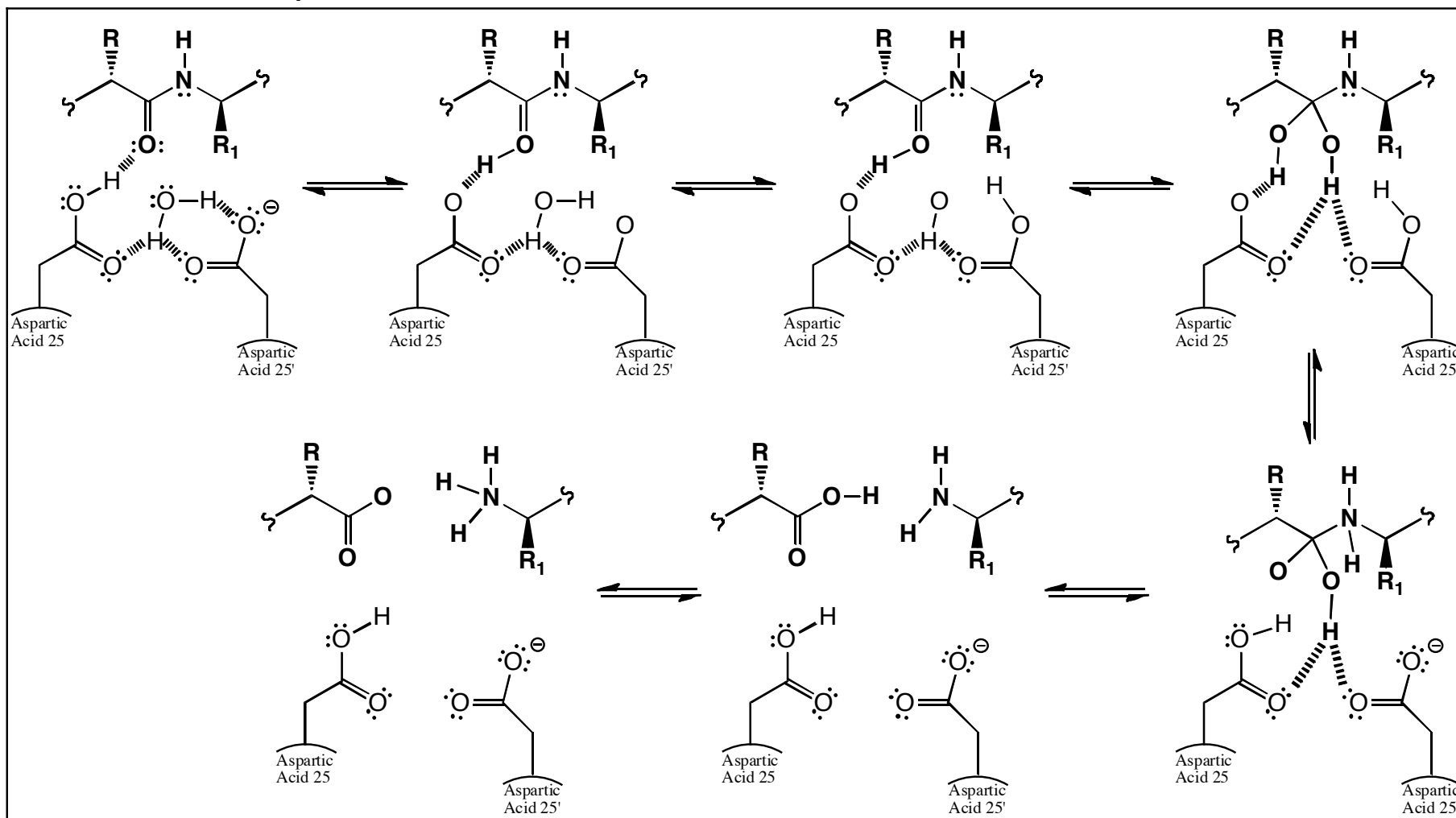
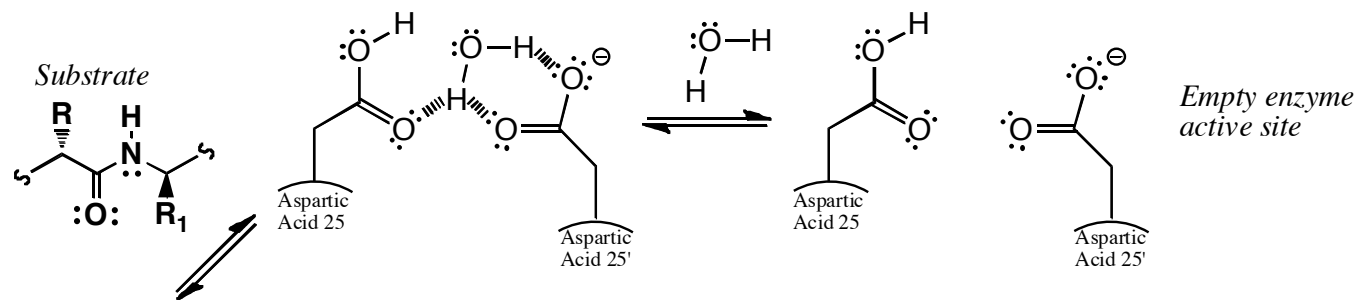


Furan



Pyran







# HIV-1 protease: mechanism and drug discovery

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## 1 Introduction

It has now been two decades since acquired immunodeficiency syndrome (AIDS) was first reported by the US Center for Diseases Control (CDC). A few years later, it was found that a retrovirus called human immunodeficiency virus (HIV) is the causative agent in AIDS.<sup>1</sup> In a short time, AIDS increased to epidemic proportions throughout the world, affecting more than 40 million people today and killing so far more than 22 million (UNAIDS, 2001).

Since the outbreak of the AIDS epidemic, tremendous efforts have been directed towards development of antiretroviral therapies that target HIV type 1 in particular (HIV-1). The identification of the HIV retrovirus and the accumulated knowledge about the role of the different elements in its life cycle led researchers around the world to develop inhibitors that target different steps in the life cycle of the virus. One of these targets is HIV-1 protease (HIV PR), an essential enzyme needed in the proper assembly and maturation of infectious virions. Understanding the chemical mechanism of this enzyme has been a basic requirement in the development of efficient inhibitors. In this review, we summarize studies conducted in the last two decades on the mechanism of HIV PR and the impact of their conclusions on the drug discovery processes.

## 2 The life cycle of HIV

HIV belongs to the class of viruses called retroviruses, which carry genetic information in the form of RNA. HIV infects T cells that carry the CD4 antigen on their surface. The infection of the virus requires fusion of the viral and cellular membranes, a process that is mediated by the viral envelope glycoprotein (gp120, gp41) and receptors (CD4 and coreceptors, such as CCR5 or CXCR4) on the target cell. As the virus enters a cell, its RNA is reverse-transcribed to DNA by a virally encoded enzyme, the reverse transcriptase (RT). The viral DNA enters the cell nucleus, where it is integrated into the genetic material of the cell by a second virally encoded enzyme, the integrase. Activation of the host cell results in the transcription of the viral DNA into messenger RNA, which is then translated into viral proteins. HIV protease, the third virally encoded enzyme, is required in this step to cleave a viral polyprotein precursor into individual mature proteins. The viral RNA and viral proteins assemble at the cell surface into new virions, which then bud from the cell and are released to infect another cell. The extensive cell damage from the destruction of the host's genetic system to the budding and release of virions leads to the death of the infected cells.

## 3 HIV protease

### 3.1 HIV protease: a logical target for AIDS therapy

Unless the HIV life cycle is interrupted by specific treatment, the virus infection spreads rapidly throughout the body, which results in the weakness and destruction of the body's immune system. From the analysis of the HIV life cycle, one could conclude that there are several steps that might be interfered with,

thus stopping the replication of the virus. For example, there are several commercially available drugs that inhibit the enzyme reverse transcriptase (RT). The first class of RT inhibitors is the nucleoside analogs such as AZT, ddI, ddC and d4T. These dideoxy compounds lack the 3'-hydroxy, causing DNA chain termination when they are incorporated into the growing DNA strand. The second class of inhibitors is the non-nucleoside inhibitors (NNIs); these inhibitors are known to bind in a pocket away from the polymerase active site, and are believed to cause a conformational change of the enzyme active site, and thus inhibit its action. Currently, there are three available non-nucleoside reverse transcriptase inhibitors (nevirapine, delavirdine, and efavirenz) for the treatment of AIDS.

Another critical step in the life cycle of HIV is the proteolytic cleavage of the polypeptide precursors into mature enzymes and structural proteins catalyzed by HIV PR. It has been shown that budded immature viral particles that contain catalytically inactive protease cannot undergo maturation to an infectious form.<sup>2</sup> The necessity of this enzyme in the virus life cycle makes it a promising target for therapy of the HIV infection.<sup>3</sup>

### 3.2 Structure of HIV protease

Navia *et al.* from Merck laboratories were the first group to obtain a crystal structure of HIV PR;<sup>4</sup> a more accurate structure was reported subsequently by Kent and coworker.<sup>5</sup> HIV PR is a 99 amino acid aspartyl protease which functions as a homodimer with only one active site which is C<sub>2</sub>-symmetric in the free form. More than 140 structures of the HIV-1 PR, its mutants and enzymes complexed with various inhibitors have been reported so far. A database dedicated to providing structural information about HIV PR has been created at the National Cancer Institute (<http://www-fbnc.ncifcrf.gov/HIVdb/>). The enzyme homodimer complexed with TL-3<sup>6</sup> is shown in Fig. 1 (PDB ID: 3TLH). Each monomer contains an extended  $\beta$ -sheet region (a glycine-rich loop) known as the flap, that constitutes in part the substrate-binding site and plays an important role in substrate binding, and one of the two essential aspartyl residues, Asp-25 and Asp-25' which lie on the bottom of the cavity. The substrate binds in its extended conformation, in which its interactions with the different amino

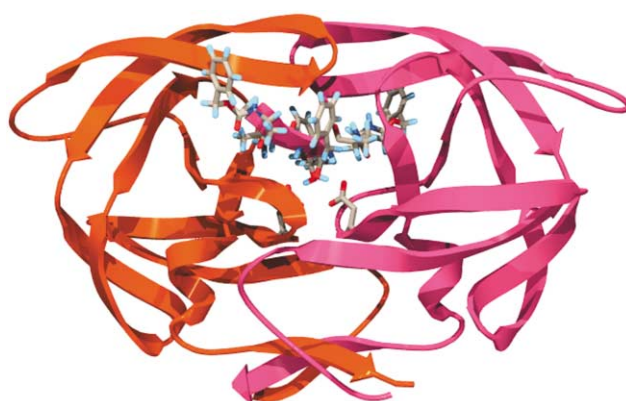


Fig. 1 Structure of HIV PR complexed with TL-3 (PDB: 3TLH).

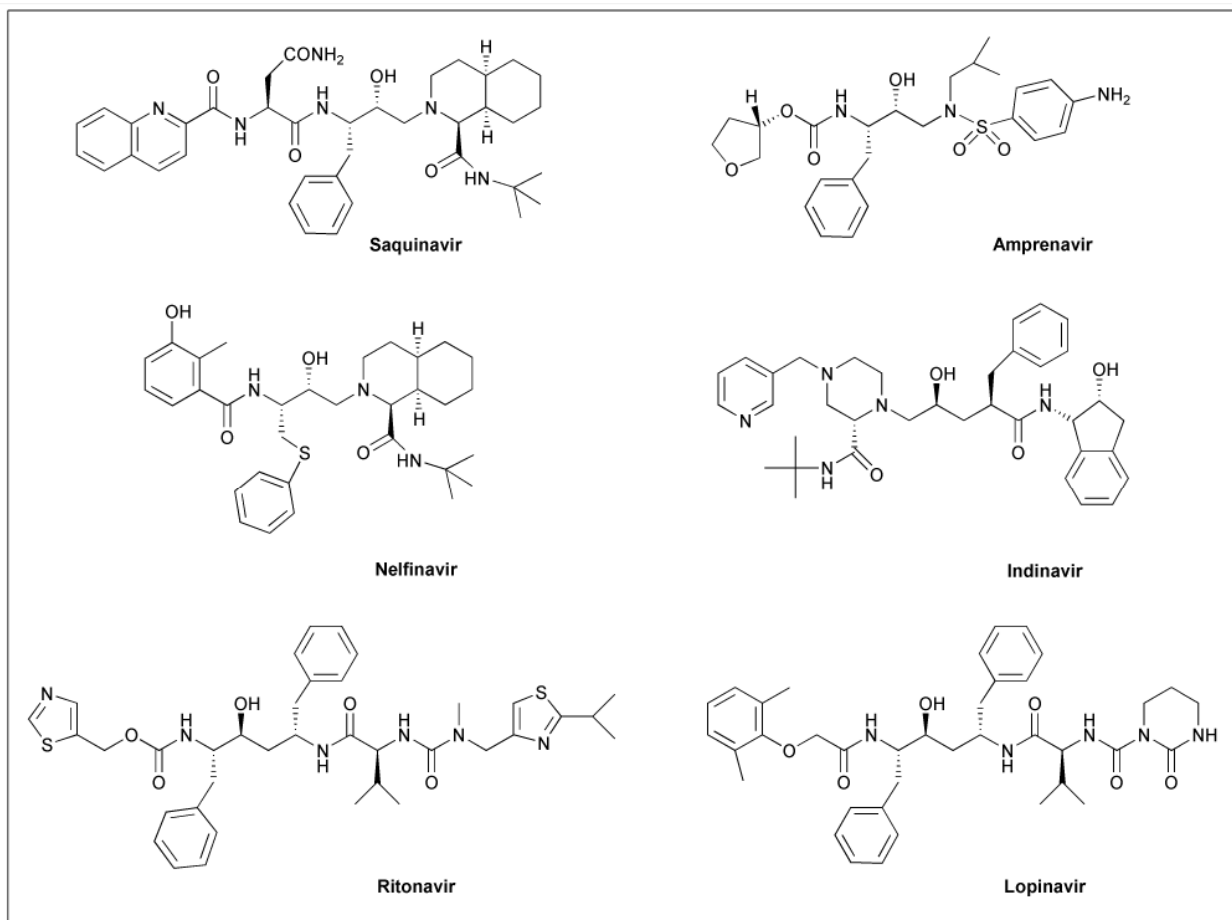
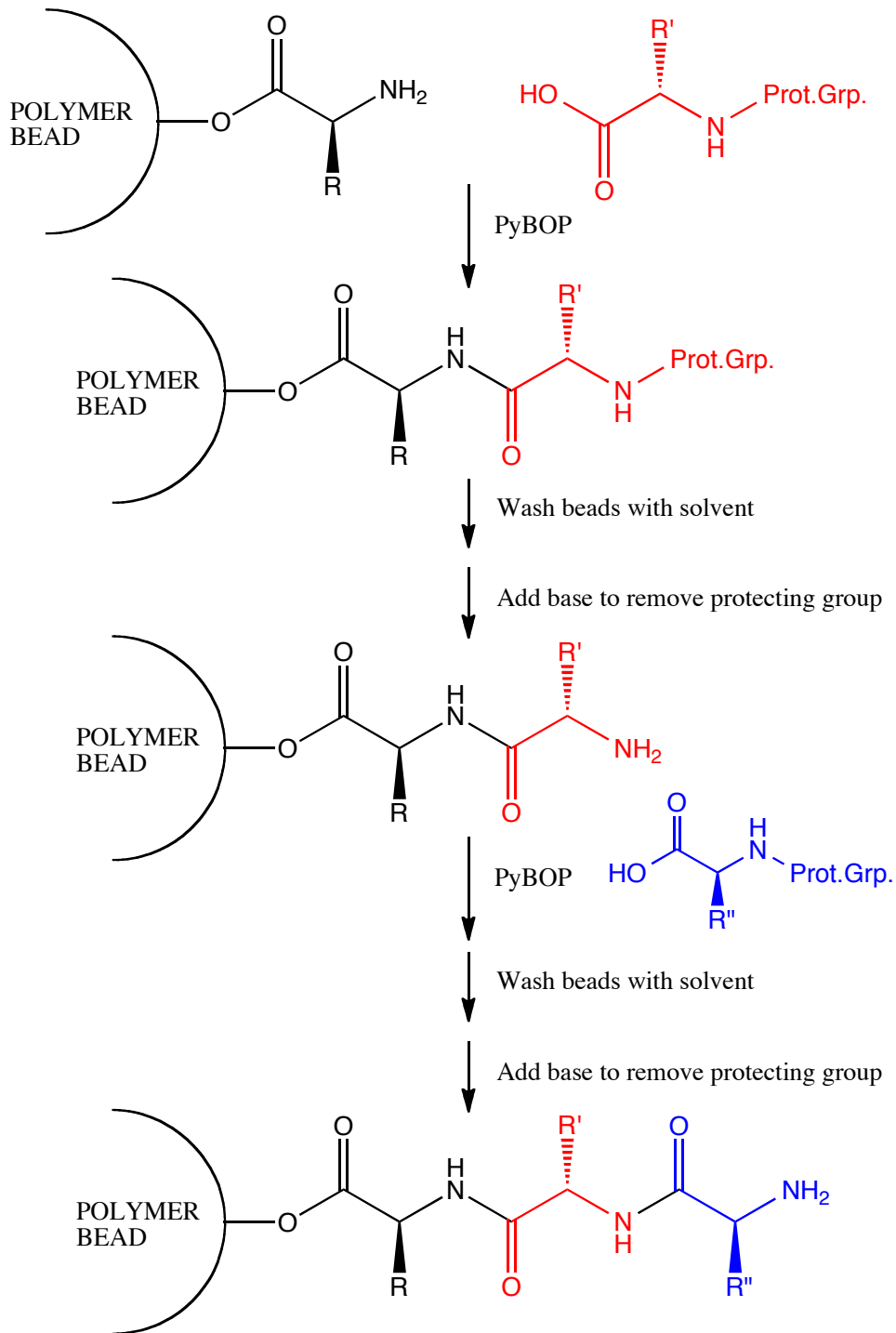
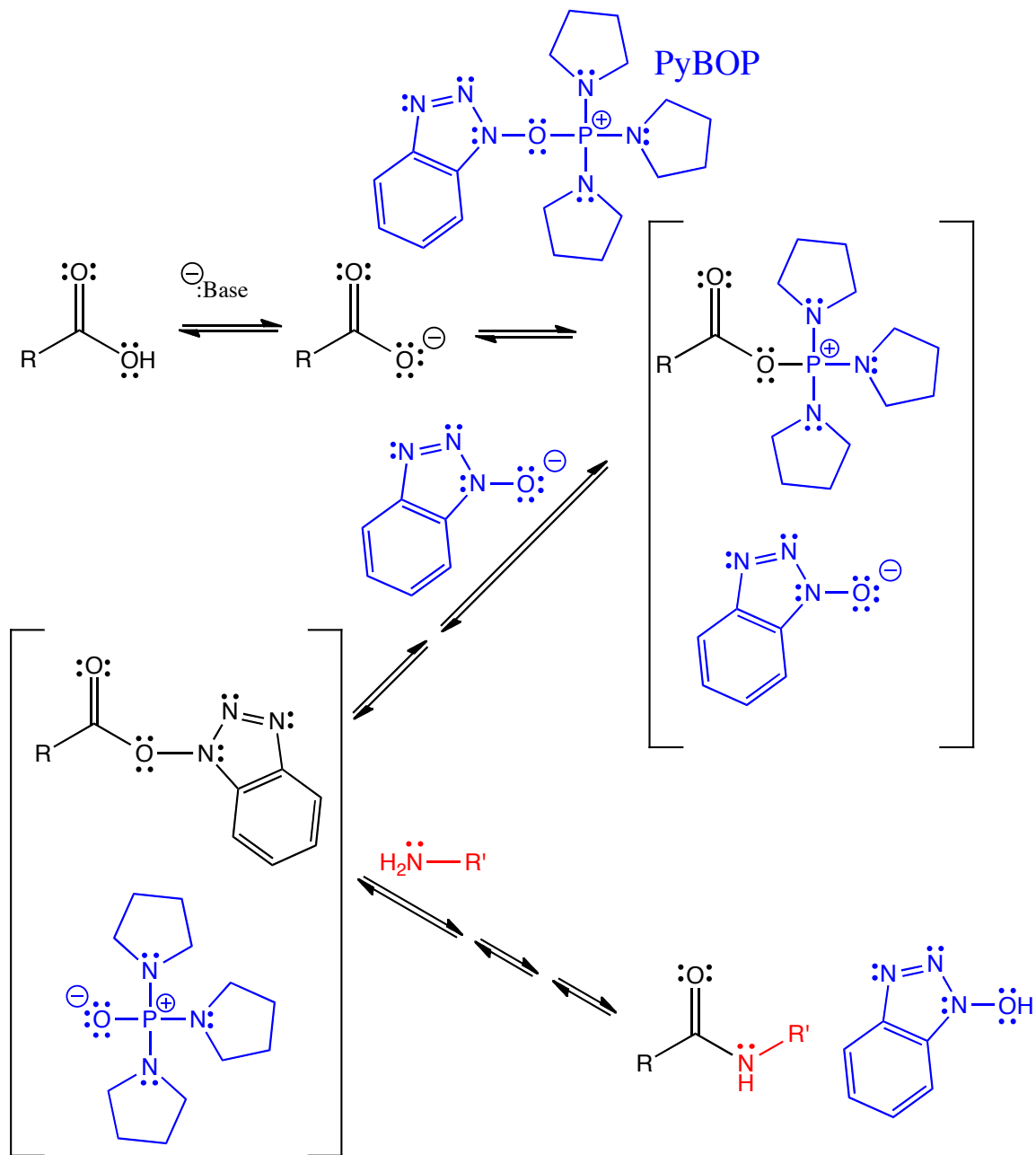
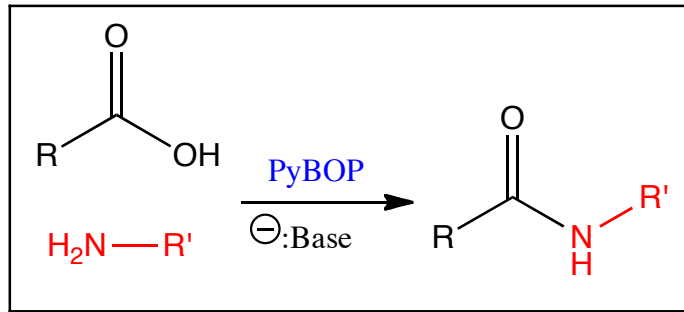


Fig. 10 FDA approved HIV-1 protease inhibitors.

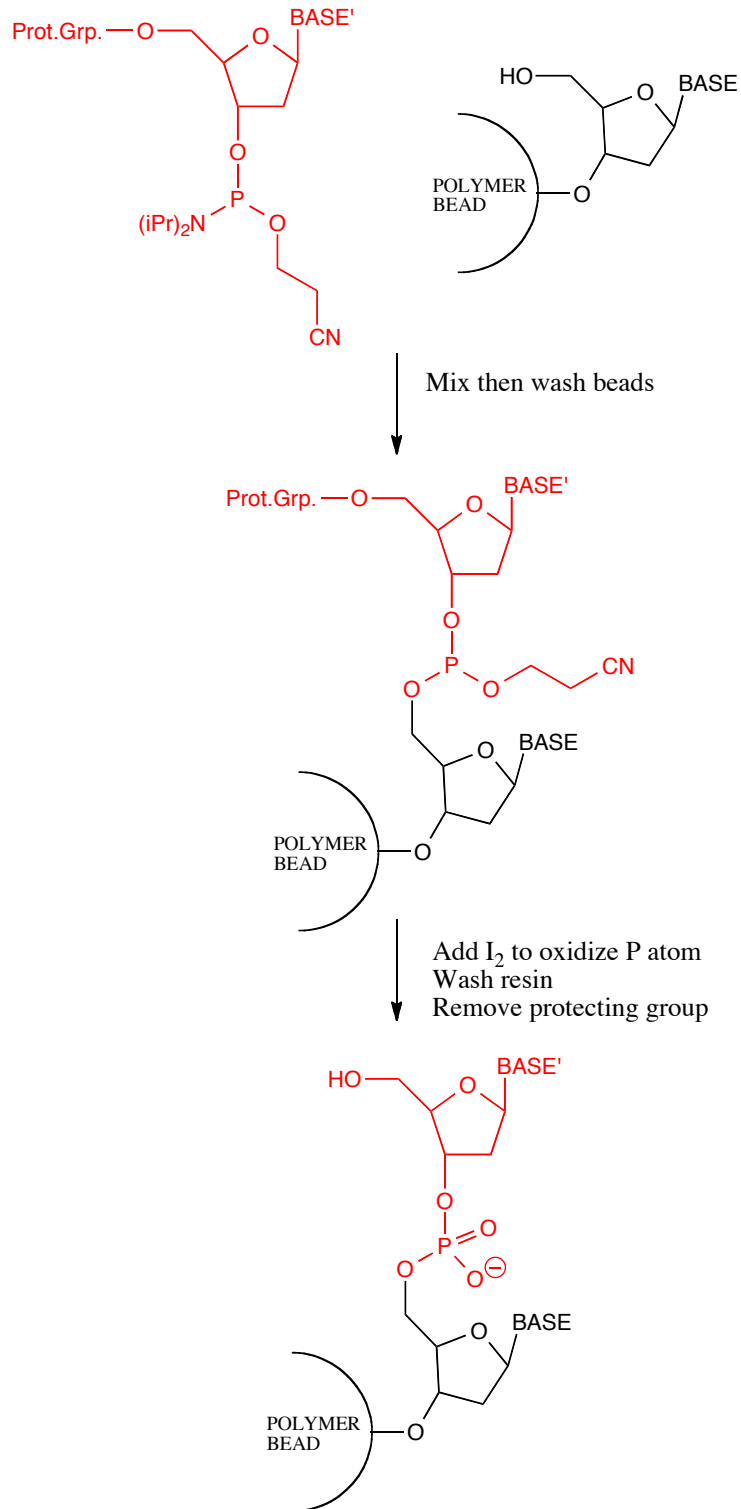
## Solid Phase Peptide Synthesis



Repeat as necessary then remove from resin. Can add up to 100 amino acids this way.



# Solid Phase Synthesis of DNA

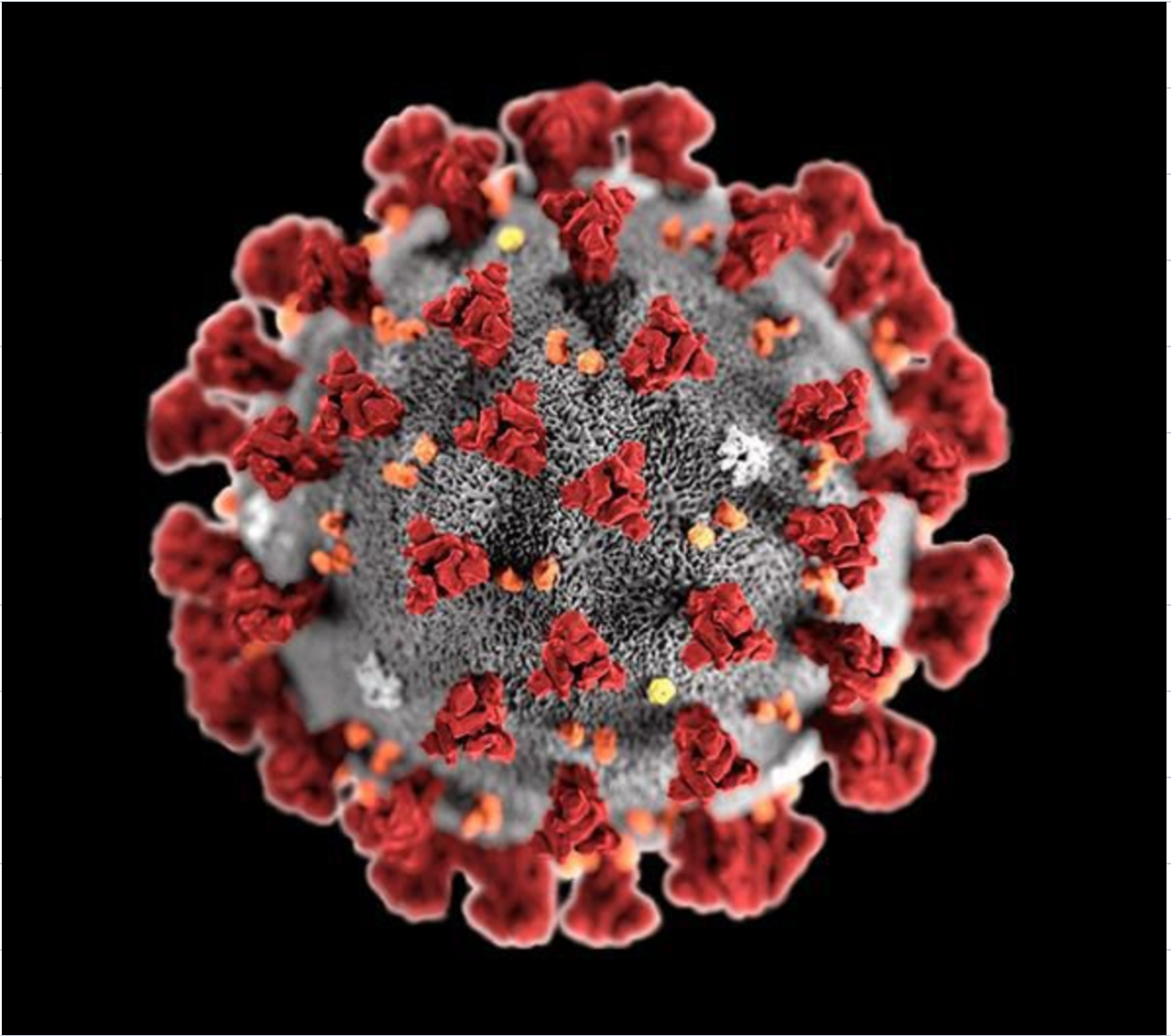


Click here to see a DNA) RNA  
Synthesis Machine

<https://shop.biosearchtech.com/nucleic-acid-chemistry-reagents-and-instruments/dna-and-rna-synthesis/dna-and-rna-oligonucleotide-synthesizers/mermade-6-and-12/c/mermade-6-and-12>

Click here to see how to order DNA

<https://www.idtdna.com/pages/products/custom-dna-rna/dna-oligos>



## New UT cases

The University of Texas said two people in its community, an unnamed student and the Dean of Undergraduate Studies Brent Iverson, had tested positive for the virus. It is unclear if the pair are included in Travis County's count of confirmed cases.





## RESEARCH

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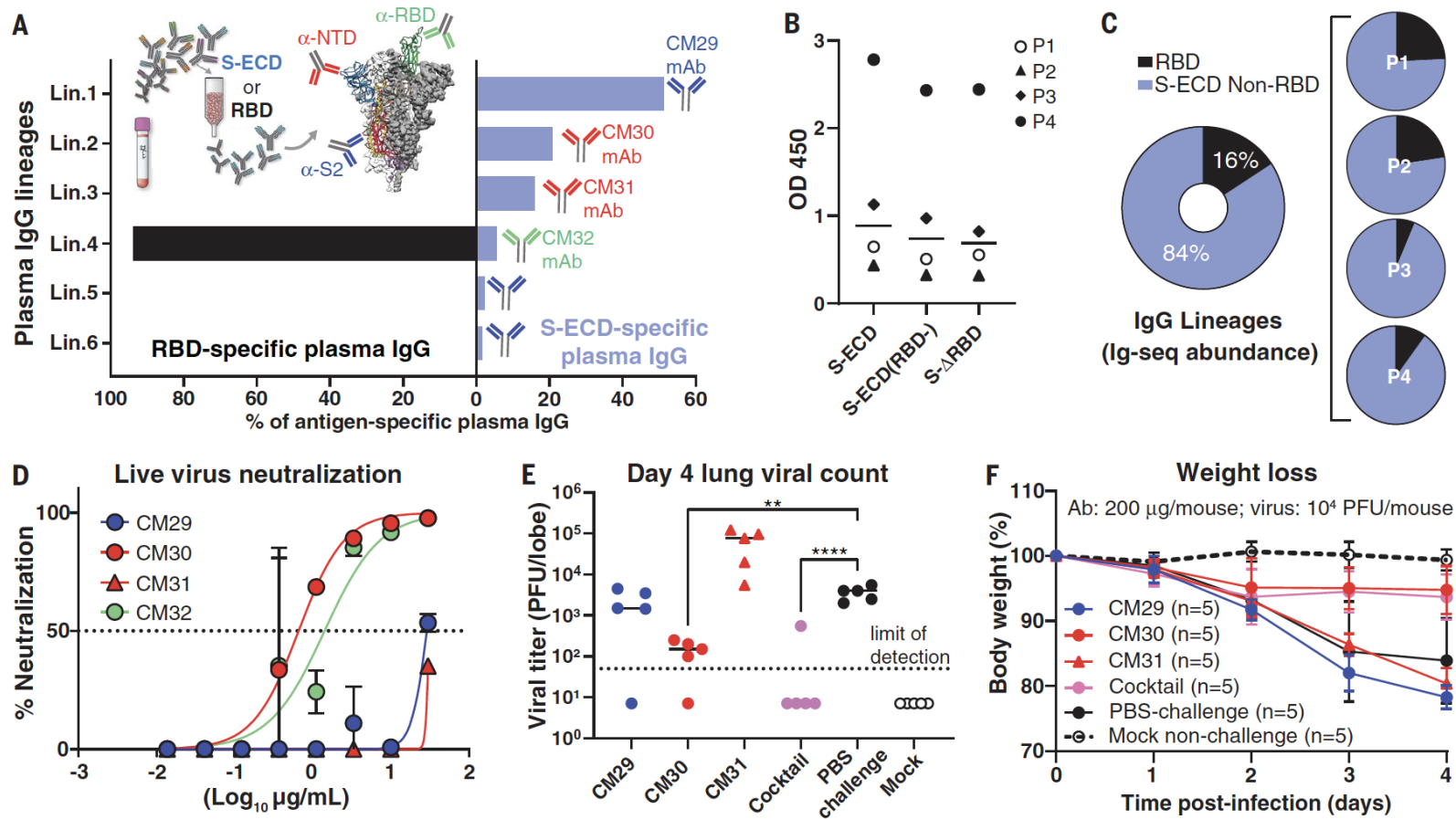
### CORONAVIRUS

# Prevalent, protective, and convergent IgG recognition of SARS-CoV-2 non-RBD spike epitopes

William N. Voss<sup>1</sup>, Yixuan J. Hou<sup>2,#</sup>, Nicole V. Johnson<sup>1,#</sup>, George Delidakis<sup>3</sup>, Jin Eyun Kim<sup>4</sup>, Kamyab Javanmardi<sup>1</sup>, Andrew P. Horton<sup>1</sup>, Foteini Bartzoka<sup>1</sup>, Chelsea J. Paresi<sup>5</sup>, Yuri Tanno<sup>3</sup>, Chia-Wei Chou<sup>1</sup>, Shawn A. Abbasi<sup>6</sup>, Whitney Pickens<sup>1</sup>, Katia George<sup>1</sup>, Daniel R. Boutz<sup>1,7</sup>, Dalton M. Towers<sup>3</sup>, Jonathan R. McDaniel<sup>8</sup>, Daniel Billick<sup>1</sup>, Jule Goike<sup>1</sup>, Lori Rowe<sup>9,10</sup>, Dhvani Batra<sup>9</sup>, Jan Pohl<sup>9</sup>, Justin Lee<sup>9</sup>, Shivaprakash Gangappa<sup>11</sup>, Suryaprakash Sambhara<sup>11</sup>, Michelle Gadush<sup>12</sup>, Nianshuang Wang<sup>1</sup>, Maria D. Person<sup>12</sup>, Brent L. Iverson<sup>5</sup>, Jimmy D. Gollihar<sup>1,7,13</sup>, John M. Dye<sup>6</sup>, Andrew S. Herbert<sup>6</sup>, Ilya J. Finkelstein<sup>1</sup>, Ralph S. Baric<sup>2,14</sup>, Jason S. McLellan<sup>1</sup>, George Georgiou<sup>1,3,4,15</sup>, Jason J. Lavinder<sup>1,3\*</sup>, Gregory C. Ippolito<sup>1,13,15\*</sup>

## CORONAVIRUS

## Prevalent, protective, and convergent IgG recognition of SARS-CoV-2 non-RBD spike epitopes



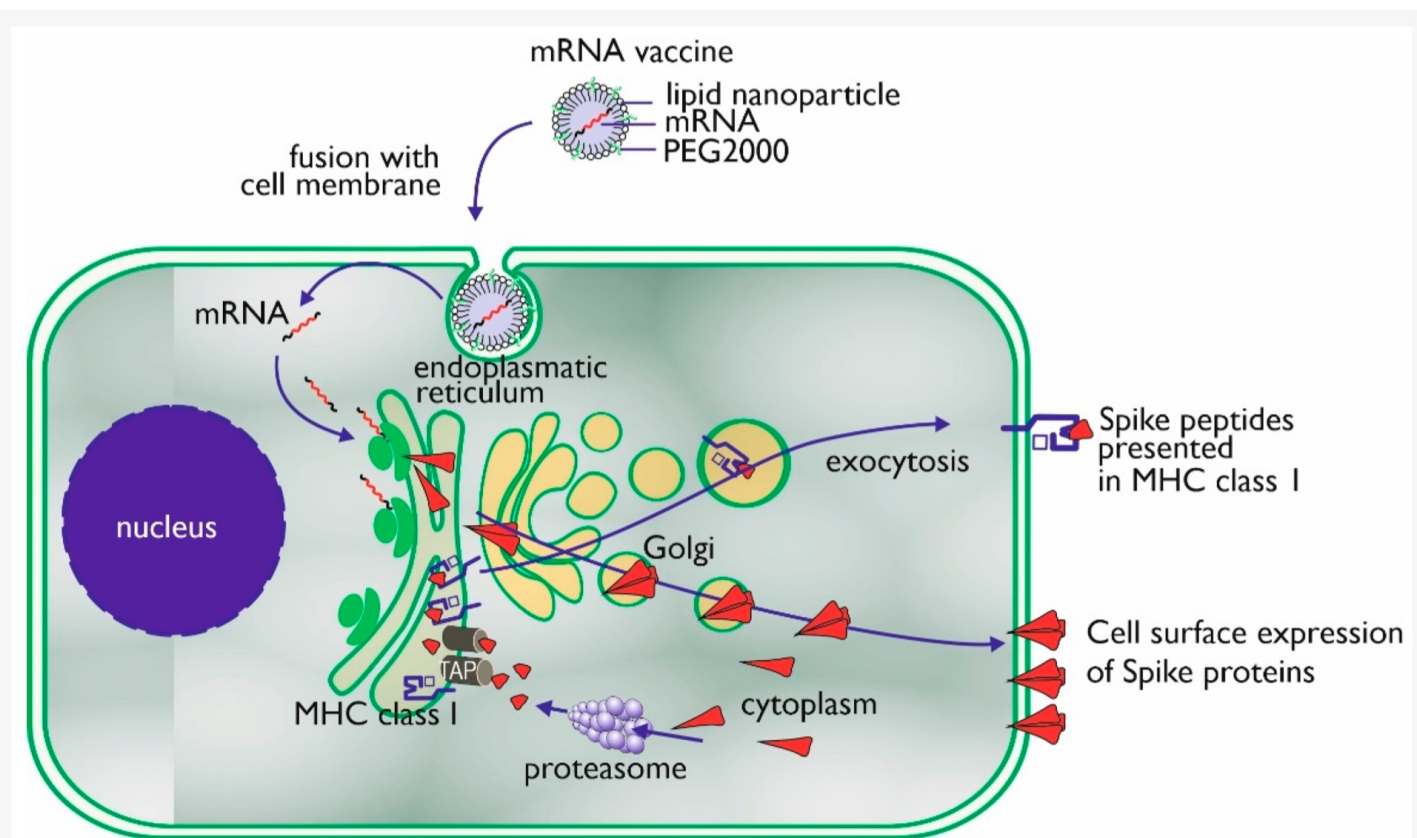
# Structure-based design of prefusion-stabilized SARS-CoV-2 spikes

Ching-Lin Hsieh<sup>1</sup>, Jory A. Goldsmith<sup>1</sup>, Jeffrey M. Schaub<sup>1</sup>, Andrea M. DiVenere<sup>2</sup>, Hung-Che Kuo<sup>1</sup>, Kamyab Javanmardi<sup>1</sup>, Kevin C. Le<sup>2</sup>, Daniel Wrapp<sup>1</sup>, Alison G. Lee<sup>1</sup>, Yutong Liu<sup>2</sup>, Chia-Wei Chou<sup>1</sup>, Patrick O. Byrne<sup>1</sup>, Christy K. Hjorth<sup>1</sup>, Nicole V. Johnson<sup>1</sup>, John Ludes-Meyers<sup>1</sup>, Annalee W. Nguyen<sup>2</sup>, Juyeon Park<sup>1</sup>, Nianshuang Wang<sup>1</sup>, Dzifa Amengor<sup>1</sup>, Jason J. Lavinder<sup>1,2</sup>, Gregory C. Ippolito<sup>1,3</sup>, Jennifer A. Maynard<sup>2\*</sup>, Ilya J. Finkelstein<sup>1,4\*</sup>, Jason S. McLellan<sup>1\*</sup>

<sup>1</sup>Department of Molecular Biosciences, University of Texas, Austin, TX 78712, USA. <sup>2</sup>Department of Chemical Engineering, University of Texas, Austin, TX 78712, USA. <sup>3</sup>Department of Oncology, Dell Medical School, University of Texas, Austin, TX 78712, USA. <sup>4</sup>Center for Systems and Synthetic Biology, University of Texas, Austin, TX 78712, USA.

\*Corresponding author. Email: maynard@che.utexas.edu (J.A.M.); ilya@finkelsteinlab.org (I.J.F.); jmclellan@austin.utexas.edu (J.S.M.)

The COVID-19 pandemic has led to accelerated efforts to develop therapeutics and vaccines. A key target of these efforts is the spike (S) protein, which is metastable and difficult to produce recombinantly. Here, we characterized 100 structure-guided spike designs and identified 26 individual substitutions that increased protein yields and stability. Testing combinations of beneficial substitutions resulted in the identification of HexaPro, a variant with six beneficial proline substitutions exhibiting ~10-fold higher expression than its parental construct and the ability to withstand heat stress, storage at room temperature, and three freeze-thaw cycles. A 3.2 Å-resolution cryo-EM structure of HexaPro confirmed that it retains the prefusion spike conformation. High-yield production of a stabilized prefusion spike protein will accelerate the development of vaccines and serological diagnostics for SARS-CoV-2.



## Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability

Katalin Karikó<sup>1</sup>, Hiromi Muramatsu<sup>1</sup>, Frank A Welsh<sup>1</sup>, János Ludwig<sup>2</sup>, Hiroki Kato<sup>3</sup>, Shizuo Akira<sup>3</sup>, and Drew Weissman<sup>4</sup>

<sup>1</sup>Department of Neurosurgery, University of Pennsylvania, Philadelphia, Pennsylvania, USA

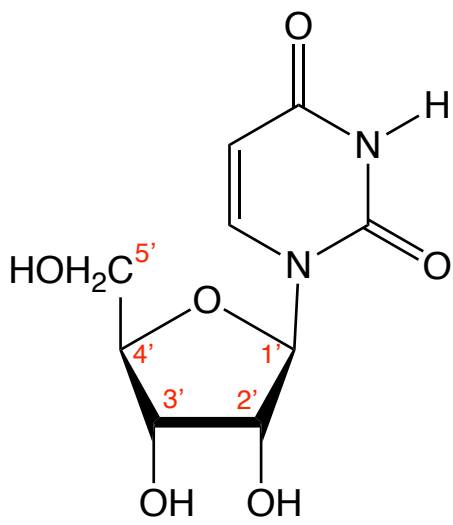
<sup>2</sup>Laboratory of RNA Molecular Biology, The Rockefeller University, New York, New York, USA

<sup>3</sup>Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

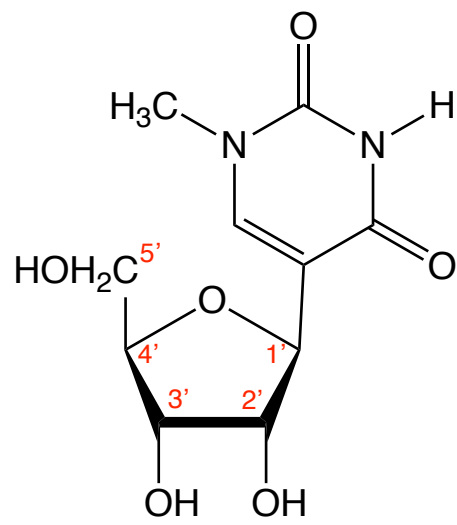
<sup>4</sup>Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

### Abstract

*In vitro*-transcribed mRNAs encoding physiologically important proteins have considerable potential for therapeutic applications. However, in its present form, mRNA is unfeasible for clinical use because of its labile and immunogenic nature. Here, we investigated whether incorporation of naturally modified nucleotides into transcripts would confer enhanced biological properties to mRNA. We found that mRNAs containing pseudouridines have a higher translational capacity than unmodified mRNAs when tested in mammalian cells and lysates or administered intravenously into mice at 0.015–0.15 mg/kg doses. The delivered mRNA and the encoded protein could be detected in the spleen at 1, 4, and 24 hours after the injection, where both products were at significantly higher levels when pseudouridine-containing mRNA was administered. Even at higher doses, only the unmodified mRNA was immunogenic, inducing high serum levels of interferon- $\alpha$  (IFN- $\alpha$ ). These findings indicate that nucleoside modification is an effective approach to enhance stability and translational capacity of mRNA while diminishing its immunogenicity *in vivo*. Improved properties conferred by pseudouridine make such mRNA a promising tool for both gene replacement and vaccination.



Uridine



*N1*-methylpseudouridine  
(m1Ψ)

Amy Rhoden Smith



## Careers in Chemistry

Amy Rhoden Smith, PhD works at Precision BioSciences, a gene editing therapeutics company. As a program development leader, Dr. Rhoden Smith works with multiple teams to lead cell and gene editing therapy programs through preclinical and early clinical development. She loves working in biotechs and startups, where she can think about how to use cutting-edge science to bring meaningful therapies to patients. Dr. Rhoden Smith earned her BS in chemistry at the College of Charleston. She received her PhD in organic chemistry from the University of Texas at Austin.

Dr. Rhoden Smith has always been interested in applying her chemical knowledge to understand biological problems, so she started her career in biotechnology by joining Moderna Therapeutics. Her team used chemistry to create novel therapeutic mRNA conjugates for improved mRNA in vivo half-life and protein expression. She then moved to Intellia Therapeutics, where she led a team focused on generating Cas9 mRNA and synthetic guide RNAs for in vivo gene editing therapeutic applications. After working on projects that were discovery-based, she moved to Precision BioSciences, where she focuses on bringing products into the clinic.

Dr. Rhoden Smith says that organic chemistry gave her an understanding of how molecules interact with each other, which applies not only to small molecules, but also much larger ones like proteins, nucleic acids, and even cells. Just as importantly, it also taught her the value of problem-solving and gave her a passion for understanding complex problems, which she uses every day.

# A Novel Amino Lipid Series for mRNA Delivery: Improved Endosomal Escape and Sustained Pharmacology and Safety in Non-human Primates

Staci Sabnis,<sup>1</sup> E. Sathyajith Kumarasinghe,<sup>1</sup> Timothy Salerno,<sup>1</sup> Cosmin Mihai,<sup>1</sup> Tatiana Ketova,<sup>1</sup> Joseph J. Senn,<sup>1</sup> Andy Lynn,<sup>1</sup> Alex Bulychev,<sup>1</sup> Iain McFadyen,<sup>1</sup> Joyce Chan,<sup>1</sup> Örn Almarsson,<sup>1</sup> Matthew G. Stanton,<sup>1,2</sup> and Kerry E. Benenato<sup>1</sup>

<sup>1</sup>Moderna Therapeutics, 200 Technology Square, Cambridge, MA 02139, USA

**The success of mRNA-based therapies depends on the availability of a safe and efficient delivery vehicle. Lipid nanoparticles have been identified as a viable option. However, there are concerns whether an acceptable tolerability profile for chronic dosing can be achieved. The efficiency and tolerability of lipid nanoparticles has been attributed to the amino lipid. Therefore, we developed a new series of amino lipids that address this concern. Clear structure-activity relationships were developed that resulted in a new amino lipid that affords efficient mRNA delivery in rodent and primate models with optimal pharmacokinetics. A 1-month toxicology evaluation in rat and non-human primate demonstrated no adverse events with the new lipid nanoparticle system. Mechanistic studies demonstrate that the improved efficiency can be attributed to increased endosomal escape. This effort has resulted in the first example of the ability to safely repeat dose mRNA-containing lipid nanoparticles in non-human primate at therapeutically relevant levels.**

## INTRODUCTION

mRNA-based therapies have the potential to revolutionize the way we treat diseases. The surging interest in mRNA as a drug modality stems from the potential to deliver transmembrane and intracellular proteins, targets that standard biologics are unable to access due to their inability to cross the cell membrane.<sup>1</sup> One major challenge to making mRNA-based therapies a reality is the identification of an optimal delivery vehicle. Due to its large size, chemical instability, and potential immunogenicity, mRNA requires a delivery vehicle that can offer protection from endo- and exo-nucleases, as well as shield the cargo from immune sentinels. Lipid nanoparticles (LNPs) have been identified as a leading option in this regard.<sup>2</sup> Moderna Therapeutics has recently validated this approach by demonstrating safe and effective delivery of an mRNA-based vaccine formulated in LNPs.<sup>3</sup>

Key performance criteria for an LNP delivery system are to maximize cellular uptake and enable efficient release of mRNA from the endosome. At the same time, the LNP must provide a stable drug product and be able to be dosed safely at therapeutically relevant levels. LNPs are multi-component systems that typically consist of an amino lipid,

phospholipid, cholesterol, and a PEG-lipid.<sup>2</sup> Each component is required for aspects of efficient delivery of the nucleic acid cargo and stability of the particle. The key component thought to drive cellular uptake, endosomal escape, and tolerability is the amino lipid. Cholesterol and the PEG-lipid contribute to the stability of the drug product both *in vivo* and on the shelf, while the phospholipid provides additional fusogenicity to the LNP, thus helping to drive endosomal escape and rendering the nucleic acid bioavailable in the cytosol of cells.

Several amino lipid series have been developed for oligonucleotide delivery over the past couple of decades.<sup>4</sup> The literature highlights direct links between the structure of the amino lipid and the resultant delivery efficiency and tolerability of the LNP. The amino lipid MC3 (DLin-MC3-DMA) is the most clinically advanced oligonucleotide delivery system, as siRNA formulated in MC3-based LNPs has progressed to phase III for the treatment of transthyretin-mediated amyloidosis.<sup>5,6</sup> More recently, literature reports have demonstrated the effectiveness of MC3-based LNPs to deliver mRNA.<sup>7</sup> LNPs of this class are quickly opsonized by apolipoprotein E (ApoE) when delivered intravenously (*i.v.*), which enables cellular uptake into hepatocytes by the low-density lipoprotein receptor (LDLr).<sup>8</sup> Concerns remain that MC3's long tissue half-life could contribute to unfavorable side effects hindering its use for chronic therapies.<sup>9</sup> In addition, LNPs can induce activation of the immune system resulting in complement activation-related pseudoallergy (CARPA), an acute immunological response that can lead to anaphylactic-like shock.<sup>10</sup>

To unleash the potential of mRNA therapies for humans, we required a class of LNPs with increased delivery efficiency along with a metabolic and toxicity profile that would enable chronic dosing in humans.

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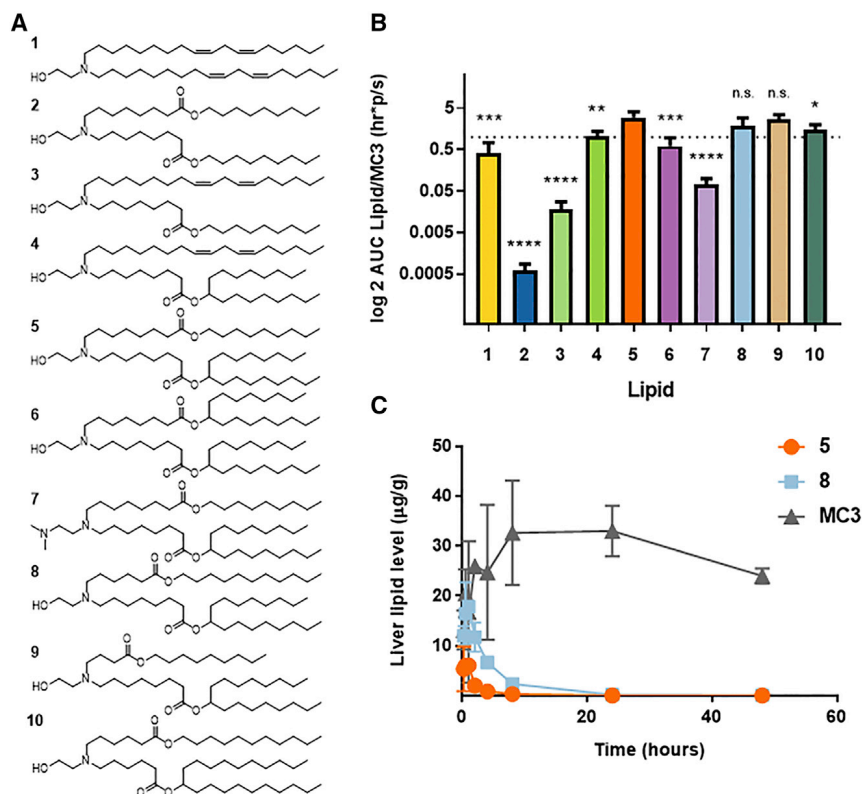
Received 20 November 2017; accepted 9 March 2018;  
<https://doi.org/10.1016/j.ymthe.2018.03.010>

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**Figure 1. Optimization of Efficiency and Clearance of Amino Lipid**

(A) Structures of amino lipids. (B) Whole-body luciferase bioluminescence AUC of novel LNPs versus MC3 LNPs, measured in CD-1 mice (n = 6 at 3 and 6 hr, n = 3 at 24 hr), 0.5 mg/kg dose firefly luciferase (ffLuc) mRNA, i.v. bolus, error bars indicate SD of the ratio of novel lipid AUC versus MC3 AUC. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001, n.s. = not statistically significant. (C) Parent amino lipid levels measured in liver tissue from Sprague-Dawley rats (n = 3 per time point), 0.2 mg/kg dose hEPO mRNA, mean ± SD, p < 0.05 for lipids 5 and 8 AUC relative to MC3.

We took a rational medicinal chemistry approach to amino lipid optimization aiming to identify structural motifs that provide chemical stability, optimal tissue clearance, and mRNA delivery efficiency. Our initial rodent screens led to the identification of a lead lipid with good delivery efficiency and pharmacokinetics. The lead LNP was profiled further in non-human primate for efficiency of delivery after single and repeat dosing. Finally, the optimized LNPs were evaluated in 1-month repeat dose toxicity studies in rat and non-human primate.

## RESULTS

Initial screening of a broad chemical space identified ethanolamine as an amino lipid head group that could effectively drive mRNA encapsulation and provide LNPs with superior physicochemical properties. Combining the ethanolamine head group with di-linoleic lipid tails (lipid 1; Figure 1; Table 1) generated an LNP with high encapsulation of luciferase mRNA, small particle size, and low polydispersity index (PDI). The LNP with lipid 1 had a surface pK<sub>a</sub> (apparent value for the particle) in the range that has been shown to be optimal for siRNA delivery.<sup>11,12</sup> To evaluate the efficiency of the new amino lipids, LNPs using the novel lipids were tested *in vivo* in mice using firefly luciferase mRNA as a reporter. An MC3 LNP was included as a control in each experiment, enabling us to compare LNPs from experiment to experiment. Measured luciferase activity also enabled us to determine protein bio-distribution. i.v. delivery of 0.5 mg/kg (mRNA dose level) of lipid 1-based LNPs to mice resulted in luciferase activity two-fold lower than an MC3 LNP control (Figure 1B).

Whole-body imaging clearly demonstrated that the majority of protein expression was localized in the liver (Figure S1). We found that the lipid had similar clearance to MC3 from liver tissue with 66% of the original dose remaining in liver tissue of mice 24 hr post-dose (Table 1).

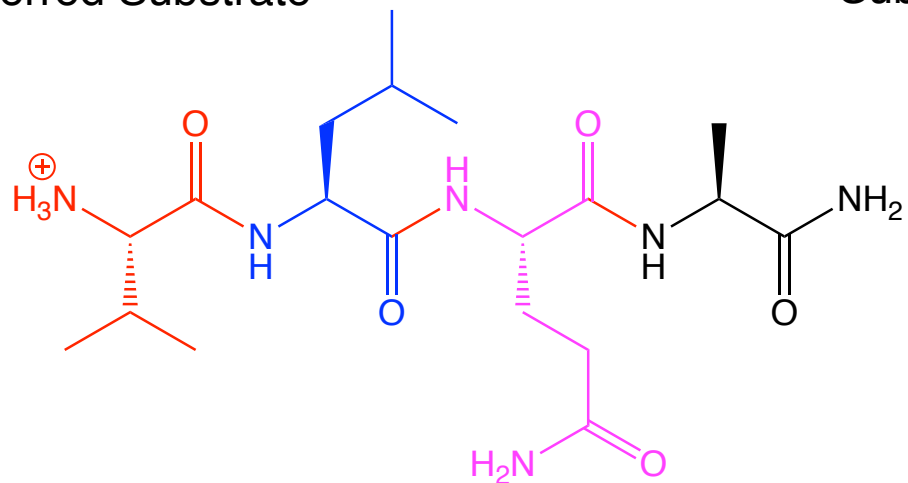
To improve tissue clearance, we introduced ester linkages in the lipid tails (lipids 2 and 3; Figure 1A), which are reported to trigger metabolism by esterases *in vivo*.<sup>13</sup> This has been shown to be a viable strategy to improve lipid clearance in a MC3-based lipid structure.<sup>9</sup> First, we established that the lipids were chemically stable by measuring ethanol stability at room temperature and 37°C (Table S1). We observed less than 1% change in purity for all lipids tested. LNPs formed with lipid 2 were significantly larger with a surface pK<sub>a</sub> > 7 (Table 1). Removal of one ester (lipid 3) afforded LNPs with improved physicochemical characteristics and lower LNP surface pK<sub>a</sub>. *In vivo*, neither lipid demonstrated efficient mRNA delivery (Figure 1B); however, we did observe rapid tissue clearance, with no lipid detected at 24 hr (Table 1).

Improvement in protein expression was observed when a secondary ester was introduced (lipid 4; Figures 1A and 1B). We observed equivalent expression to MC3 LNPs, but the clearance rate was slower than lipids 2 and 3 (67% lipid remaining; Table 1). Replacement of the linoleic tail with a primary ester-containing lipid tail (lipid 5; Figure 1A) provided increased expression (3-fold higher than MC3; Figure 1B) and optimal tissue clearance (no lipid detected at 24 hr; Table 1). To further increase expression an additional secondary ester was introduced (6), but this resulted in a lowering of the surface pK<sub>a</sub> to 6.00 and lower luciferase activity. In addition, the lipid had a significantly slower tissue clearance with 68% remaining at 24 hr.

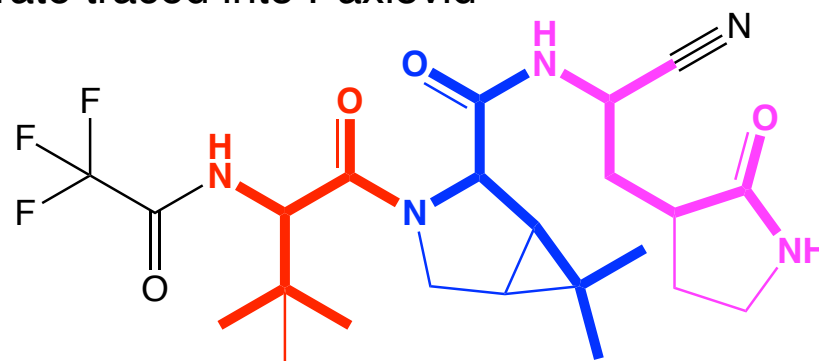
With an optimal lipid tail structure identified we re-visited the ethanolamine head group. Lipid 7 is one representative example (Figure 1A) where the alcohol functionality is replaced with a dimethylamine. This generated an LNP with comparable physicochemical properties, but complete loss of delivery efficiency (Figure 1B).



Preferred Substrate



Substrate traced into Paxlovid



Paxlovid

