Inhibitors of HIV Integrase

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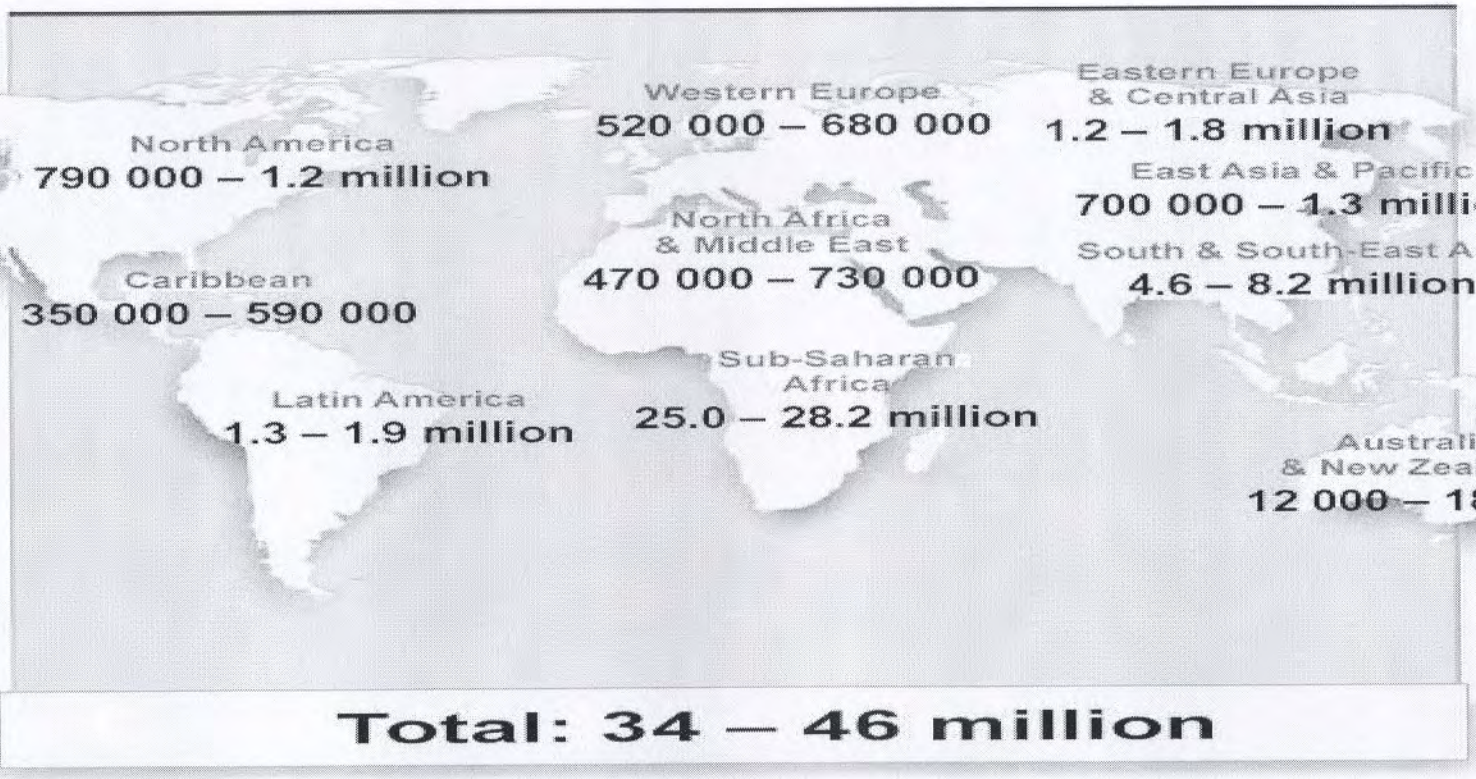
ADULTS AND CHILDREN ESTIMATED TO BE LIVING WITH HIV/AIDS, END 2003



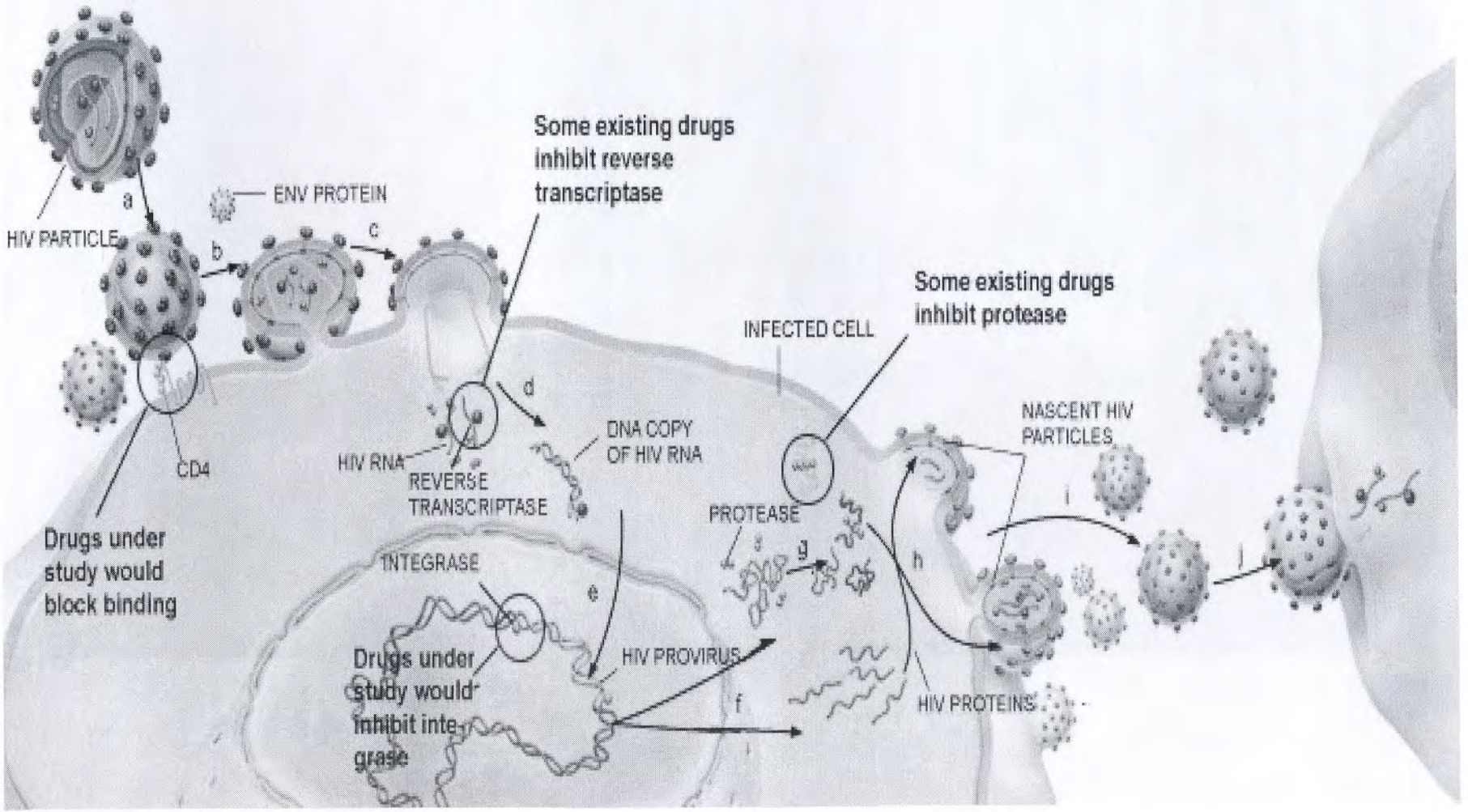
AIDS epidemic update: December 2003

World Health Organization

UNAIDS

New HIV Infections in 2003: 5 million
Deaths due to HIV/AIDS in 2003: 3 million
Predicted HIV Infections in 2010: 100 million

The HIV Viral Life Cycle



1998 Scientific American

HIV Treatment

- HIV is a manageable but incurable disease
- Current oral therapies all target 2 viral enzymes
  - Reverse transciptase
    - nucleoside (NRTI)
    - nonnucleoside (NNRTI)
  - Protease (PI)
- Current treatment guidelines recommend combination therapy with triple drug regimen for example:
  - 2 NRTI's + 1 NNRTI

  or
  - 2 NRTI's + 1 PI

Challenges in Treatment of HIV/AIDS

- Acute and Long Term Toxicities
- Non-Adherence
- Emergence of Resistant Viruses

- Resistance mitigates initial efficacy AND durability of antiretroviral therapy.
  - 78% of treated patients resistant to one class
  - 50% of treated patients resistant to multiple classes
  - Increasing incidence of resistance in acute infection
    - <5% pre1999, 13% in 1999, 20% in 2002

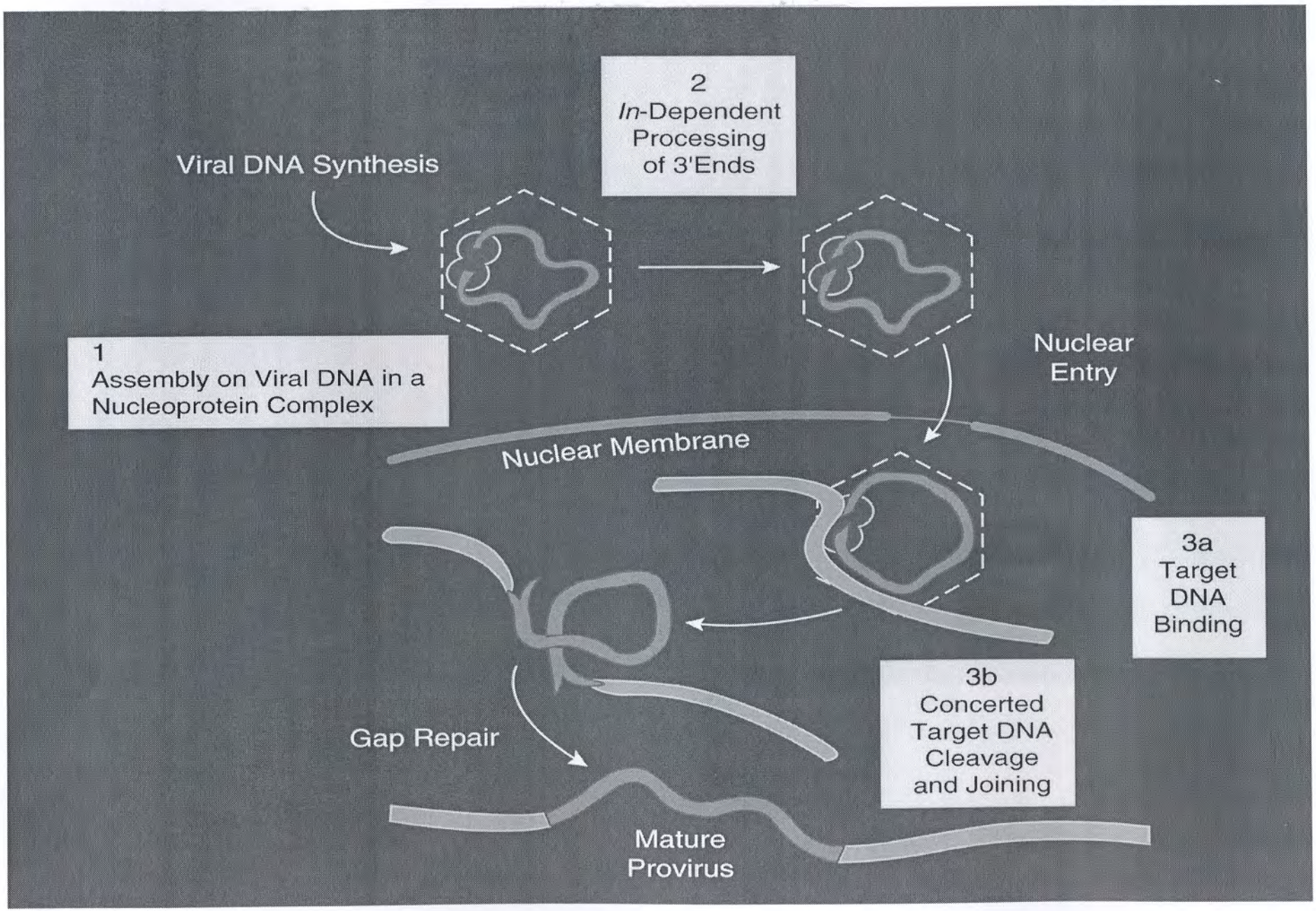
- Leads to therapy failure

⇒ Need for novel therapies

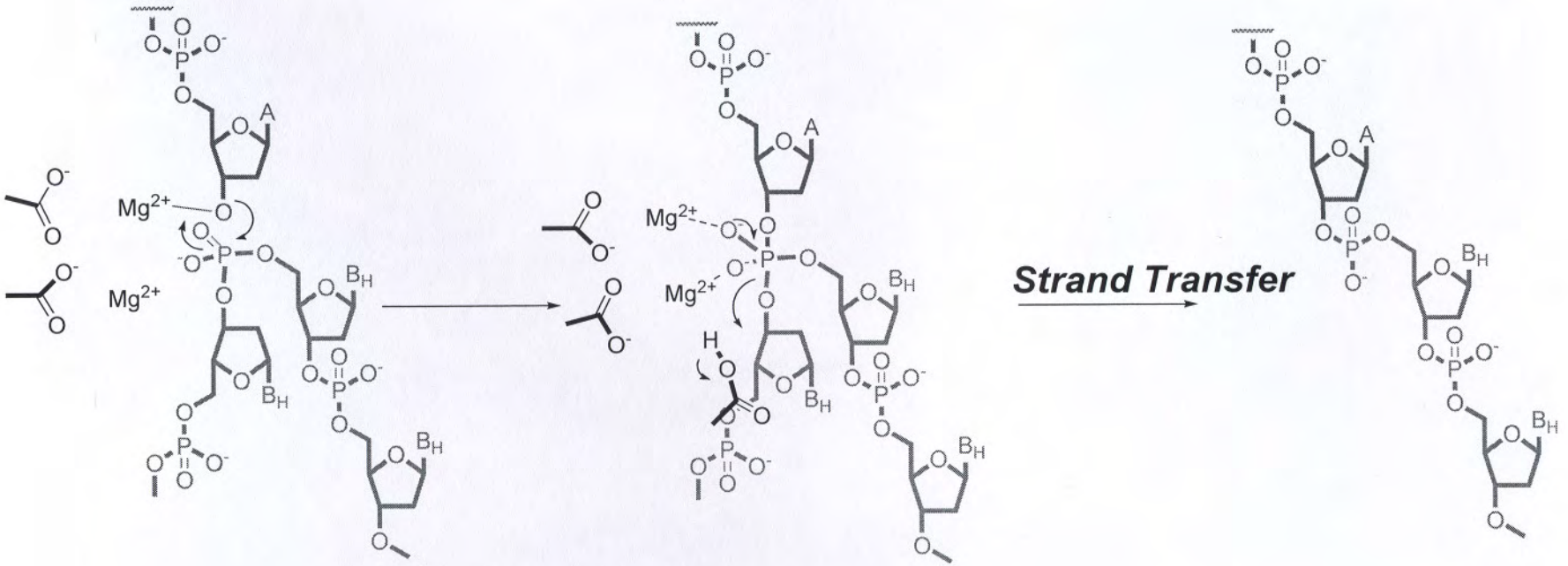
Integrase Is Essential For Viral Replication

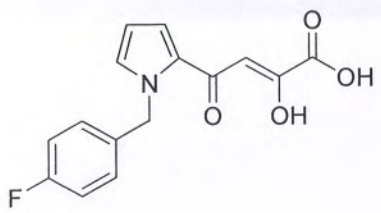
- HIV Integrase
  - Is one of three enzymes encoded by the viral genome
  - Like the other two, reverse transcriptase and protease, HIV integrase is essential for viral replication
  - Retroviruses lacking integrase or containing a non-functional integrase do not replicate

Integration Is A Multi-Step Process

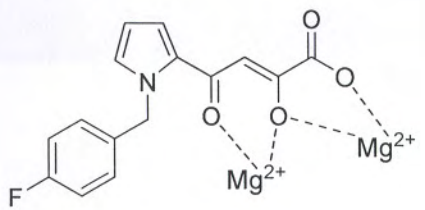


The Chemistry of HIV Integrase



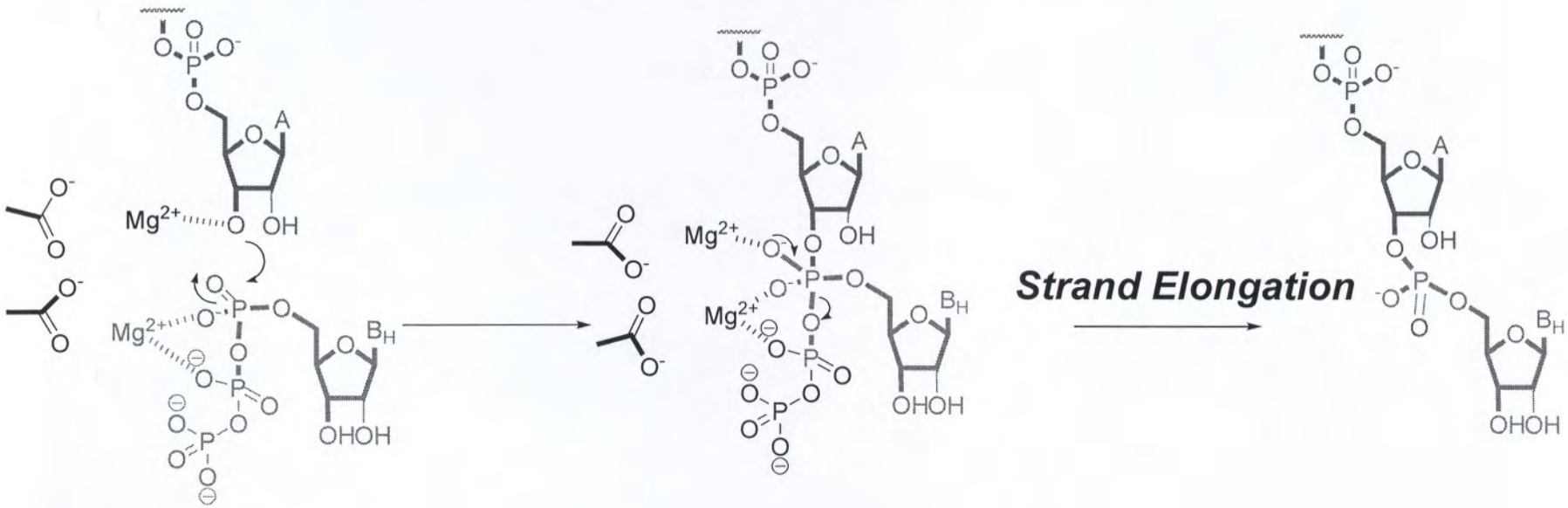


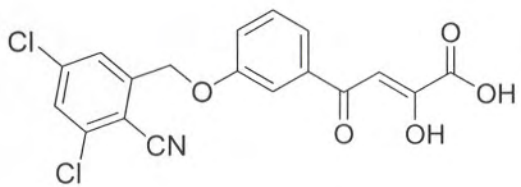
IC_{50} = 0.01 uM



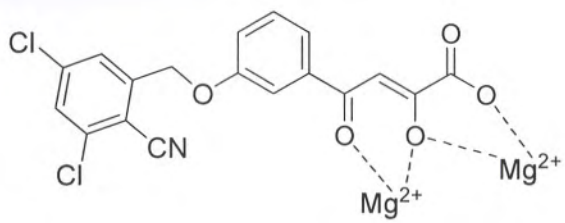
A mechanistically related enzyme - HCV Polymerase

- An RNA dependent RNA Polymerase

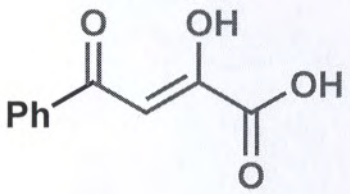




IC_{50} = 0.04 uM



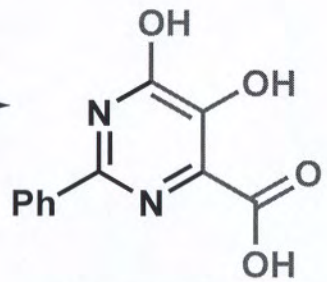
HCV Polymerase Leads



IC_{50} = 6 μM

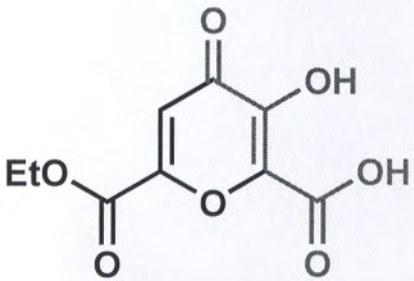
Biologically unstable
- covalently binds to proteins

Design



IC_{50} = 30 μM

Does not decarboxylate
Does not bind covalently to proteins

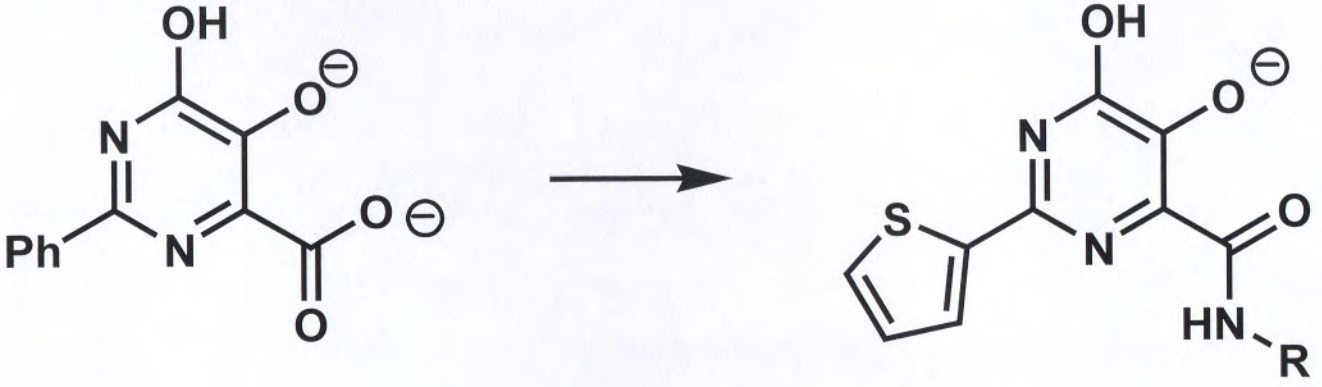


IC_{50} = 2 μM

Chemically unstable
- decarboxylates

HCV Polymerase leads from screening

From Polymerase to Integrase



Bis **anion at physiological pH**
- poor cell penetration

Lead for HIV-Integrase
(inactive on HCV Polymerase)

Assays

- Integrase Strand Transfer (QUICKIN IC_{50}):
  - Measures the ability of the test compound to inhibit the integration of preprocessed donor DNA fragment into target DNA.
- Viral Spread (CIC_{95}):
  - A 3 day multiple-cycle infectivity assay measuring the inhibition of viral spread with H9/iiib virus in MT4 cells to >95% as detected by p24 ELISA.

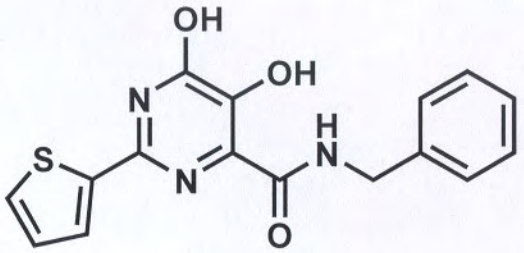
Therapeutic target

- Complete inhibition of viral replication in man
  - Plasma concentrations always > CIC_{95}
  - Need potent compounds (< 100 nM)
- Also need good Pharmacokinetics
  - High oral bioavailability (percentage of drug absorbed when dosed orally)
  - Low clearance (rate at which drug is removed from the body)
    - This leads to long half life

Plasma Protein Binding

- Drugs bind to plasma protein
  - Protein binding reduces activity (less free drug)
  - Measure activity in 10% foetal bovine serum (minimum) and in 50% normal human serum (maximum)
  - 10% FBS activity reflects 'cell penetration'
  - 50% NHS activity reflects protein binding

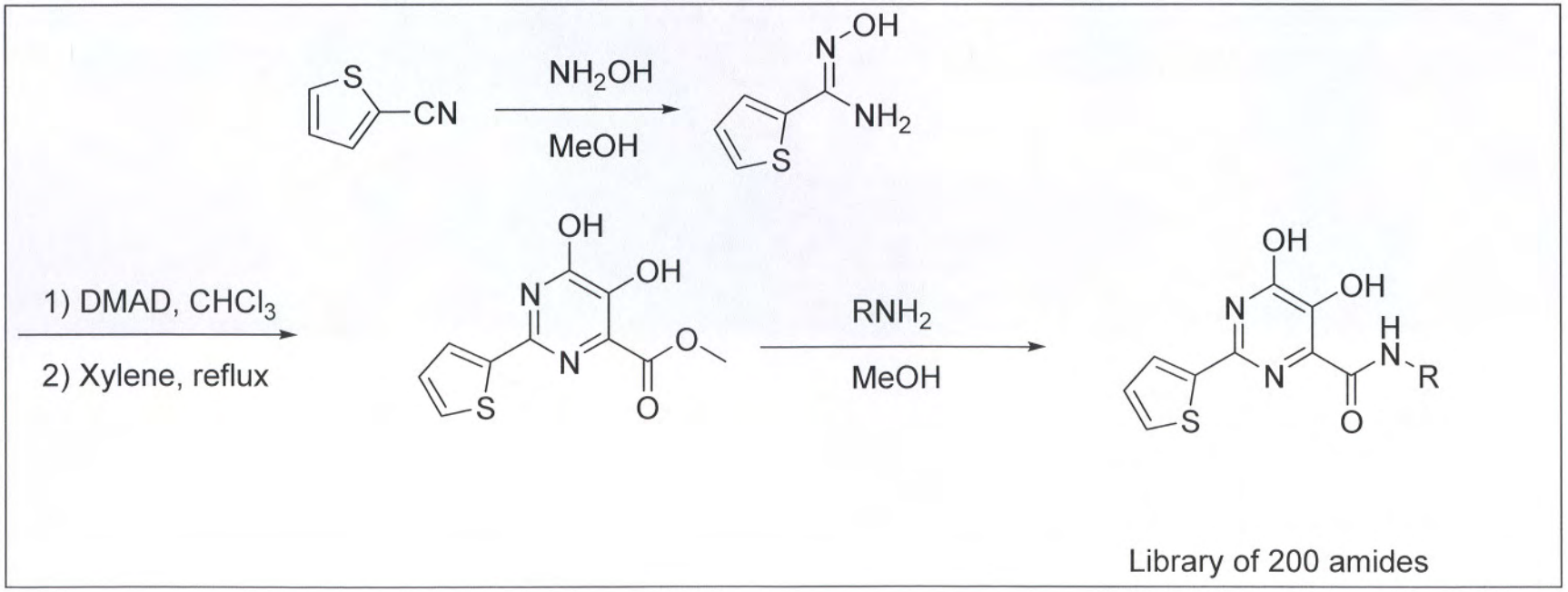
The Lead Structure



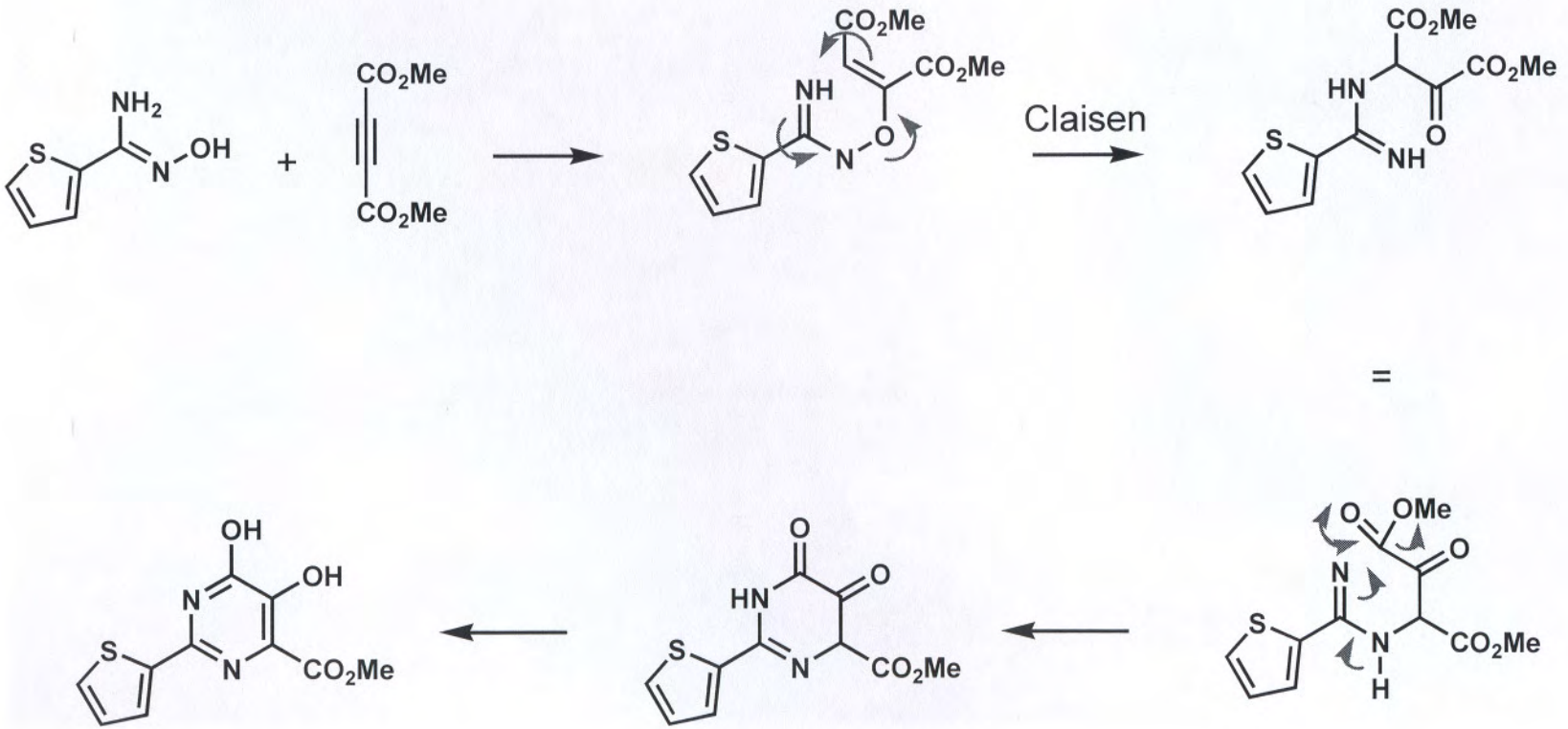
QUICKIN IC_{50} 80 nM

Rat Pharmacokinetics

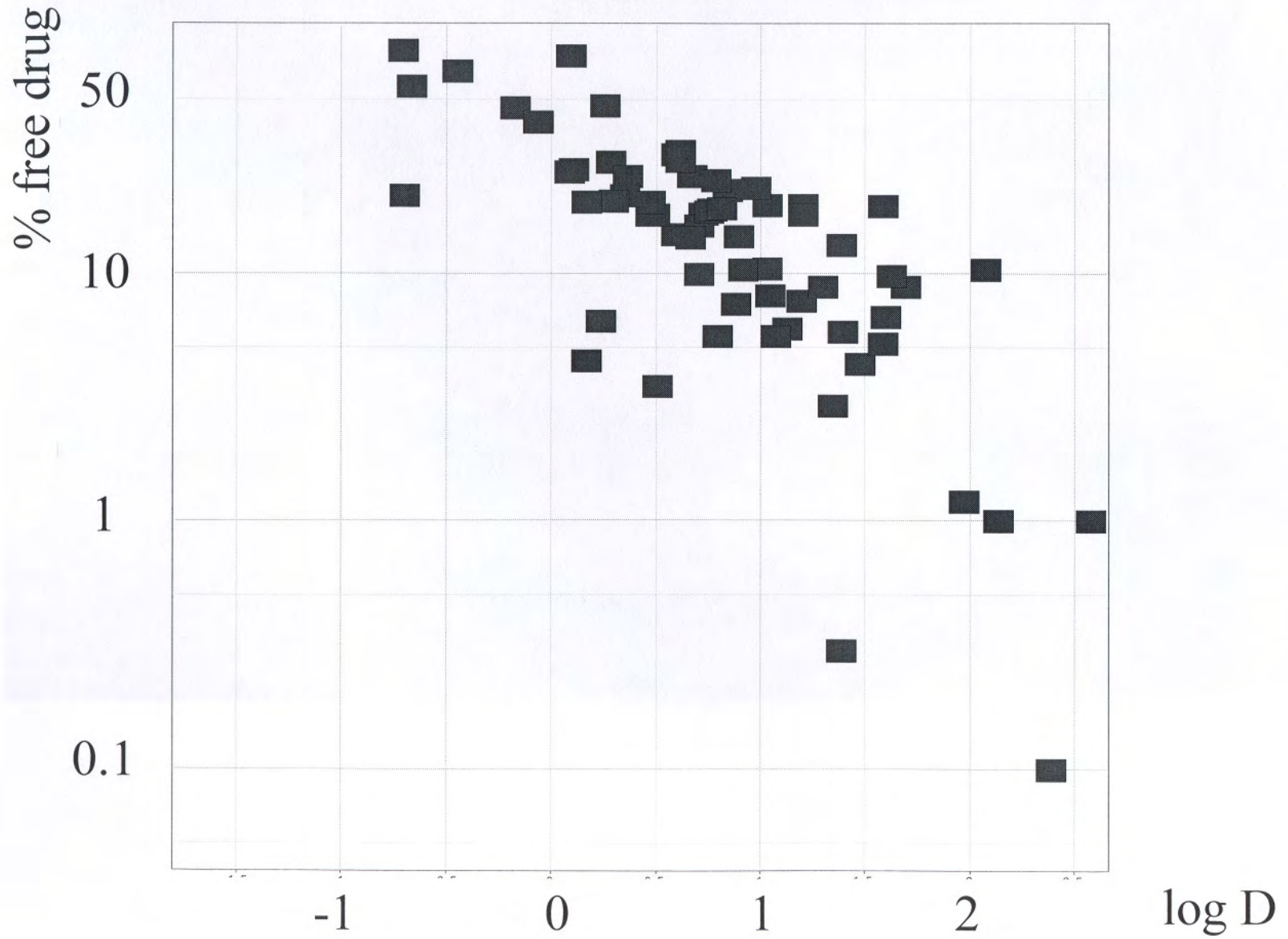
Biovailability (F)	Clearance	Half life
15%	5 ml/min/kg	3 h



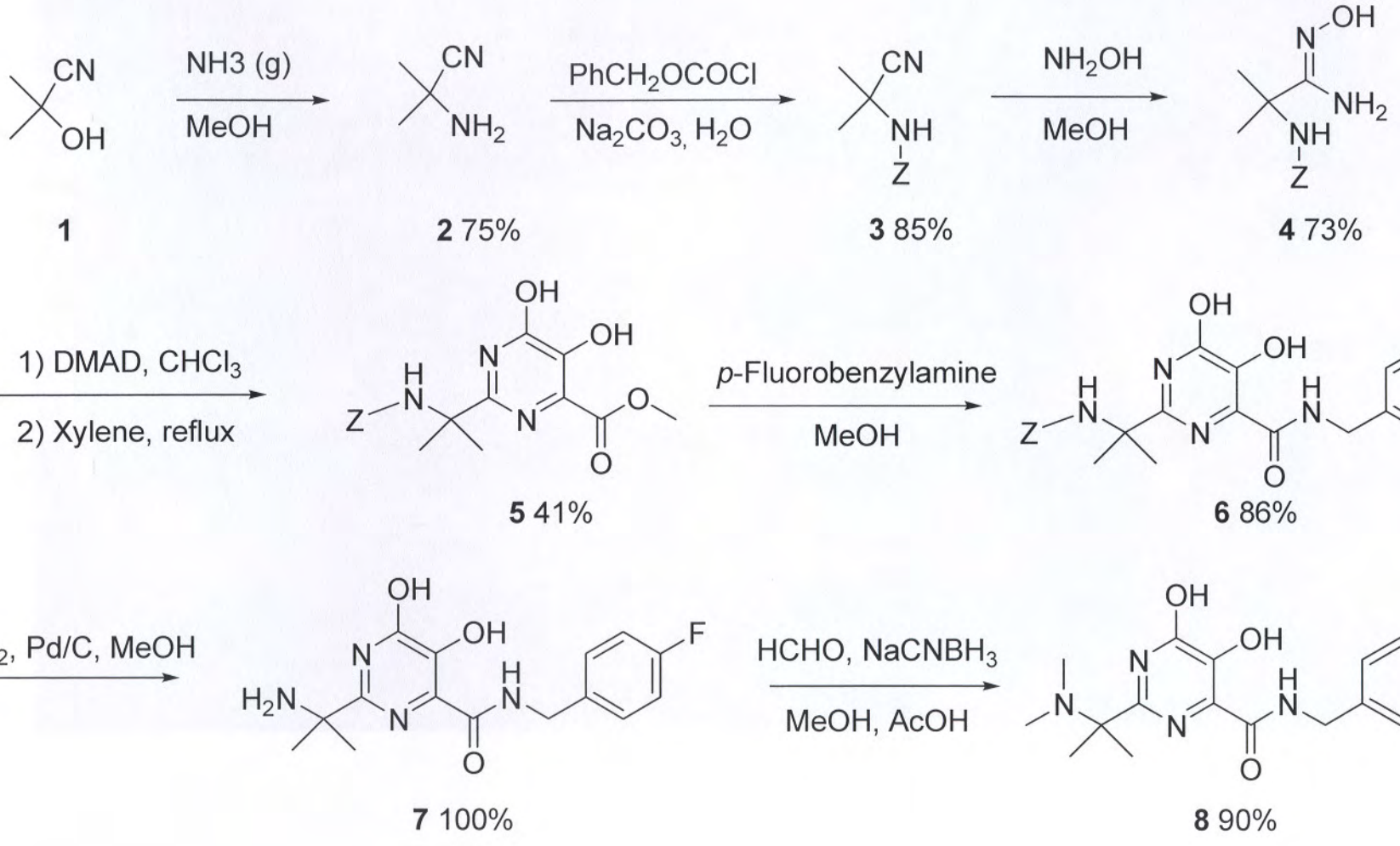
Mechanism?



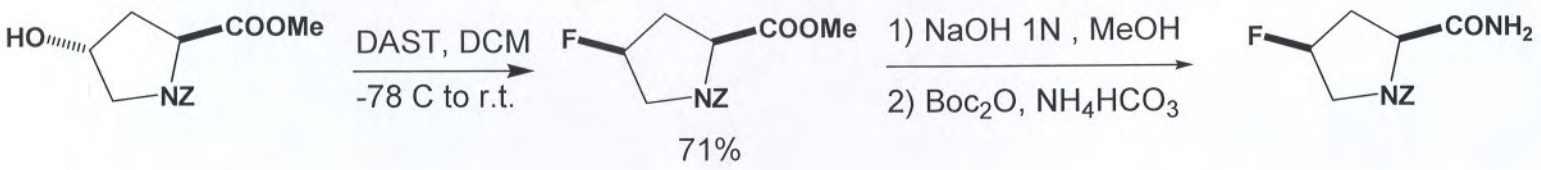
Protein binding

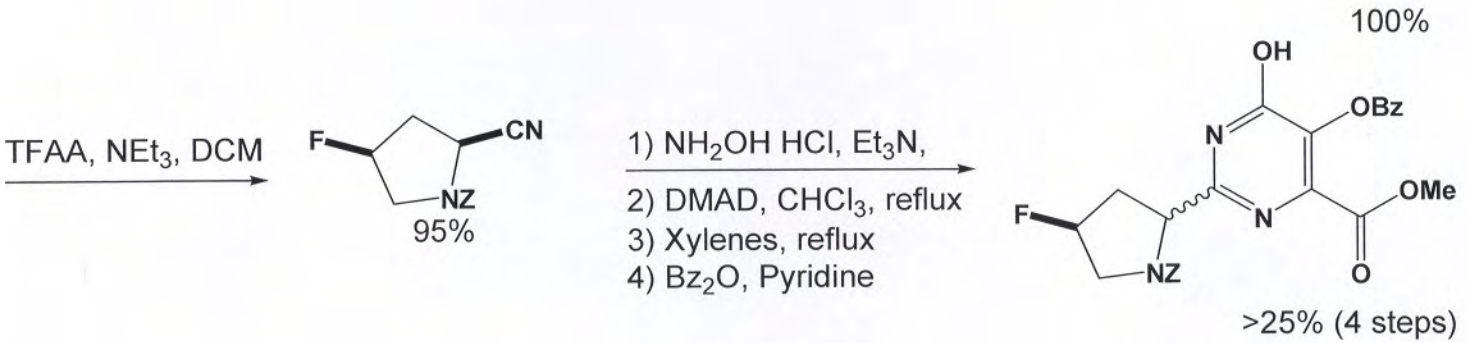


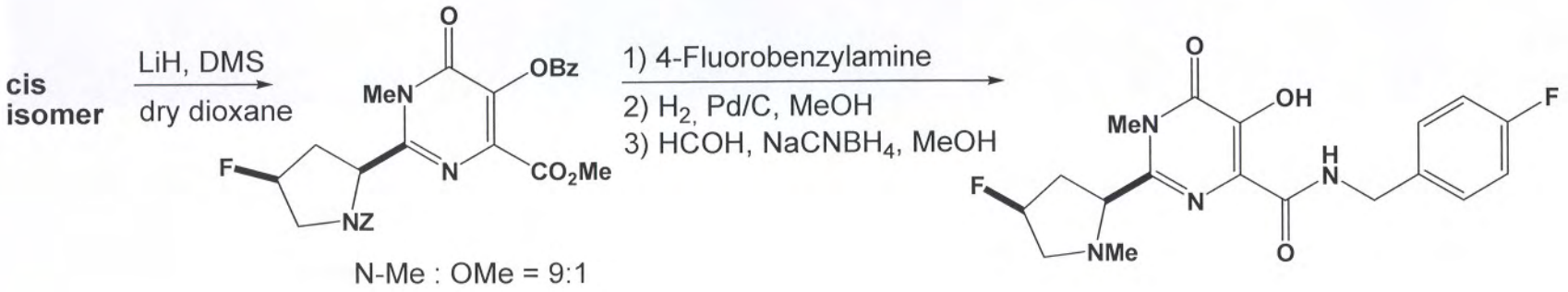
Synthesis



Fluoropyrrolidine synthesis







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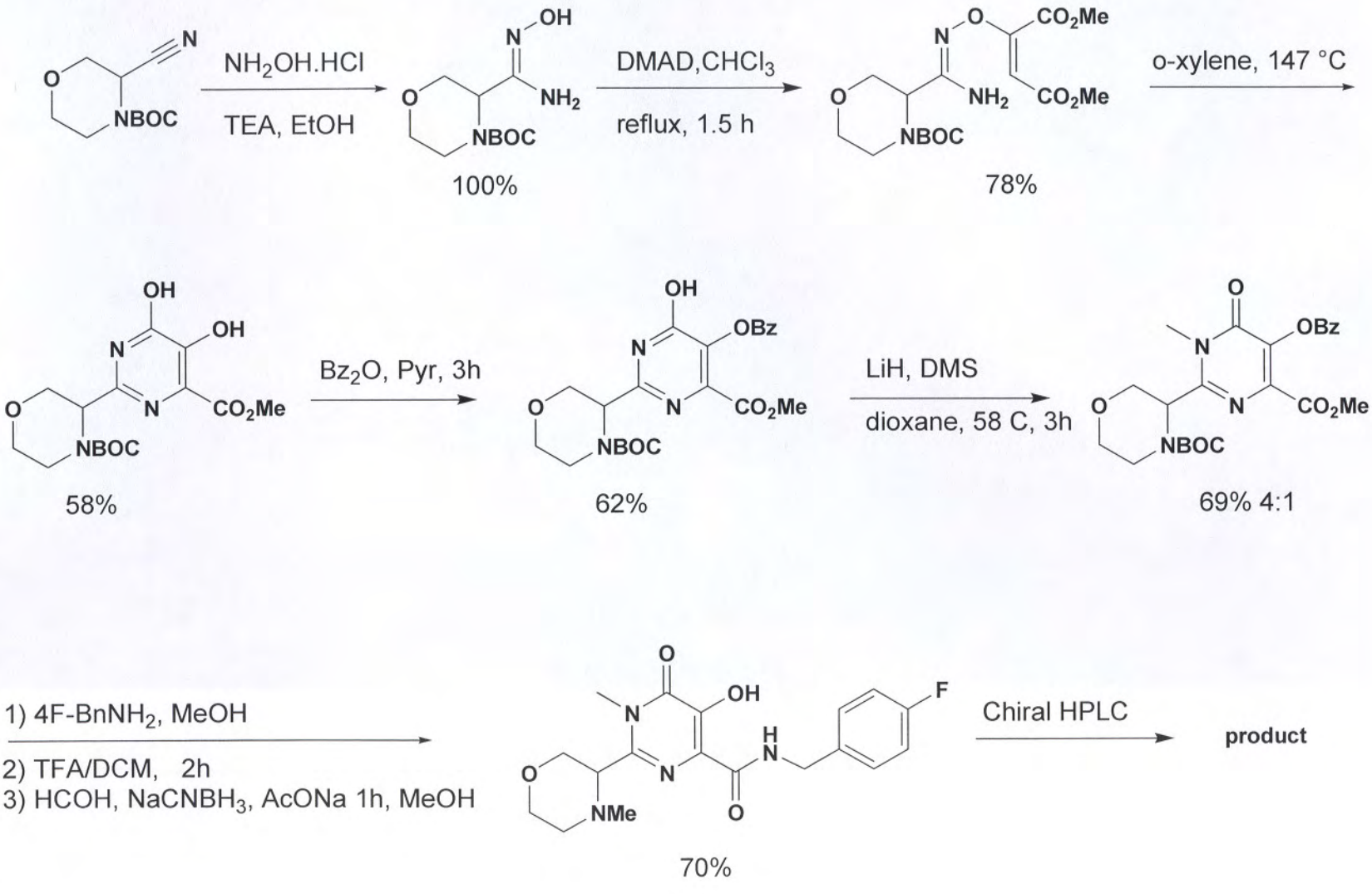

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