# Fascinating Excursions into Chiral Chemistry:
## An Insider's Perspective

The Fun and Joy of Process Chemistry

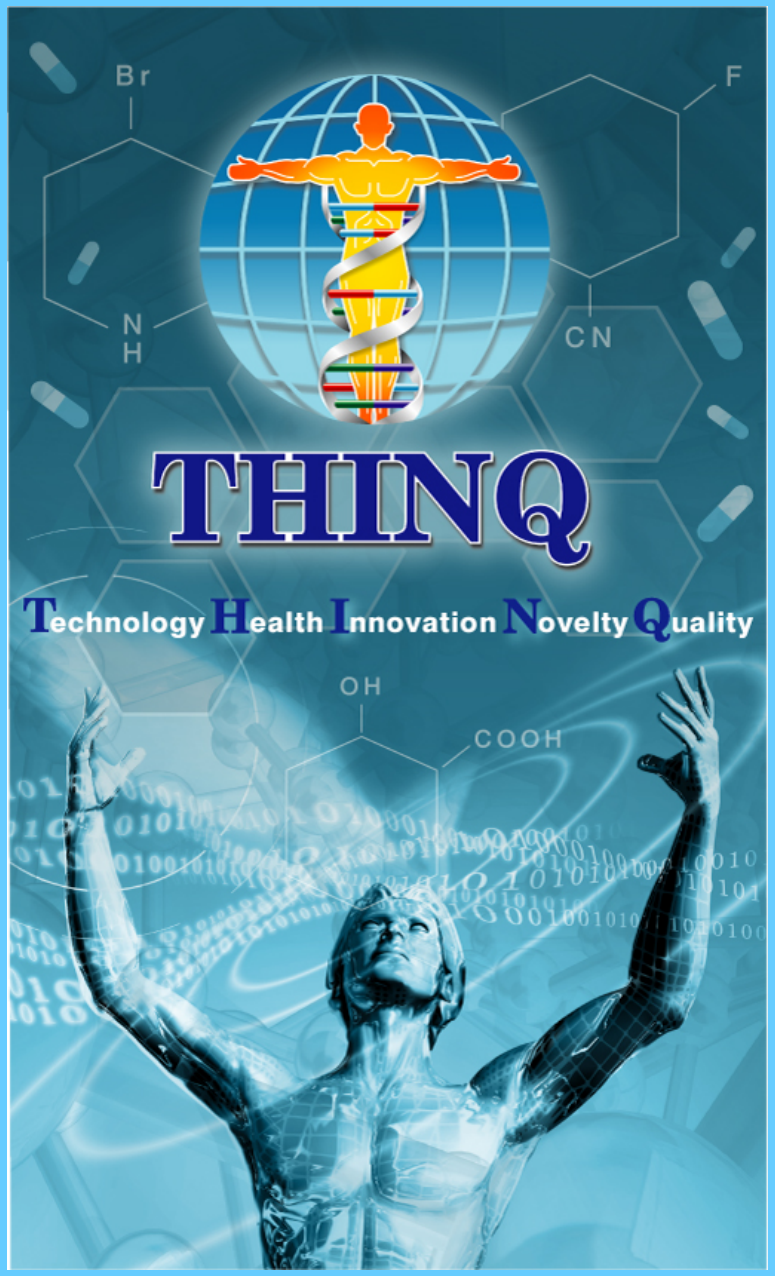
**Mukund S. Chorghade, Ph. D.**
**President and CSO**

**THINQ Pharma/MVRC Research**

**Past-Chair, SCHB and NESACS**

**Chair-Elect Princeton Section, ACS**

**Chair, RSC Process Chemistry and Technology Group**


Br
F
N
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THINQ
Technology Health Innovation Novelty Quality
OH
COOH

## Hindrances to Efficient Globalization

- A highly apocryphal story concerns a United Nations Project wherein nations were asked to participate in the following survey:

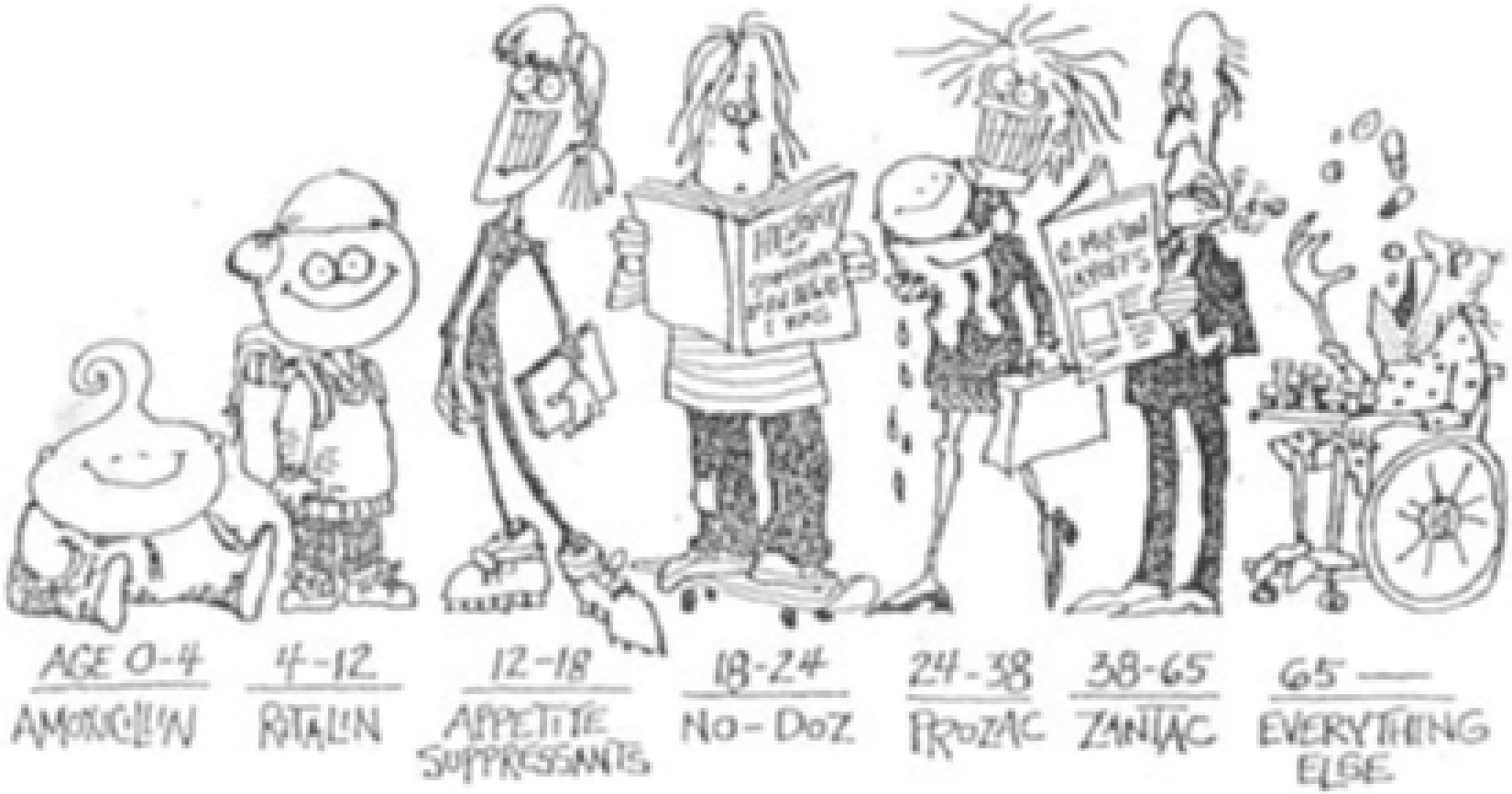
- “In your honest opinion, predict the availability of pure drinking water in the rest of the world”

- Overall the survey was a disaster because……..

# Hindrances to Efficient Globalization

- In Nigeria, nobody knew what “honesty” was
- In China, there was an absence of “opinion”
- In Europe there was no familiarity with “predict”
- In Africa there was no availability
- In Bangladesh there was a dearth of “drinking water”
- In the USA, there was no awareness of the **“rest of the world”**

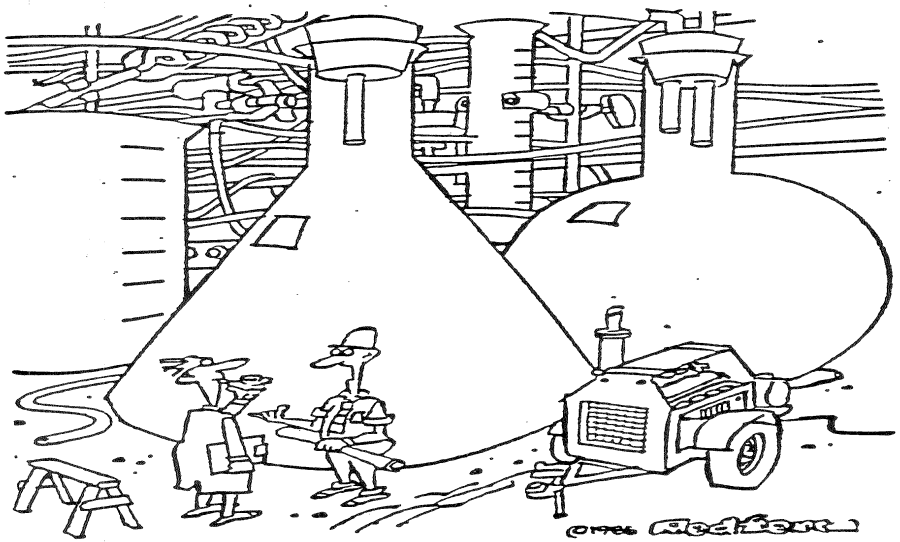
# DRUG-FREE AMERICA




Signe Wilkinson
Philadelphia Daily News
Creators Syndicate

**Sir John Cornforth, "Chemistry in Britain", 342, 1975.**

"It does, for example, no good to offer an elegant, difficult and expensive process to an industrial manufacturing chemist, whose ideal is something to be carried out in a disused bathtub by a one-armed man who cannot read, the product being collected continuously through the drain hole in 100% purity and yield"

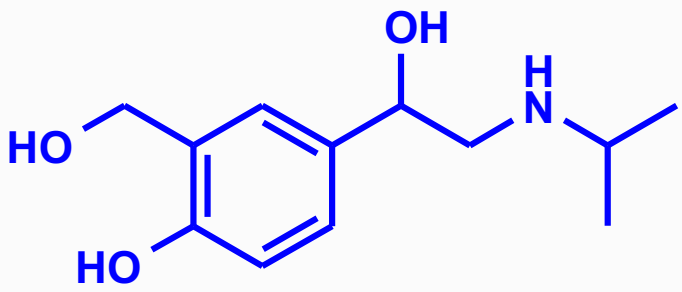


"Got a few problems going from lab scale up to full-scale commercial."

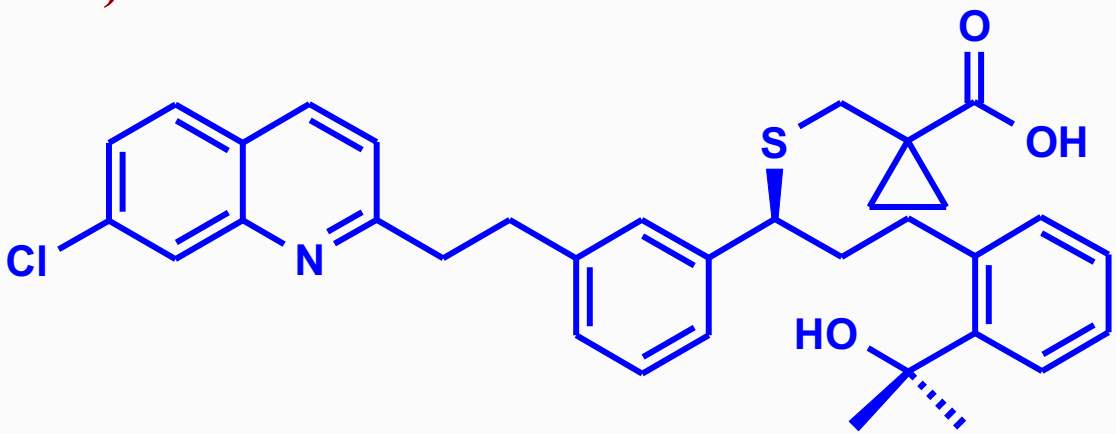
## The Contemporary Process Chemist's View

**Design and execute safe, efficient and reproducible manufacturing processes for active pharmaceutical ingredients through a synergy between organic chemistry, analytical chemistry and chemical engineering**

# Dramatic Progression in Structure Complexity of Industrially Feasible Drug Molecules

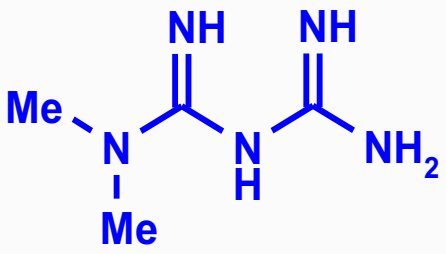



**Albuterol**
**(SALBUTAMOL)**

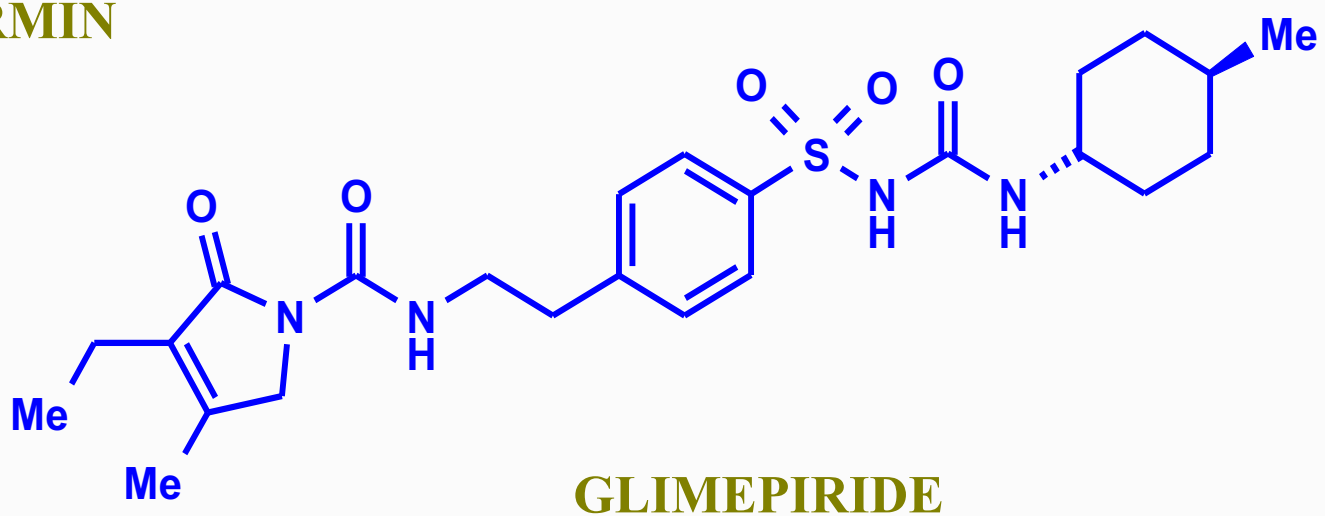



**MONTELUKAST**

# Dramatic Progression in Structure Complexity of Industrially Feasible Drug Molecules

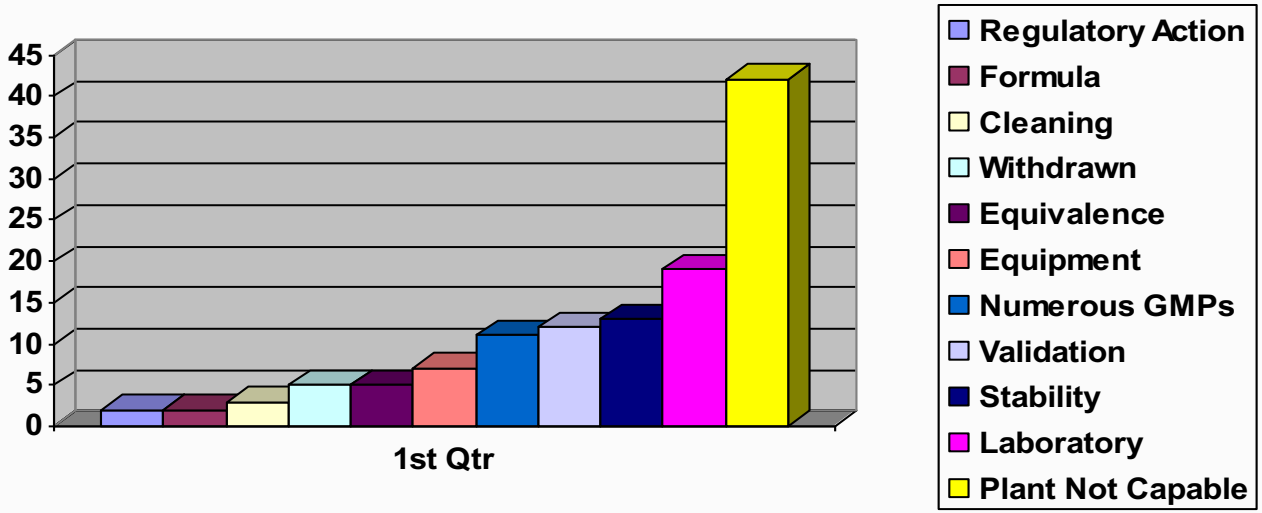



**METFORMIN**




**GLIMEPIRIDE**

# Reasons for NDA Non-Approval

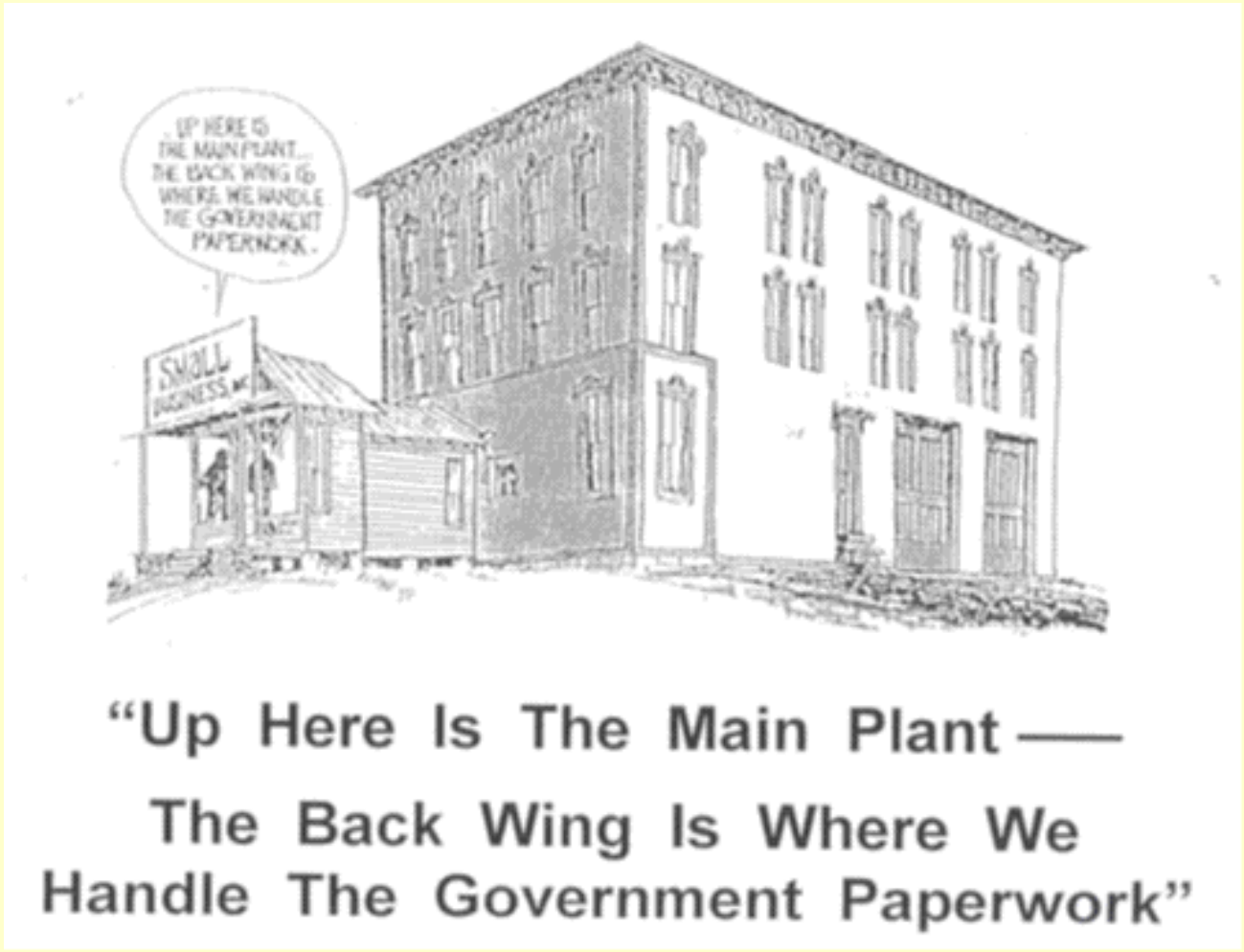



## Reasons for Non-Approval:

- Plant Not Capable
- Equipment Not Available or Qualified
- Plant Not Listed in Filing
- Facility Not Qualified
- Insufficient Personnel / Untrained personnel
- Process Development Incomplete

# Development Criteria

- Route Selection
  - Cost effective, Raw Material Availability, Wastes
- Reagent and Solvent Selection
  - Atom efficiency, Toxicity, Availability, Cost
- Running the Reaction
  - Safety, Temperature, Reproducible, Plant Adaptable-Engineering
- In-Process Controls
- Purity/Impurity Profile
  - Potency, Analytical Method Development, Specifications
- Purification
  - Chromatography versus Crystallization
- Final Product Form
  - Polymorphs

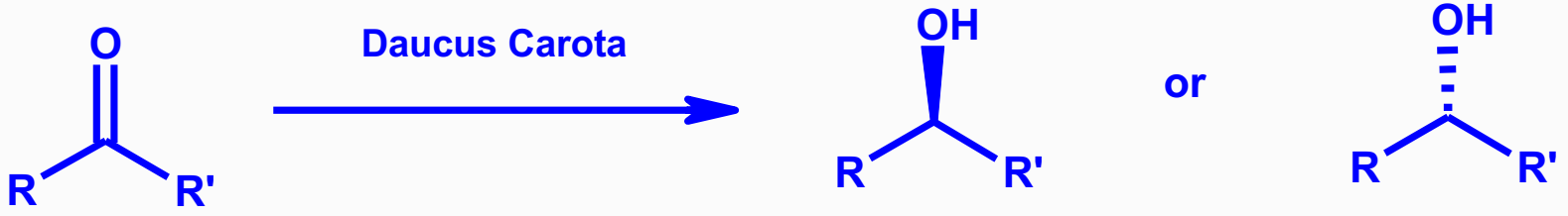



"Up Here Is The Main Plant —— The Back Wing Is Where We Handle The Government Paperwork"

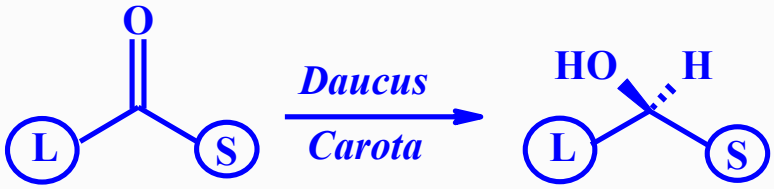

GATEWAY TO INTERNATIONAL COLLABORATION

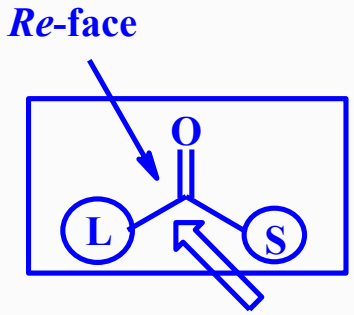
**GRAND AVENUE** **BY STEVE BREEN**

# REDUCTION OF PROCHIRAL KETONES



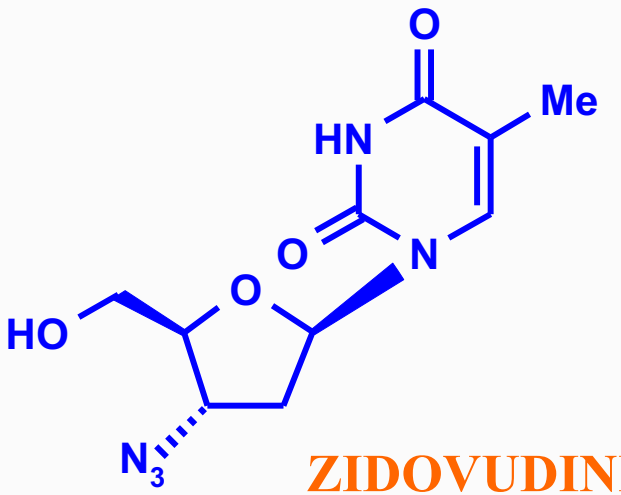

**Aliphatic & aromatic ketones, cyclic ketones, β-ketoesters, azidoketones.**



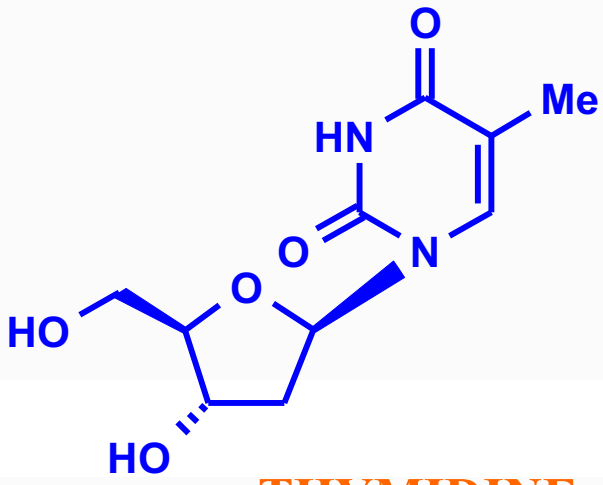




**Hydrogen attack from Re-face**

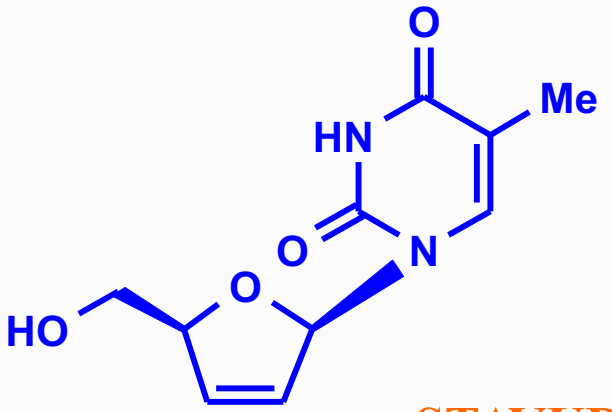
# Thymidine: Starting Material for Anti-HIV Drugs




ZIDOVUDINE
(AZT)



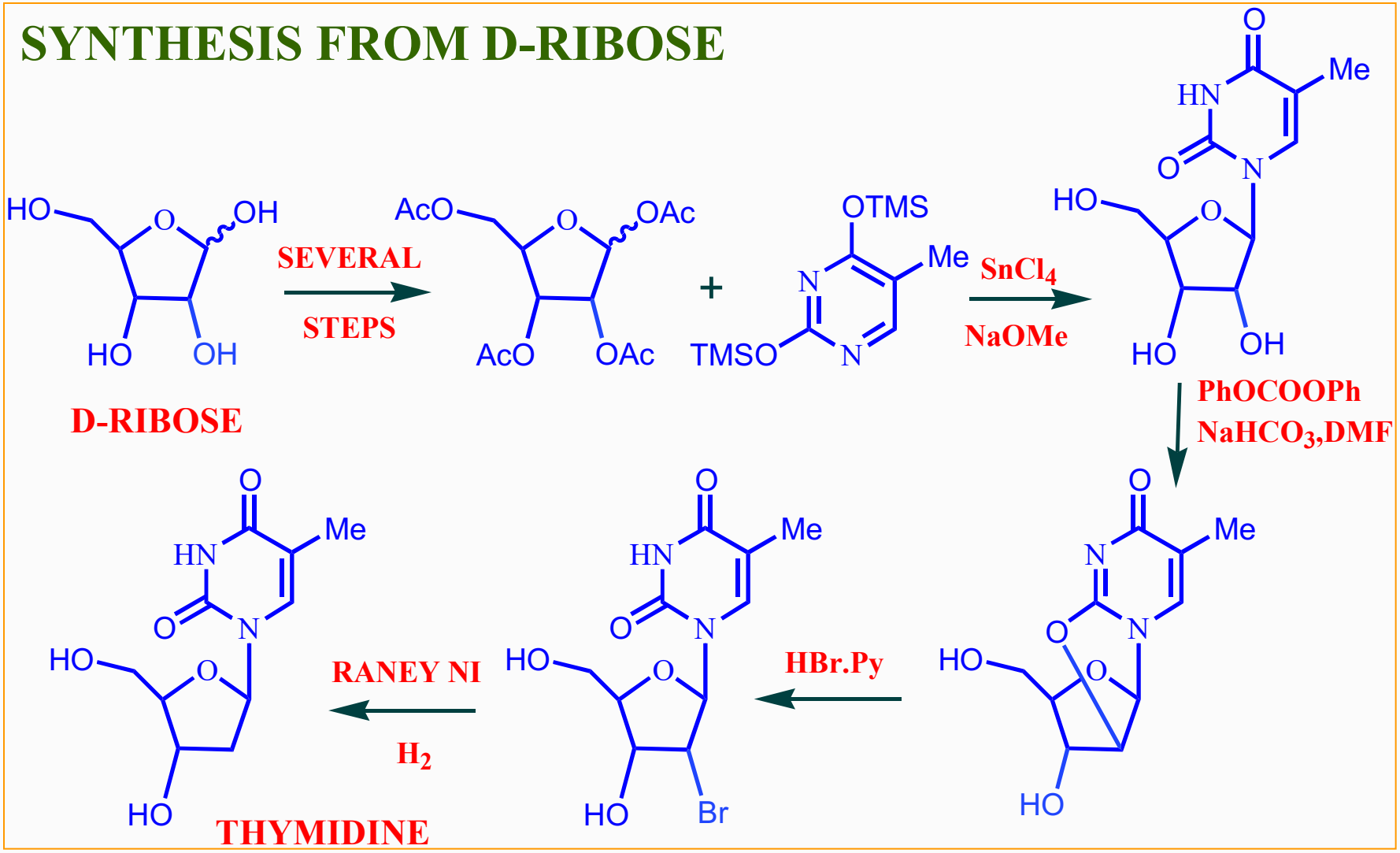

THYMIDINE




STAVUDINE

# Synthesis of Thymidine

## SYNTHESIS FROM D-RIBOSE




*US Pat. No.* 4,914,233 (CA 1990, 113, P59790n)

# Anti-AIDS Drugs

## COST ANALYSIS

| COMPOUND | US $/Kg |
|---|---|
| AZT | 350 |
| Stavudine | 500 |
| β-Thymidine | **150** |

**Raw Material for β-Thymidine**

D-Ribose **50** $ per Kg

**Cheap and Abundant D-Pentose in the World Market**

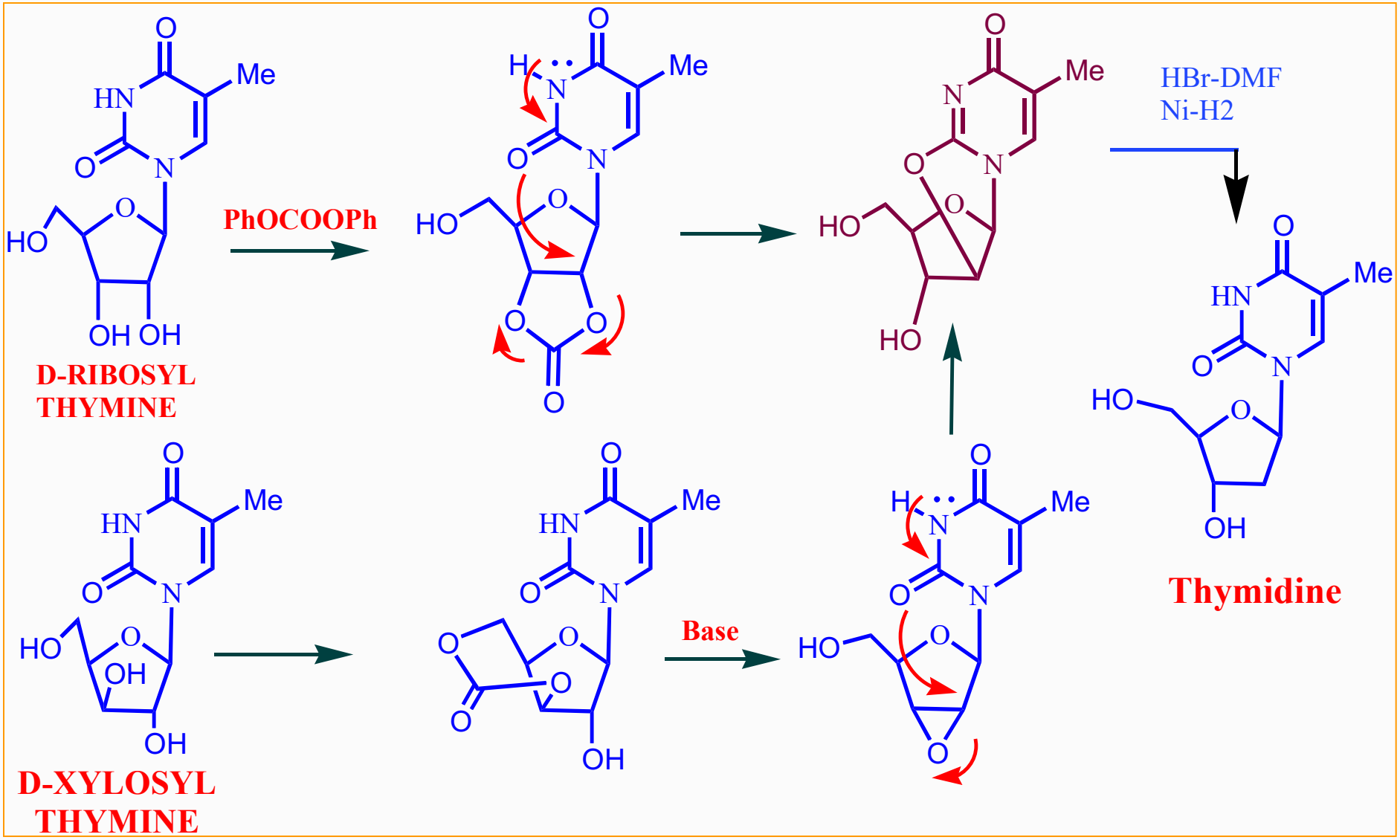
D- Xylose **6** $ per Kg

**Inference:**

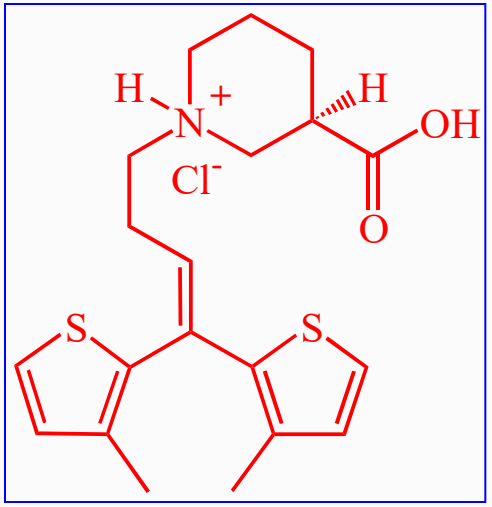
The raw material for β-thymidine Synthesis Should be **D-Xylose**

# Synthesis of Thymidine

## SYNTHESIS FROM D-RIBOSE



# TIAGABINE



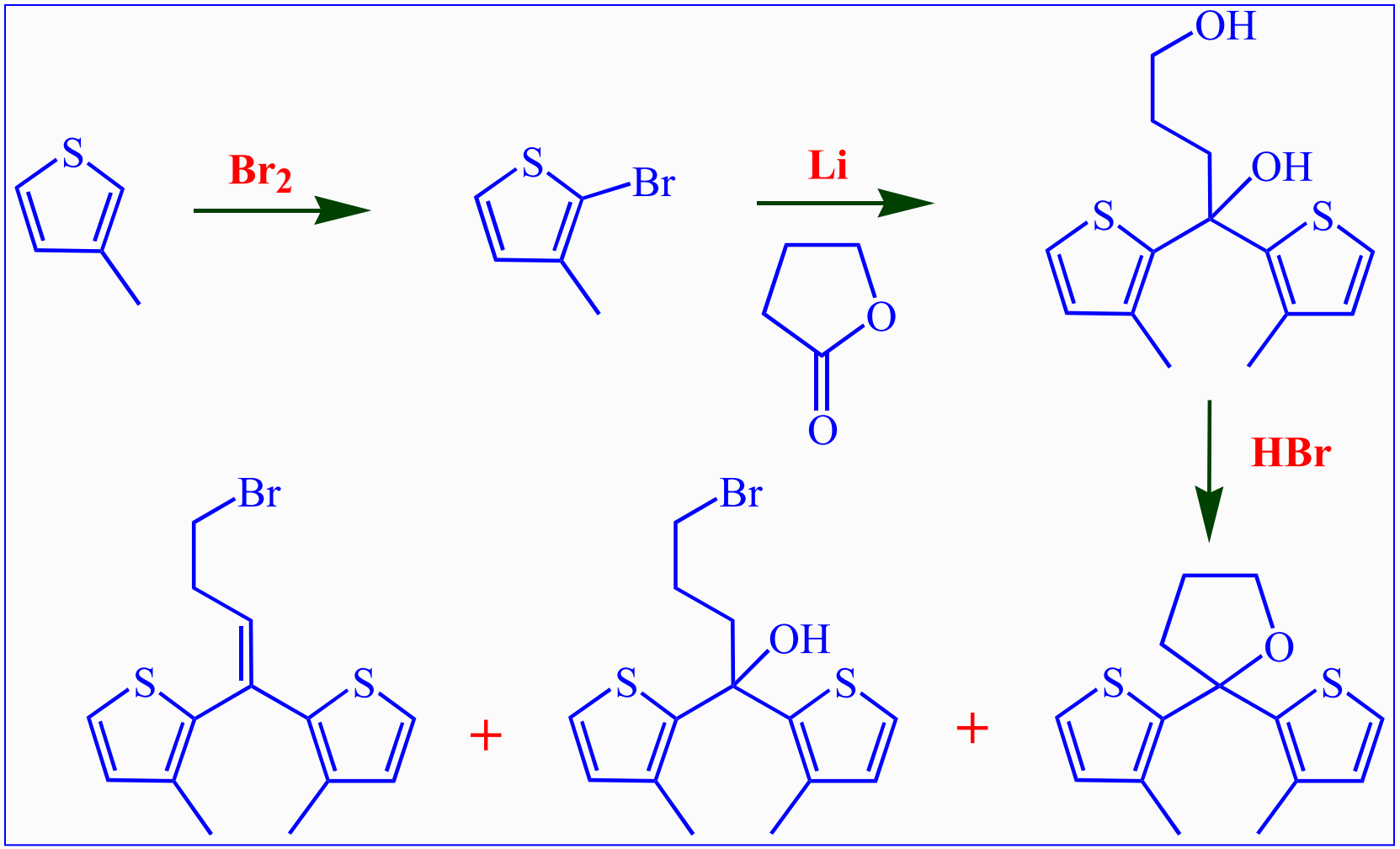

**Discovered in Novo-Nordisk Copenhagen, Denmark**

**The most effective Anti-epileptic drug known**

**Easier penetration of blood brain barrier**

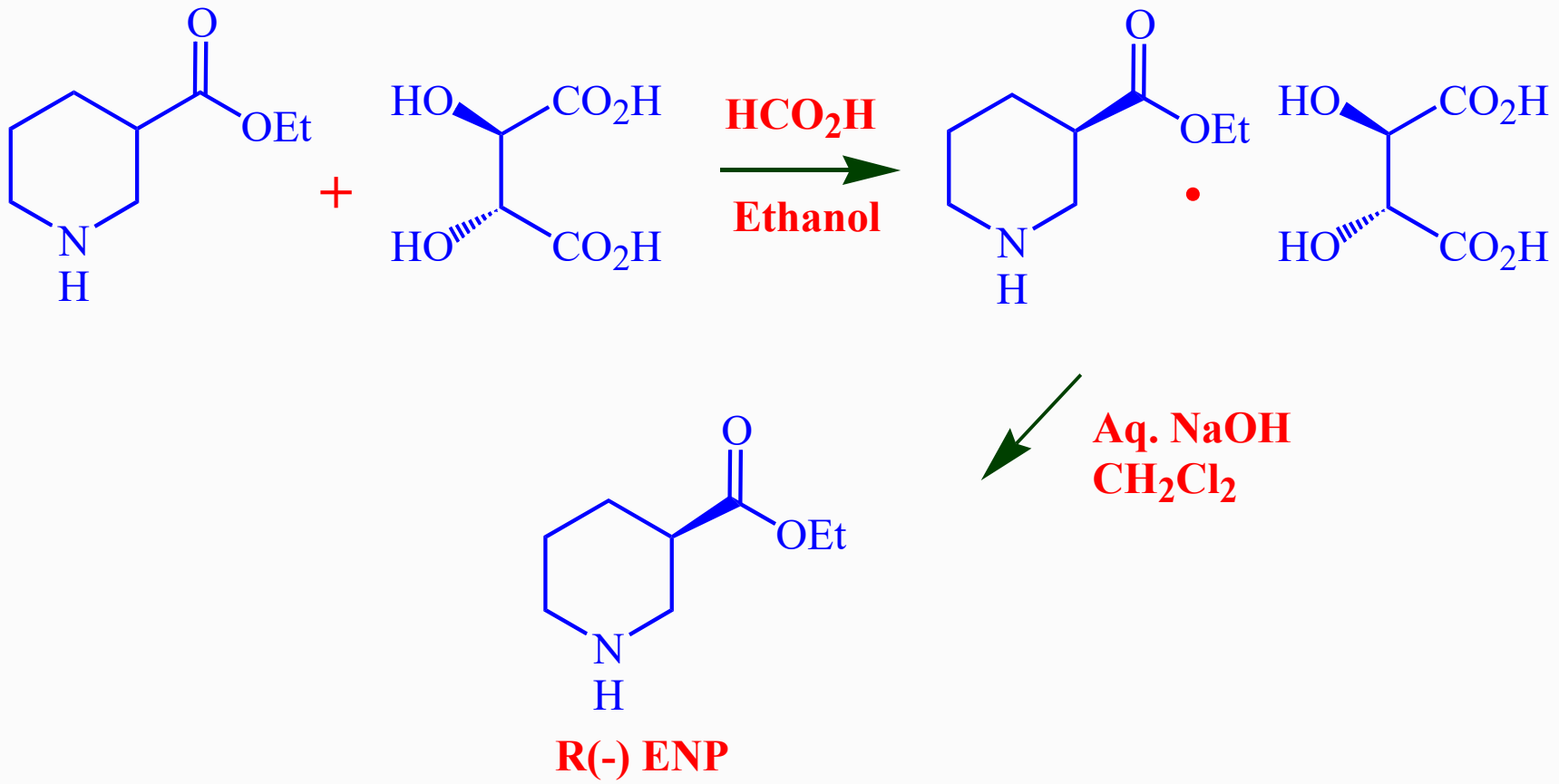
# DISCOVERY ROUTE

## Step 1



# DISCOVERY ROUTE

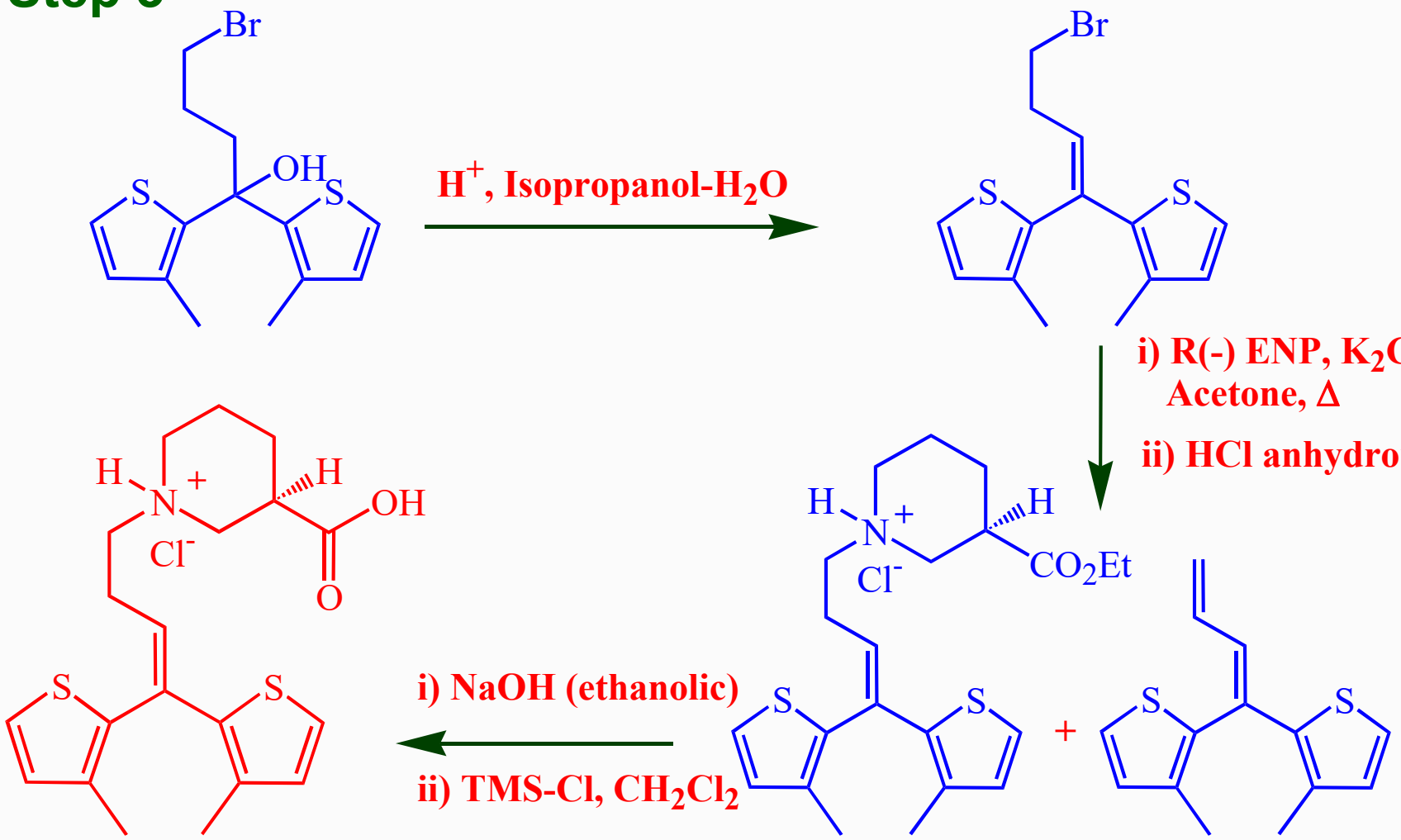
## Step 2



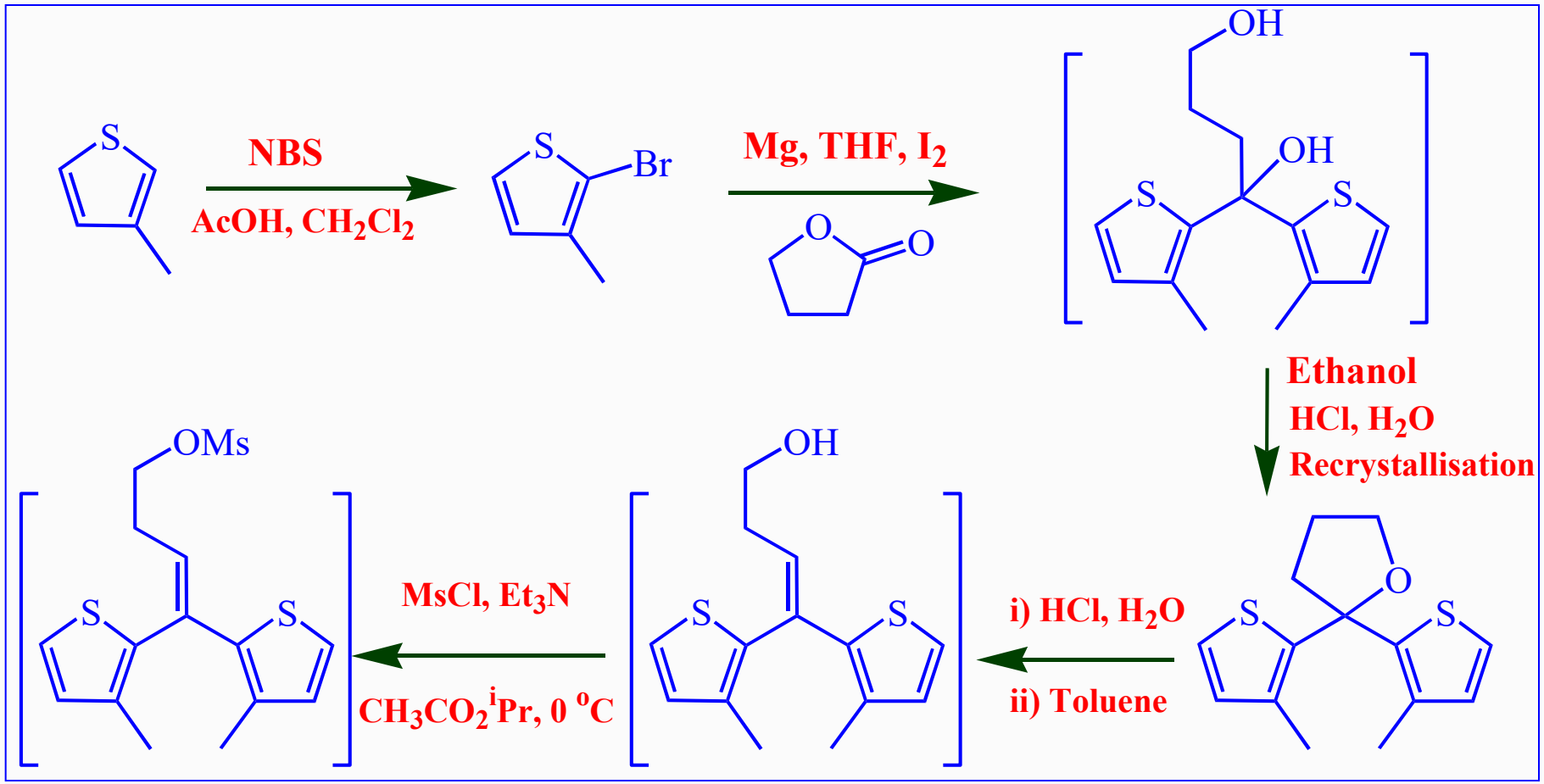

R(-) ENP

# DISCOVERY ROUTE

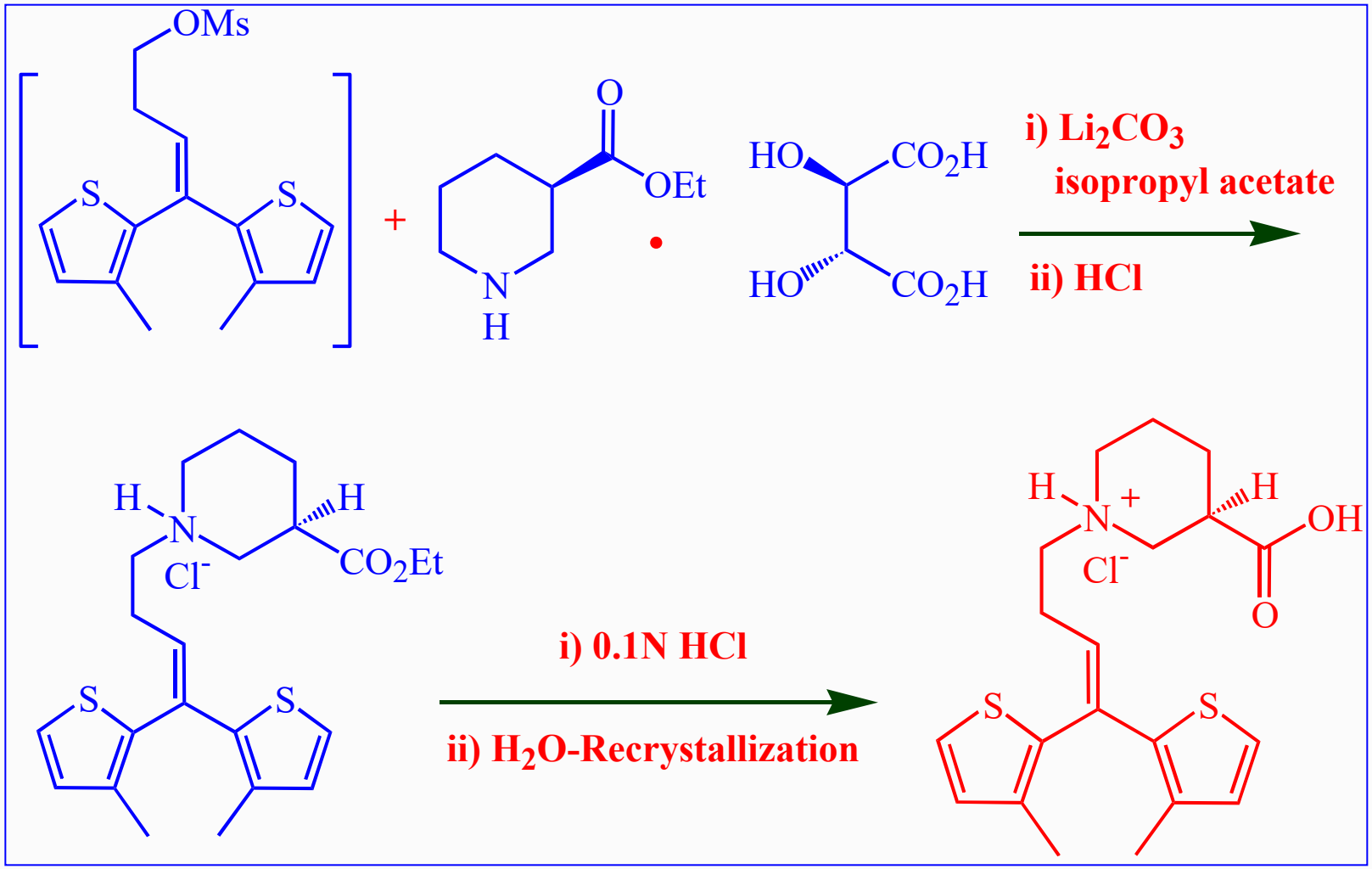
## Step 3



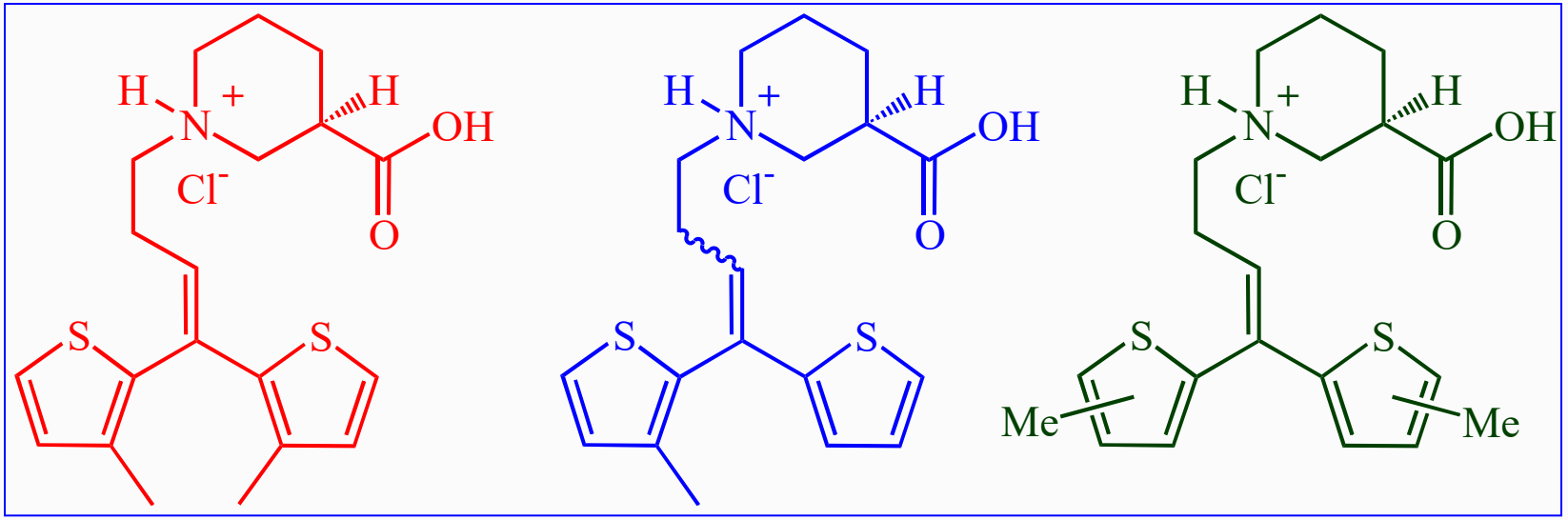
# Abbott Process Route



# Abbott Process Route

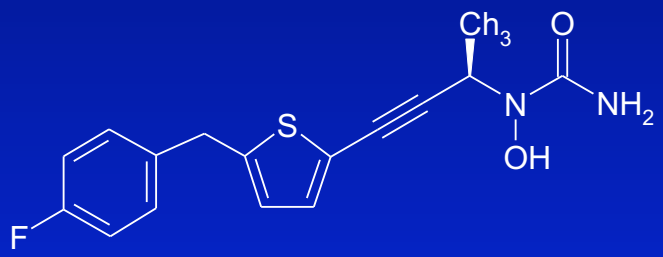


# ANALOGUES



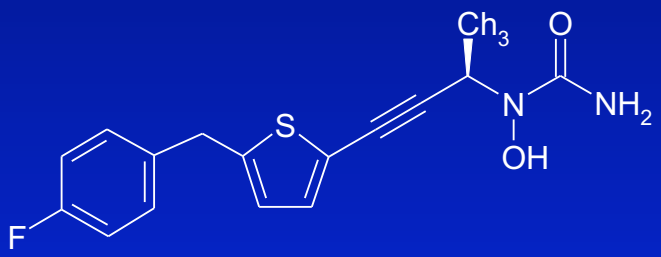

**TIAGABINE** **DESMETHYLTIAGABINE** **REGIOISOMERS OF TIAGABINE**

# ABT-761

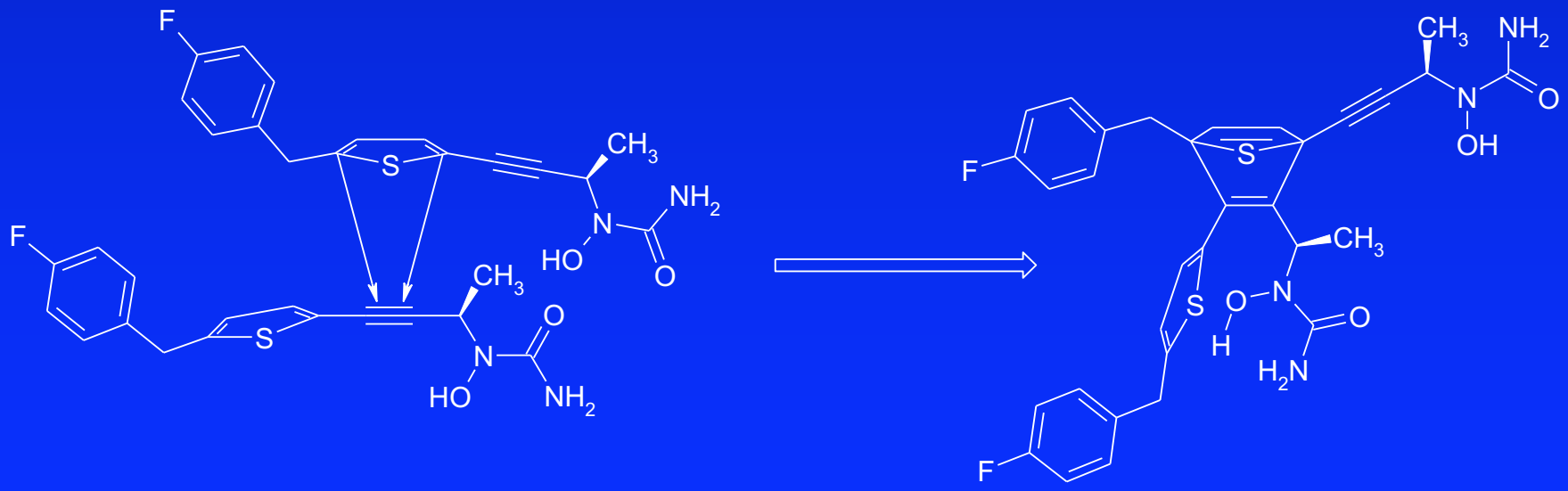



- **Fails in Phase III Clinical due to undisclosed toxicity**
  - **Toxicity is associated with the chemical nature of the molecule that should have been evaluated during the discovery process**
  - **Toxicity was uncovered during the formulation of a pill form of the drug**

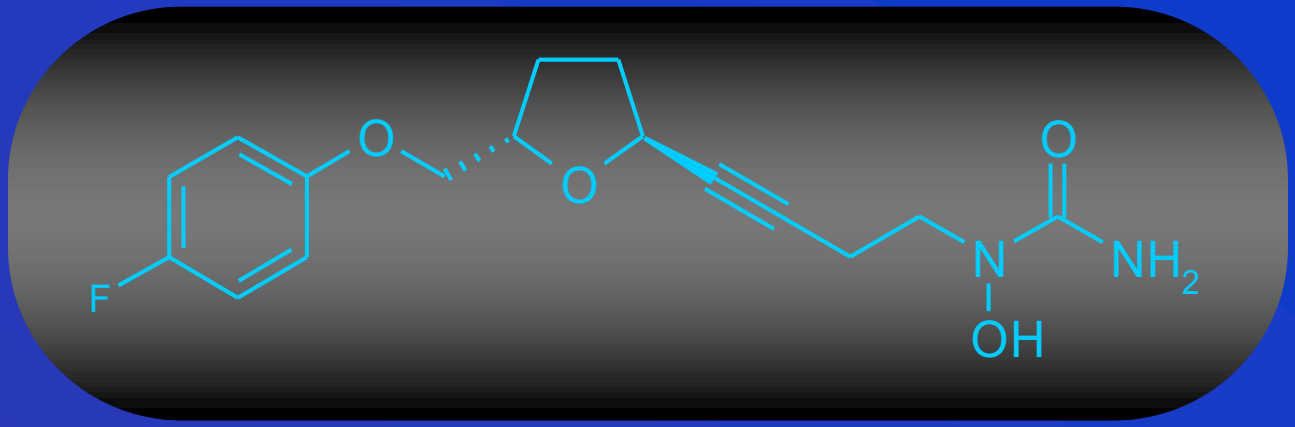
# ABT-761




- **Under Pressure of pill formation ABT-761 undergoes Diels Alder reaction to toxic products**

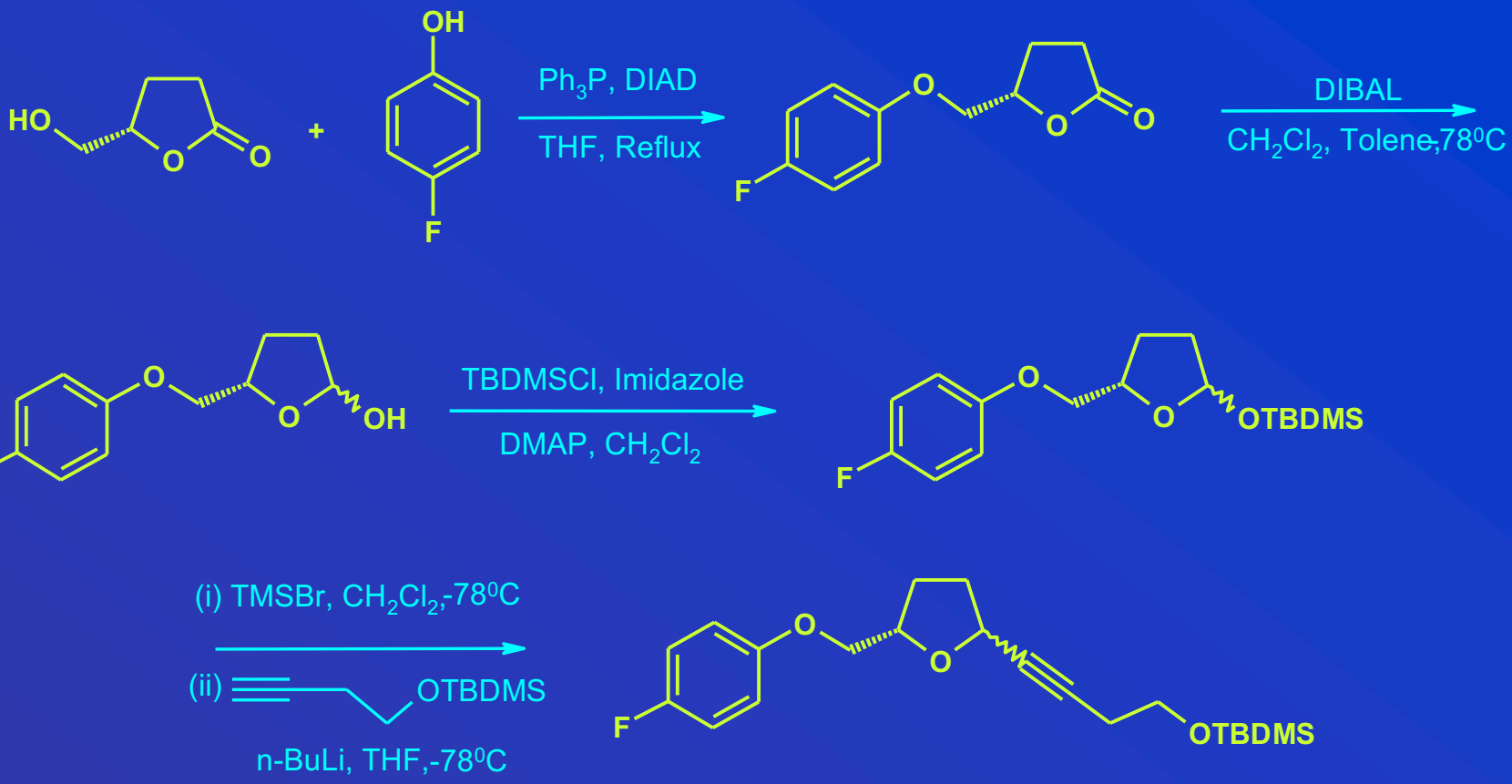


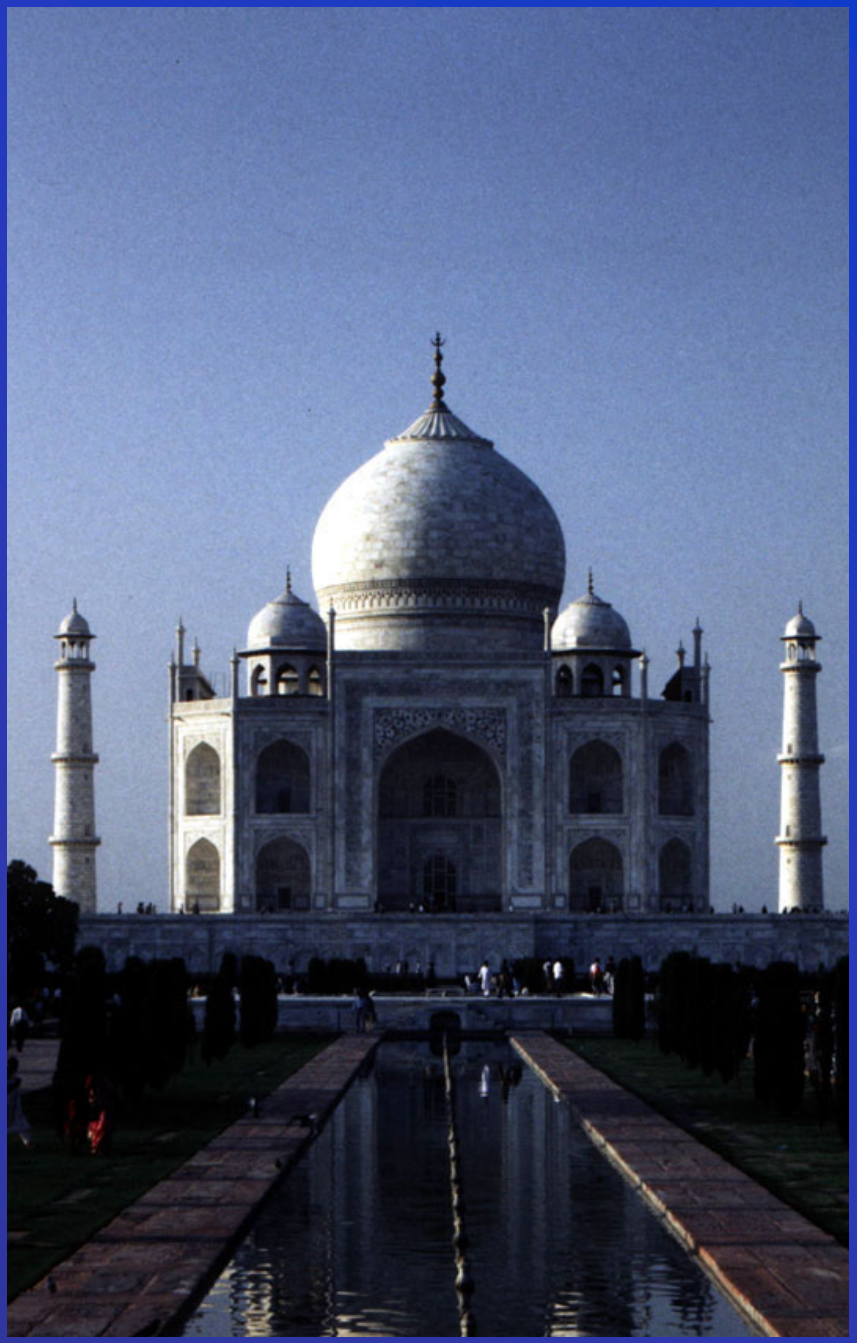
# CMI-977




(2*S*, 5*S*)-*Trans*-5-(4-fluorophenoxymethyl)-
2-(1-*N*-hydroxyureidyl-3-butyn-4-yl)-tetrahydrofuran

# Discovery route to CMI-977



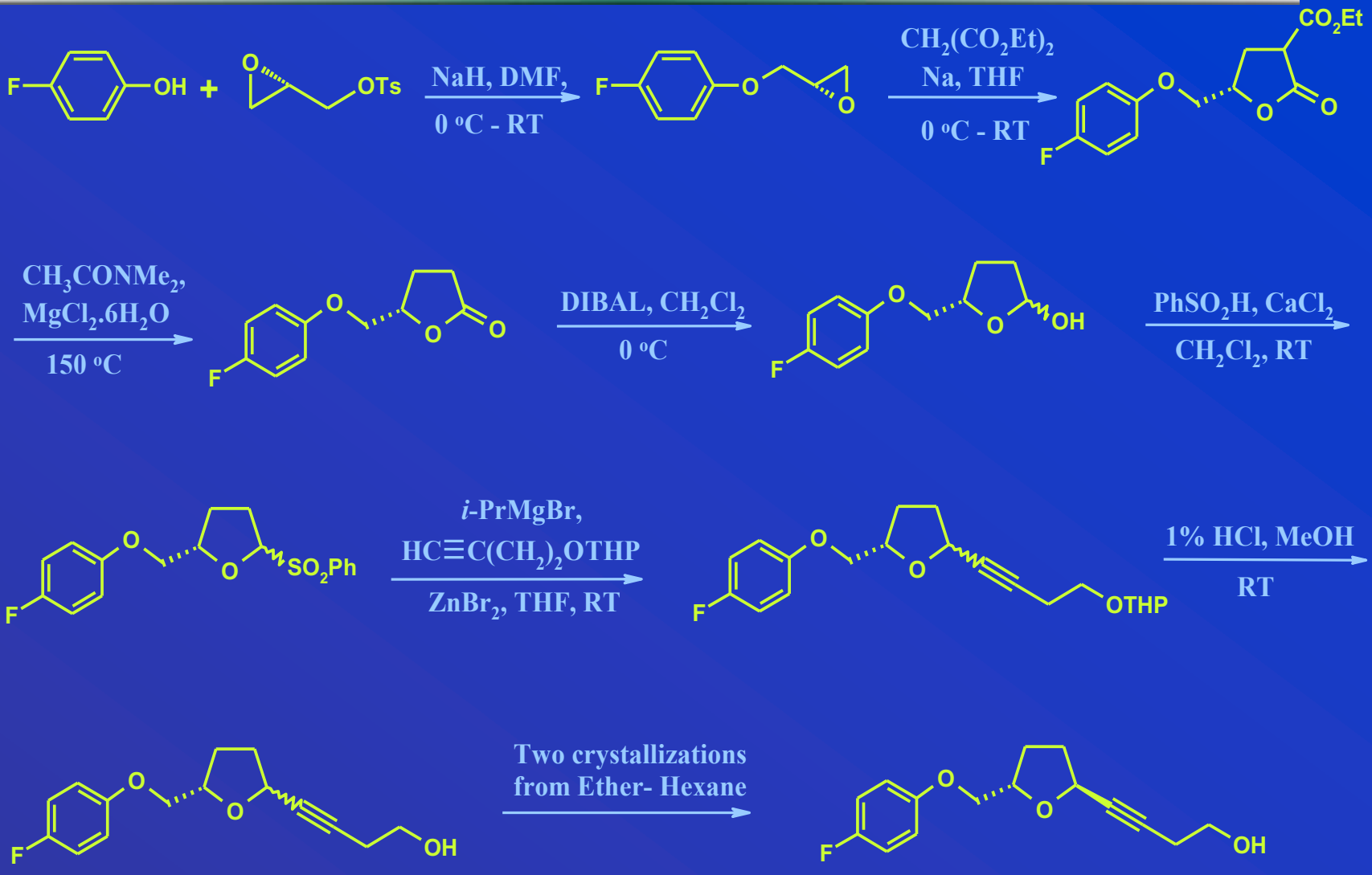


***NECESSITY IS THE MOTHER OF INVENTION***

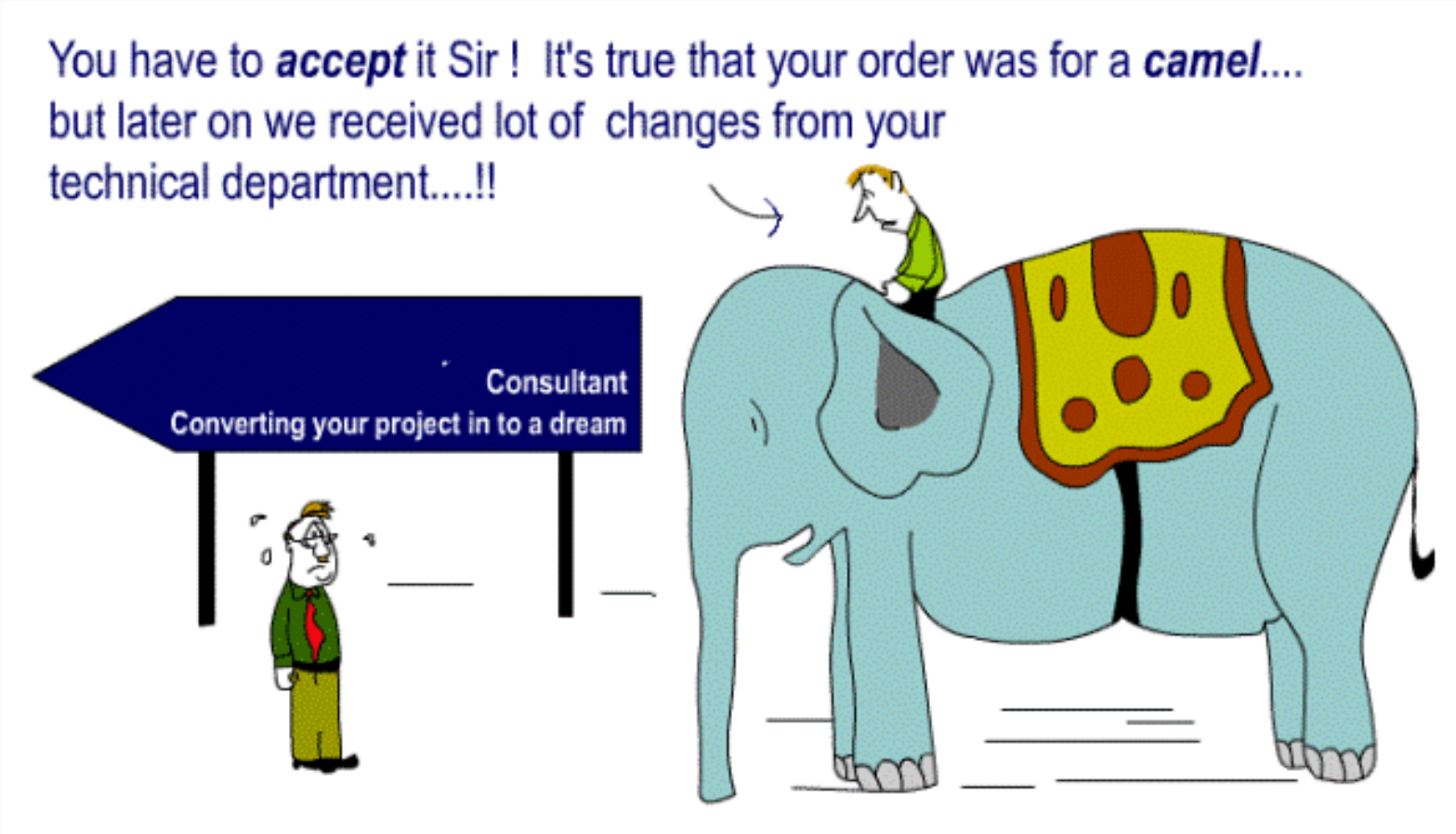
***Moreover,***

***FRUSTRATION IS THE MOTHER OF INNOVATION***

# Novel Route to CMI-977



# A SMALL GLITCH IN NCE DEVELOPMENT




THINQ

***NECESSITY IS THE MOTHER OF INVENTION***

***Moreover,***

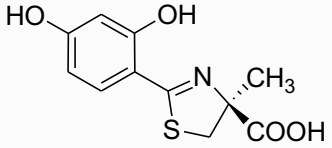
***FRUSTRATION IS THE MOTHER OF INNOVATION***

# Case Study of a Drug to treat Thalassemia

- Although essential for normal physiology, excess iron reveals some toxicity due to its involvement in production of reactive oxygen intermediates leading to cellular damage. Humans regulate iron absorption via intestinal transporters and a series of transport proteins; however excretion of any excess iron cannot be upregulated. Under conditions of excess iron intake, such as chronic transfusion therapy, the consequences of iron overload can be lethal.
- Beta-thalassemia is an autosomal recessive disorder in which severe anemia develops in the first year of life. The beta-chain of hemoglobin cannot be synthesized, leading to inefficient erythropoiesis. Treatment involves frequent transfusions of packed red blood cells. Prior to the development of iron chelation therapy, toxicity from iron overload led to death within the first decade of life. The only, currently available, standard of care is desferrioxamine. Because of its lack of oral absorption and short serum half-life, desferrioxamine must be given as a continuous subcutaneous infusion over 8-12 hours, 6 days per week. This leads to subcutaneous side effects and poor compliance. An alternate oral iron chelator, deferiprone, can be somewhat less effective and is associated with side effects such as agranulocytosis. With current chelation therapy, survival has increased substantially, but iron overload frequently causes morbidity and premature mortality.

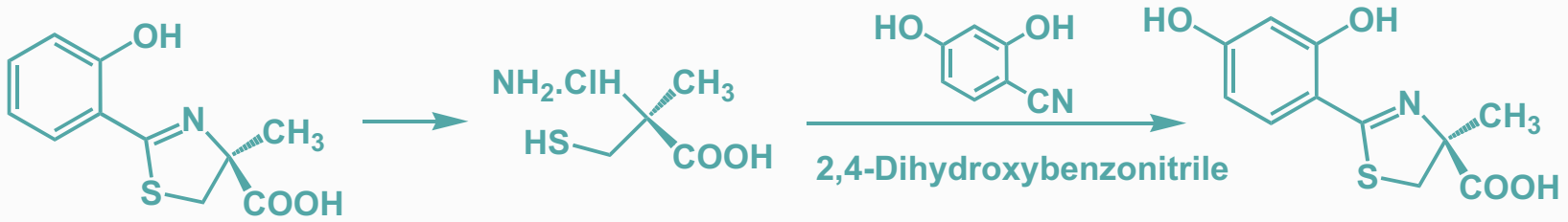
# Case Study of a Drug to treat Thalassemia

- A new compound, a dihydroxylated aromatic in the desazadesferrithiocin class of compounds is an orally available iron chelator that forms a 2:1 complex with ferric iron. It is being explored for safety and efficacy in transfusion related chronic iron overload in patients with beta-thalassemia and sickle cell anemia. It could be active when administered orally to *Cebus apella* monkeys, a species in which iron metabolism closely resembles that in humans.




- Discuss the appropriate process for this compound? What problems might you encounter in Phase I clinical trials?

# Desferrithiocine as an Iron Chelator

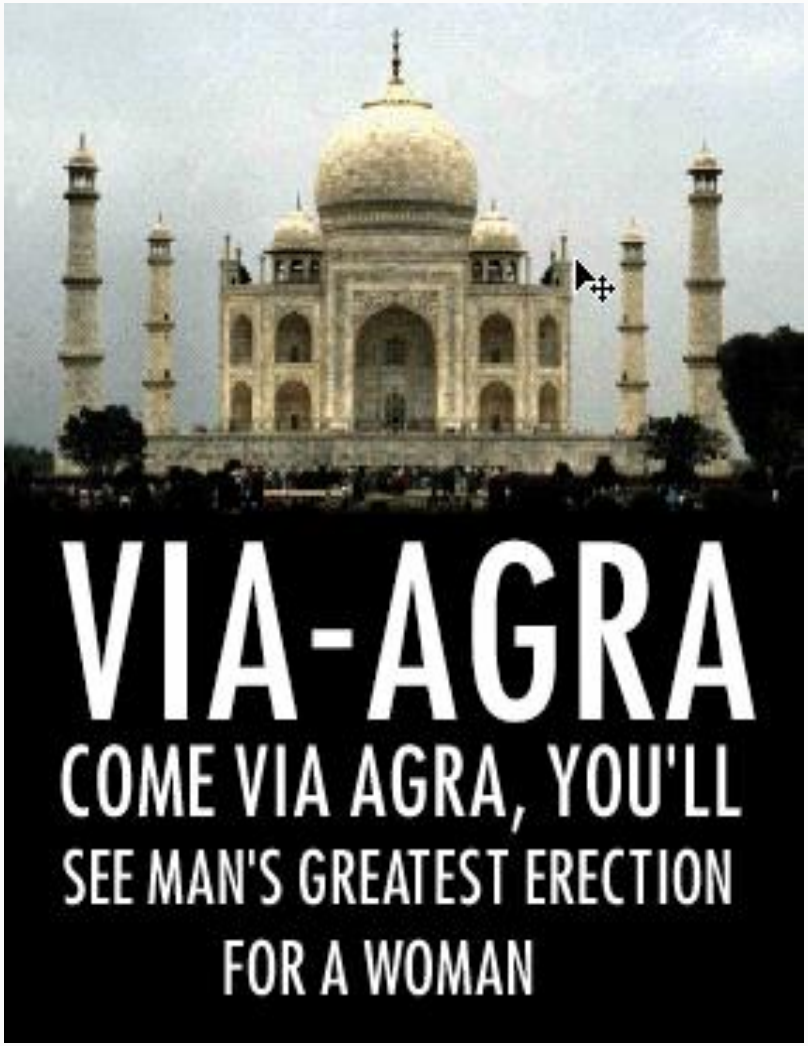



**Desferrithiocine**

**(S)-a-Methylcysteine**

**(*S*)-4,5-dihydro-2-(2,4-dihydroxyphenyl)-4-methyl thiazole-4-carboxylic acid**

# India’s contribution to Viagra



Medieval environmentalist