SYNTHESIS OF COMMERCIAL DRUGS
INTRODUCTION

General Evolution of a Synthetic Route

Discovery Phase “expedient” –
(Medicinal Chemistry): the identification and synthesis of a viable drug candidate

Development Phase “practical” –
- first kg for safety and early clinical studies. Typically uses the Med Chem route as a starting point
- pilot plant scale “efficient” production, 100’s of kg

Marketing Phase “optimal” –
factory scale for commercialization, 1000’s of kg

Rationale for changing a synthetic route can be assessed based on the SELECT criteria:

1) SAFETY
2) ENVIRONMENT
3) LEGAL
4) ECONOMICS
5) CONTROL
6) THROUGHPUT

SAFETY: “If a route cannot be scaled up safely, then it should not be scaled up at all”

Issues:
thermal runaway
Gas evolution
Explosive or shock sensitive materials
Highly corrosive materials
Acute toxicity
Chronic toxicity
Genotoxicity
Pyrophoric/flammable materials

SYNTHESIS OF LYRICA (pregabalin)

**Pfizer** (2004): nerve pain and epilepsy medication

Sales 2007 - $1.8 billion

Off patent - 2018

*Original synthesis*: Silverman and Andruszkiewicz, 1989 *C&E News*, 86(10), pg. 60

**Evans diastereoselective alkylation**

Pregabalin was soon licensed to Parke-Davis (later acquired by Pfizer)

Evans diastereoselective alkylation = a very powerful tool for asymmetric synthesis

The addition of the enolate to the electrophile occurs on the less sterically hindered face, that is to say, on the opposite side to the R² group of the chiral auxiliary.

SYNTHESIS OF LYRICA (pregabalin)

Modified Discovery Route:

- Final neutral hydrogenation
- Overall yield improved to 33%
- Used to prepare 100’s kg

After extensive optimization: average 90% yield per step, but still 10 linear steps and 6x the desired cost factor...not good enough!
SYNTHESIS OF LYRICA (pregabalin)

Manufacture route

CHO

EtO₂C

CO₂Et

n-Pr₂NH

AcOH

KCN

EtOH

Lipolase (8 mol%)

pH 7.0

150 nM Ca(OAc)₂

3 M in substrate

recycling

NaOEt, Tol

110 °C

(racemization)

<99% ee

85-90% ee

not isolated

1- KOH - H₂O

2- Ni sponge (H₂)

reflux

80 - 85 °C

>99% ee

85-90% ee

99.5% purity

99.75% ee

40-45% overall yield after one recycle

*All reaction run in aqueous media

*Ratio of kg waste/kg pregabalin produced
   Classical resolution route 86:1
   Chemoenzymatic route 17:1

*Solvent use per 1000 kg pregabalin
   Classical resolution route 50,042 kg
   Chemoenzymatic route 6230 kg

SYNTHESIS OF PRILOSEC-NEXIUM (omeprazole-esomeprazole)

Astra Zeneca (1985)
Proton pomp inhibitor used in the treatment of gastric reflux disease
Sales 2007 = $5 billion
Off patent in 2014

First synthesis: preparation in racemic form

Improvement: omeprazole to esomeprazole

1987 – Prilosec found to display significantly varying efficacy depending on rate of metabolism of patient. Program launch to find a compound with increased bioavailability that won’t be cleared by the liver so quickly to give “slow metabolizers” a chance.

1989-1994 – 30 scientists and several hundred compounds later...four candidates are identified

Only one compound survives pharmacokinetics, efficacy and safety assessments... **esomeprazole**, the S-enantiomer of omeprazole.

First development campaign – 40 kg of omeprazole was converted to 500 g of pure esomeprazole enantiomer

- 6 weeks to perform first 3 steps on 250-500 L pilot scale
- provided 5.5 kg of unresolved mandelate
- and only 430 injections on a 15cmx100cm HPLC column later....

Next supply requirement was for 5 kg and would have required 60,000 L of eluant to support the HPLC separation
SYNTHESIS OF PRILOSEC-NEXIUM (omeprazole-esomeprazole)

Improvement: omeprazole to esomeprazole

Formation of the sulfoxide by using of the Kagan's oxidation (Sharpless oxidation modified)

\[
\text{MeO} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{OMe}
\]

\[
\text{PhOOH} \quad 10 \text{ mol}\% \quad (-) \text{-DET} \\
\text{5 mol}\% \quad \text{Ti(O^1)Pr}_4 \quad \text{Pr}_2\text{NET} \quad \text{H}_2\text{O}, \text{toluene}
\]

92% yield \\
94% ee \\
74% yield \\
99.9% ee

<table>
<thead>
<tr>
<th>route</th>
<th>steps from sulfur</th>
<th>manufacture of esomeprazole (5 kg in plant)</th>
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<tr>
<td>medicinal route</td>
<td>6</td>
<td>14 weeks</td>
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<tr>
<td>new route</td>
<td>1</td>
<td>2 weeks</td>
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SYNTHESIS OF LIPITOR (atorvastatin calcium)

Chiral side chain: 220 ton / year

Cholesterol: a very important biological molecule
- most cholesterol is not dietary, it is synthesized internally.
- cholesterol is bound to lipoproteins and transported through blood.
- 2 kinds of lipoproteins:
  - high density lipoprotein (HDL): “good”
  - low density lipoprotein (LDL): “bad”

atherosclerosis

coronary heart disease & other cardiovascular diseases

One of the leading causes of death in the world today!

Pfizer (1997): treatment of hypercholesterolemia via inhibition of cholesterol biosynthesis
Sales 2007 - $12.7 billion
Off Patent - 2011
SYNTHESIS OF LIPITOR (atorvastatin calcium)

A solution: the suppression of the cholesterol biosynthesis
The story of statins drugs

SYNTHESIS OF LIPITOR (atorvastatin calcium)

**Timeline | History of the statins**

- **Mid-1970s**: Discovery of compactin, the first potent inhibitor of cholesterol synthesis.
- **1978**: Lovastatin shown to be effective in healthy volunteers in early clinical trials; compactin withdrawn from clinical trials, causing suspension of further trials withLovastatin.
- **1980**: Lovastatin becomes available for prescription, first of the class.
- **1984**: Unequivocal reduction of mortality with simvastatin in 4S trial resolves the cholesterol controversy.
- **1987**: Withdrawal of cerivastatin due to excessive risk of rhabdomyolysis.

**Potent inhibitors of HMG-CoA reductase**

- Penicillium citrinum
  - 600L of culture filtrate
  - 23 mg mevastatin (compactin)
  - **2001**: Mevacor, 1987 (lovastatin)
  - **2002**: Zocor, 1988 (simvastatin)

- **Stanyl: Pravastatin**
  - **1989**: Sankyo-BMS (pravastatin)
SYNTHESIS OF LIPITOR (atorvastatin calcium)

The synthesis of atorvastatin lactone

Separation of enantiomers (resolution via diastereomeric esters synthesis)
SYNTHESIS OF LIPITOR (atorvastatin calcium)

The enantioselective synthesis of atorvastatin lactone (labor approach)

12 linear steps
3 columns and 1 recrystallization
Low temperature steps
Low yields
Low yielding final purification

Poor potential for kg scale
SYNTHESIS OF LIPITOR (atorvastatin calcium)

The enantioselective synthesis of atorvastatin calcium: the solution

Synthesis of Paal-Knorr precursor 1

Synthesis of Paal-Knorr precursor 2
SYNTHESIS OF LIPITOR (atorvastatin calcium)

The enantioselective synthesis of atorvastatin calcium: the solution (2)
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Roche (1995)
Anti-viral drug to slow the spread of the Influenza virus
Sales 2009 = 2.7 billion €
Review = Chem. Rev. 2009, 109, 4398
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Inhibition of the viral neuraminidase

[Diagram showing the mechanism of Tamiflu's action on viral neuraminidase]
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Enzymatic mechanism of the viral neuraminidase

- sialosyl cation
- glycosyl-enzyme
- cell

R = HO

R' =
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Oseltamivir: structure design

Goal of the design:
✓ establishment of a competitive inhibitor of the sialic acid
✓ preparation of an analogue of the transition state

Transition state

Sielic Acid

DANA (1974)

Zanamivir (1989)

Oseltamivir Phosphate (1995)
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Oseltamivir phosphate: the first synthesis

1. (-)-Shikimic acid
   - $\text{Ph}_3\text{P}, \text{DEAD}$, THF, 0 °C to rt, 1.5 h, 77%
   - $\text{MOMCl, DIPEA}$, CH$_2$Cl$_2$, reflux, 3.5 h, 97%

2. $\text{NaN}_3, \text{NH}_4\text{Cl}$, MeCH$_2$H$_2$O, reflux, 15 h, 86%

3. $\text{MsCl}, \text{TEA}$, CH$_2$Cl$_2$, 0 °C, 15 min, 99%
   - $\text{Ph}_3\text{P}, \text{THF}$, 0 °C, 3 h, then TEA, H$_2$O, rt, 12 h, 78%
   - $\text{NaN}_3, \text{NH}_4\text{Cl}$, DMF, 70 °C, 21 h, 77%
   - HCl, MeOH, rt, 4 h, 99%

4. $\text{BF}_3\cdot\text{OEt}_2$, 3-pentanol, 70 °C, 2 h, 69% over 2 steps
   - $\text{Ac}_2\text{O}, \text{DMAP}$, pyridine, rt, 18 h

5. $\text{Ph}_3\text{P}, \text{THF/H}_2\text{O}$, 50 °C, 10 h, 90%
   - KOH, THF, rt 40 min, then Dowex 50WX8, 75%

14 steps, 15% overall yield
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Oseltamivir phosphate: the Roche synthesis

- 21% overall yield, 10 steps
- industrial synthesis
- minor drawback: the sourcing (shikimic acid)
- major drawback: the use of azide chemistry
SYNTHESIS OF GLIVEC (imatinib)

Novartis (2001)
Treatment of Chronic Myeloid Leukemia (CML)
First protein kinase inhibitor to reach the market
Selective inhibitor for a hybrid tyrosine kinase (Bcr-Abl)
Sales 2007 = $3 billion
Off patent in 2015

The clinical development was particularly rapid, as can be seen by comparison with the typical drug discovery and development times.
SYNTHESIS OF GLIVEC (imatinib)

Glivec : structure design

The phenylaminopyrimidine structure identified
- as Protein Kinase C (a serine-theonine kinase) inhibitor,
- by random screening of compound libraries.

N
N
H
N
N
N
H
N
O

inhibition of PKC

inhibits Tyrosine Kinase
(IC 50 = 50 µM)

Conformational blocker

IC 50 = 50 µM

IC 50 = 0.1 µM

Imatinib (Glivec)

- increase activity vs tyrosine kinases
- no activity against serine-threonine kinases

-spacer inserted to avoid aniline structure
-piperazine increases activity, selectivity and water solubility

SYNTHESIS OF GLIVEC (imatinib)

Glivec: Zimmermann’s route (1993)

1) Na, MeOH, rt
toluene, HCO₂Et
2) H₃NMe₂, toluene, rt
3) HOAc

HNO₃, EtOH
H₂N-CN
reflux, 21 h

α-PrOH
NaOH, reflux
12 h

H₂, Pd/C
THF

Pyr. 24 h

Gleevec
(imatinib mesylate)
SYNTHESIS OF GLIVEC (imatinib)


1. Methylation of 2-acetylbenzoic acid with methanol and Pt/C, 5 bar, H₂, 80 °C, 20 h, 70%

2. 1-Methylpiperazine cross-coupled with compound 9, trimethylaluminium toluene, Ar, 40 °C, 30 min, 75%

3. Reaction of compound 10 with sodium tert.-butylate, rac-BINAP, Pd₂(dba)₃CHCl₃ in Ar, xylene, reflux, 5 h, 72%

Buchwald-Hartwig cross-coupling reaction