Route and Process Design
to
Drug Substance Manufacture

A Sustainable approach to reduce Carbon foot print

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New Medicines-"From Discovery to Launch"

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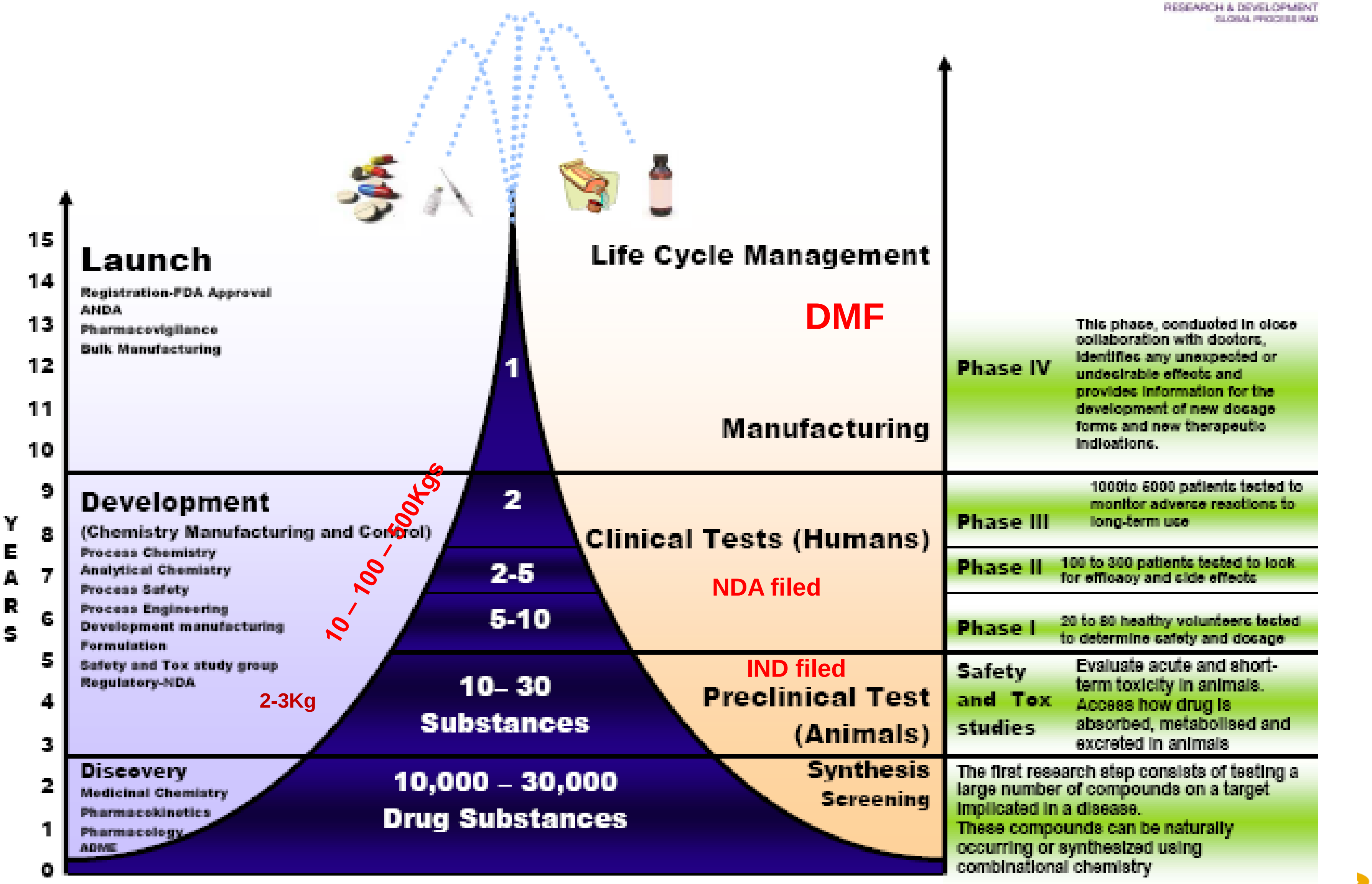
GLOBAL PROCESS R&D



Research Focus and Major outcome

Focus	Outcome	Environ Impact
Drug Design and Development	Drug substance manufacturing process and supply	High
Formulation Design development	Drug product manufacturing process and supply	Low to Medium
Clinical Research	Phases of clinical studies and supporting data	Low

Environment Impact

EB = P x A x T

EB: Environmental Burden

P: Population

A: Affluence(Consumption)

T: Technology/Process

Technology/Process need for minimizing EB:

a) efficient(Yield and atom efficiency)

b) safe(nature of Hazard)

c) no pollution or minimum pollution(quantity generated per Kg out put)

Technology Efficiency Measurement

$$T_i = E_i \times S_i \times H_i$$

T_i = Overall Technology/Process efficiency

E_i = Efficiency factor

Yield, cost, Selectivity Etc.

S_i = Sustainability factor

Waste (PMI), Energy etc.

H_i = Process Hazard, material hazard.

Drug Substance – Recent Trends

Structure:

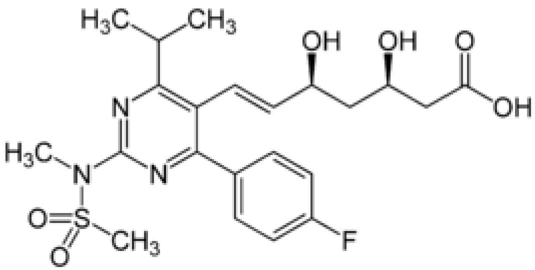
- Complex structure with increasing molecular weight
- increasing number of hetero atom
- Increasing number of chiral center

Synthesis:

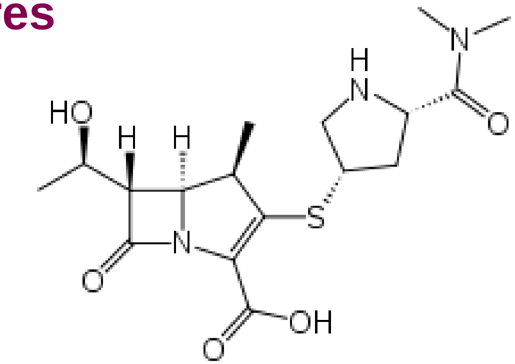
- Number of synthetic steps and many possible **routes**
- Too many **possible** processes
- Complex Raw materials and their availability
- increasing cost and delivery time

AZ marketed Drug molecules

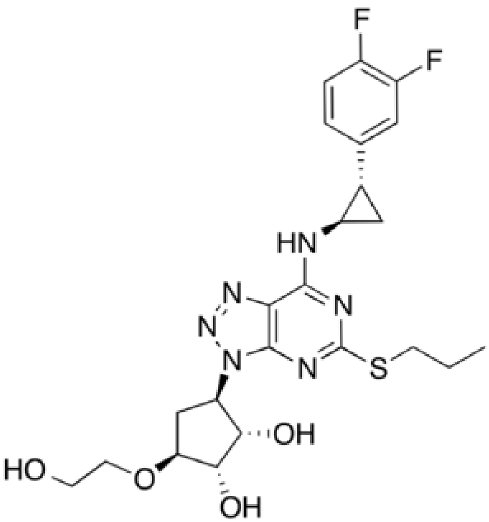
Examples for complex structures



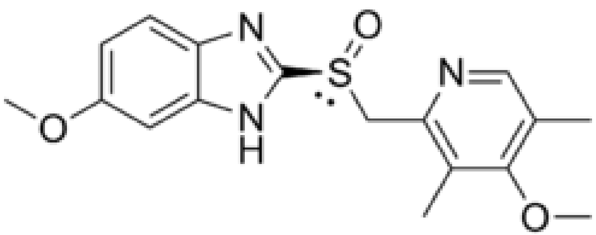
Rosuvastatin(Crestor)



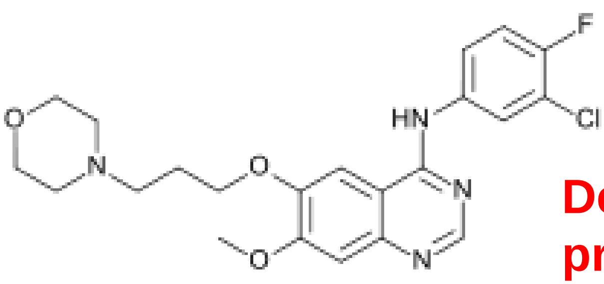
Meropenem(Monan)



Ticagrelor(Brilinta)

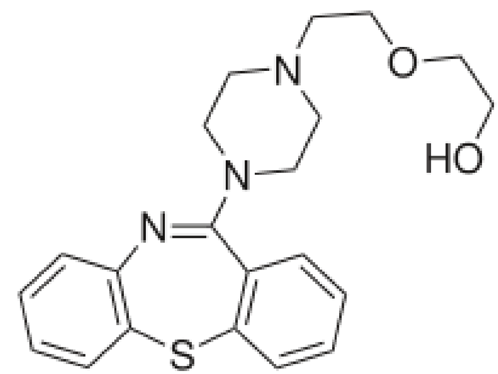


Esomeprazole(Nexium)



Gefitinib(Iressa,)

Development of a sustainable process needs investment in time, resources and money



Quetiapine(Seroquel)

Source: Wikipedia

Challenges to RD/PD during developmental stage

- Cost of initial development v/s Attrition Rate and development time
- How much to do(Route selection v/s delivery)
    - **Fit for the purpose**
- Chemistry develops over a period - New Ideas
- Frequent change in Route/Process not preferred as this impacts
    - impurity profile(Route/Process related)
    - regulatory documentation(Physical, Pharmacological and toxicological)

Danger of getting fixed with inefficient process

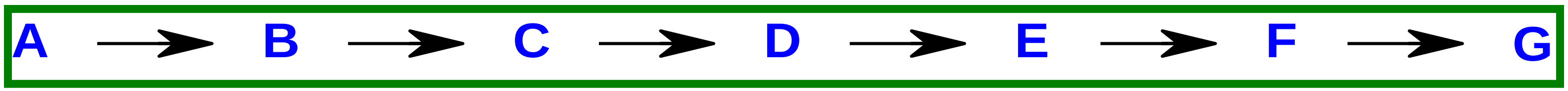
- Route/Process improvement will have positive impact on SHE, Cost and efficiency.

Ambition is to have the best synthetic route and sustainable process as early as possible to support manufacture/market

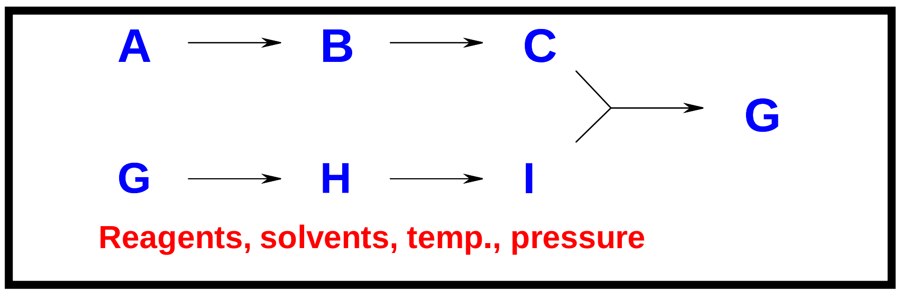
How do we do it?

Route and Process

Route: A path to sequentially build the intermediate that leads to target molecule through chemical transformation



Linear Route



Convergent Route

Process: A set of reaction parameters, reagents and activities that is used to bring chemical transformation of one intermediate to other leading to target molecule

Phases of Process Development

SHE assessment

Route Design

- Retrosynthesis, and Evaluation of various possible routes
- Prioritization of routes for lab trials
- Route selection from <u>SELECT</u>

SHE assessment

Enables long term route selection

Process Design

- Solvent and reagent selection (Solvent/Reagent selection guide)
- Understanding influencing factors
- Developing appropriate workup procedure
- Identification of impurities
- Analytical method development
- Isolation/teliscoping of steps

SHE assessment

Enables long term solvent and reagent selection

Process Optimization

- Reagents and solvents quantity optimization
- Optimizing process parameters
- Specification for raw materials, intermediates and final molecules.
- Process and analytical method validation

SHE assessment

Sustainable process

Manufacture

SHE assessment

All impurities are fixed at the early stage of development

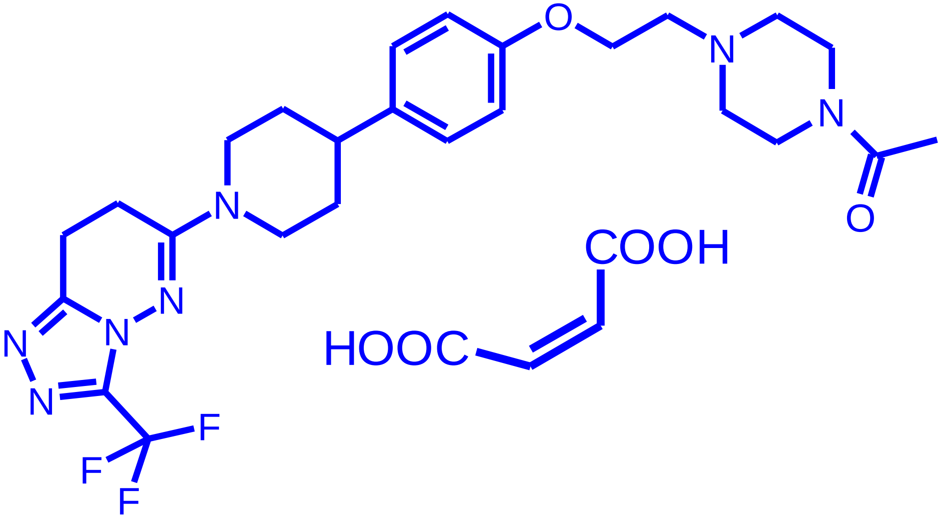
Route / Process Selection - SELECT Guidance

Safety	Are there any toxic reagents/intermediates, including PGI's? Are there any operational hazards (potential explosives, highly flammables etc.)?
Environmental	Is there significant waste generated? What type of waste generated? Does the process require significant energy consumption (temperature extremes, long processes etc)? Are there any emissions or solvents/reagents of concern?
Legal	Is there freedom to operate? Is there existing patent protection? Are there any IP opportunities?
Economics	Are there any expensive reagents/starting materials? Are there high operational costs (long routes/processes)? Does the route meet long term cost targets?
Control	Are there controlled isolation points with stable intermediates? Is there good control of processes and impurities? Are processes robust and reproducible with respect to yield and quality? Is there a robust supply chain?
Throughput	Are the processes efficient and high yielding? Is the route convergent? Are any of the processes high dilution?

Expectation is to reach a safe, efficient and sustainable process

***Chemical Reviews* 2006 July edition**

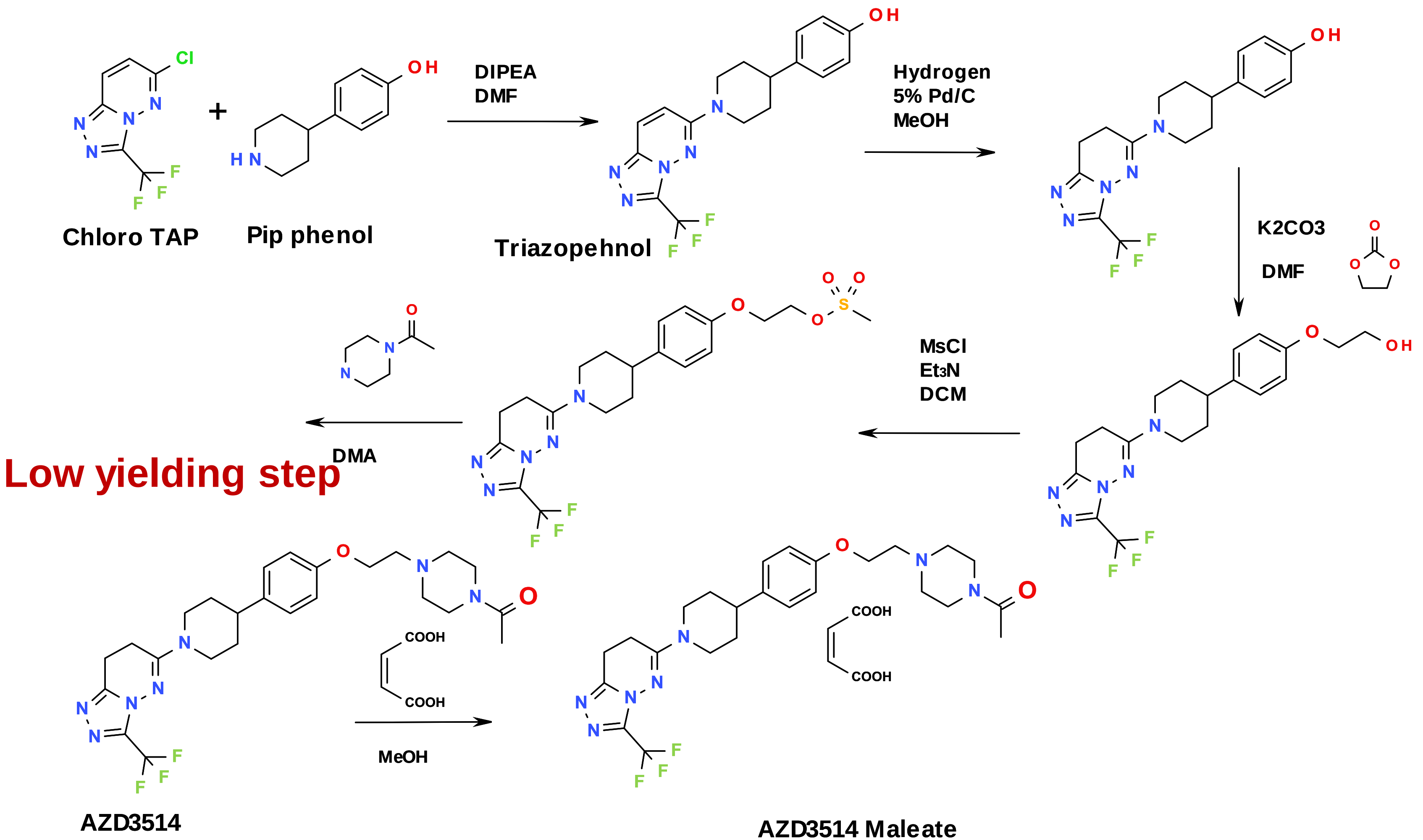
Evolution in synthetic routes for AZD3514



AZD3514 Maleate

Selective Androgen Receptor Down regulator

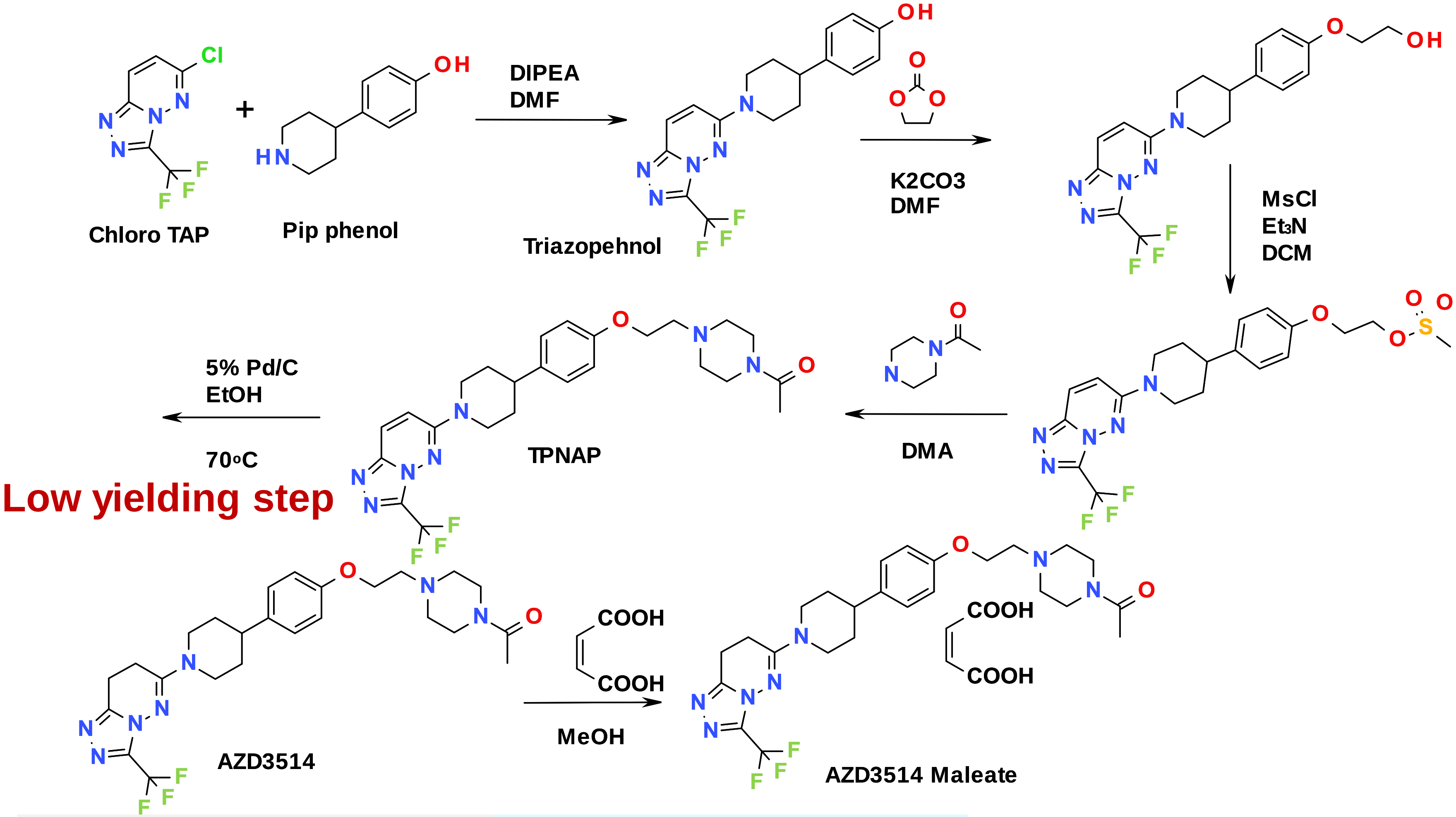
SYNTHETIC ROUTE 1 – 1st Generation Route (Med chem)



Highlights: Diverse oriented synthesis

Drawbacks: Linear with 6 stages, Low yield(27%), use of MsCl(corrosive)

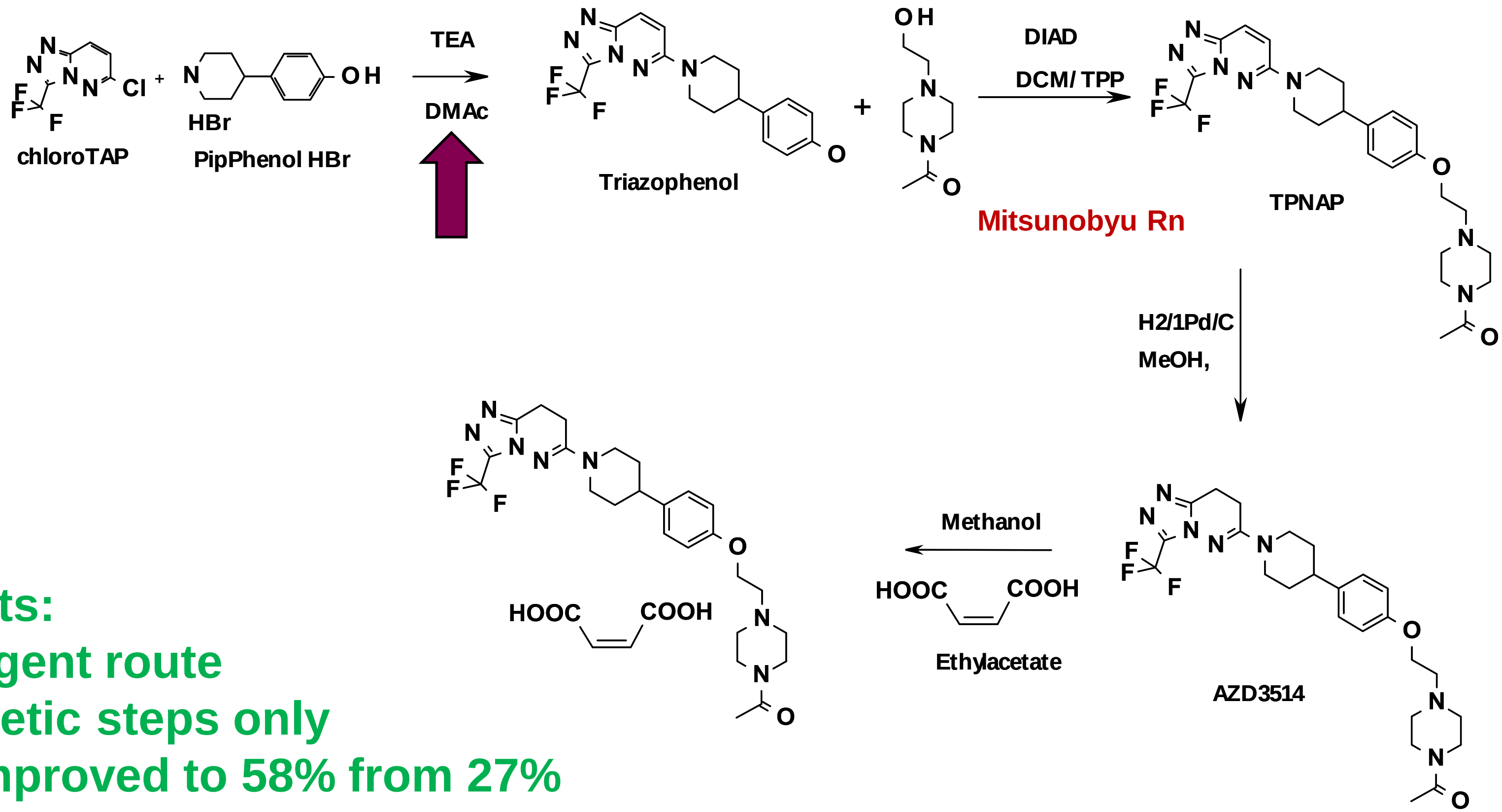
SYNTHETIC ROUTE – 2nd Generation Route



No. of stages : 6	Overall yield : 24.5%

SYNTHETIC ROUTE – 3rd Generation route

(Mitsunobu Route)



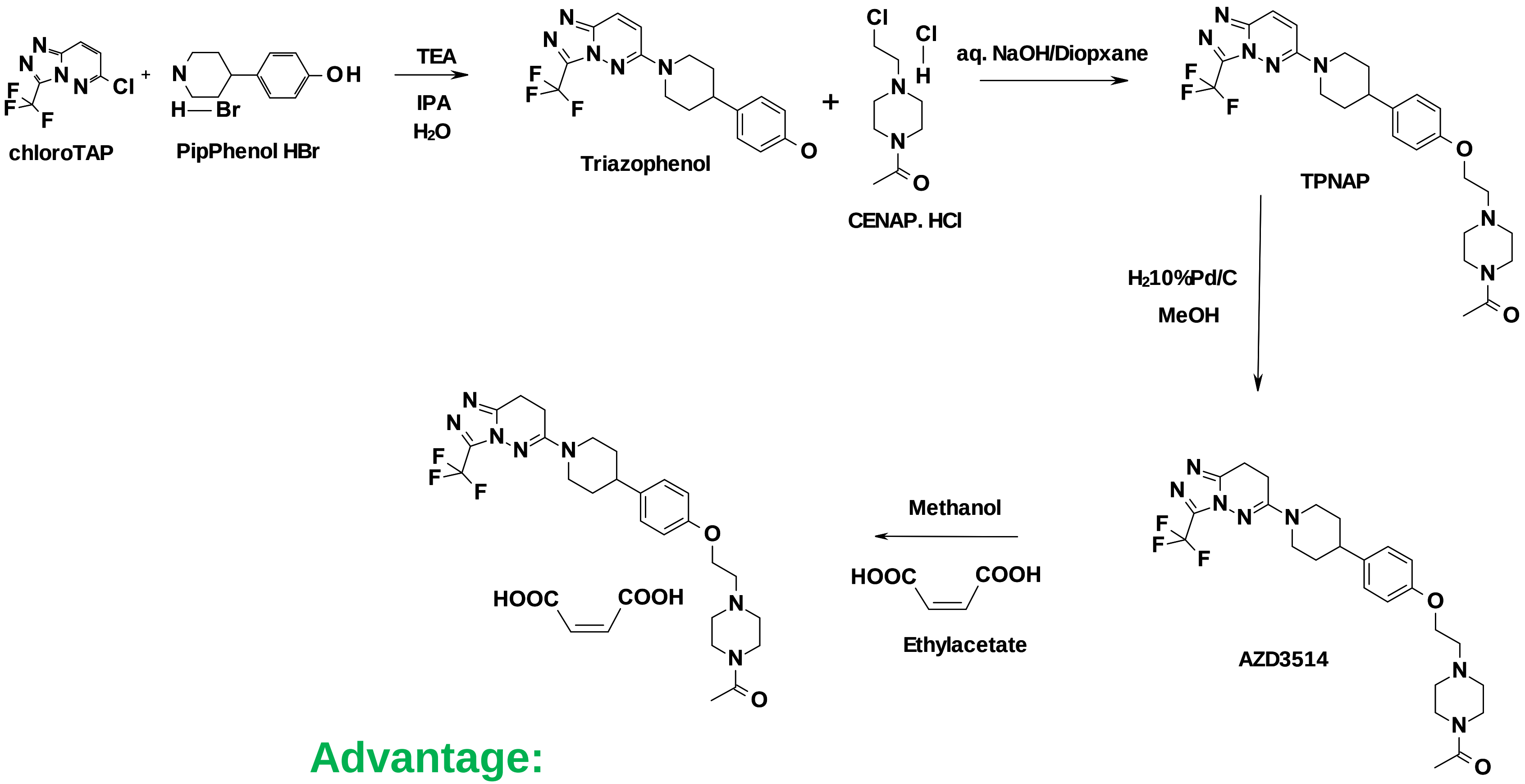
Highlights:

- convergent route
- 4 synthetic steps only
- yield improved to 58% from 27%

SHE Assessment:

- DMAC needs to be avoided.
- Mitsunobu – not a green reaction

SYNTHETIC ROUTE – 4th Generation route



Advantage:

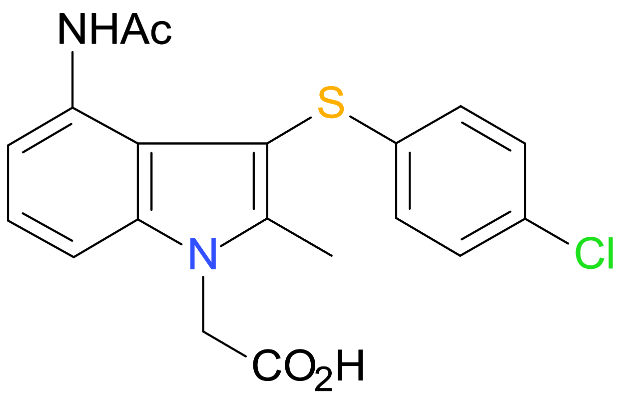
- **No DMAC; No Mitsunobu reaction**
- **4 stages only; Yield improved to 67%**
- **Greener route and process**

RATIONAL FOR route SELECTION

Synthetic route	Product	Remarks
1 Generation(Med chem approach)	Yes	No. of stages : 6; Overall yield : 27.6% More number of stages and low yield
2nd Generation	Yes	No. of stages : 6; Overall yield : 24.5% More number of stages and low yield
3rd Generation	Yes	No. of stages : 4; Overall yield : 58.4% High effluent & use of hazardous chemicals
4th Generation	Yes	No. of stages : 4; Overall yield : 67.1%

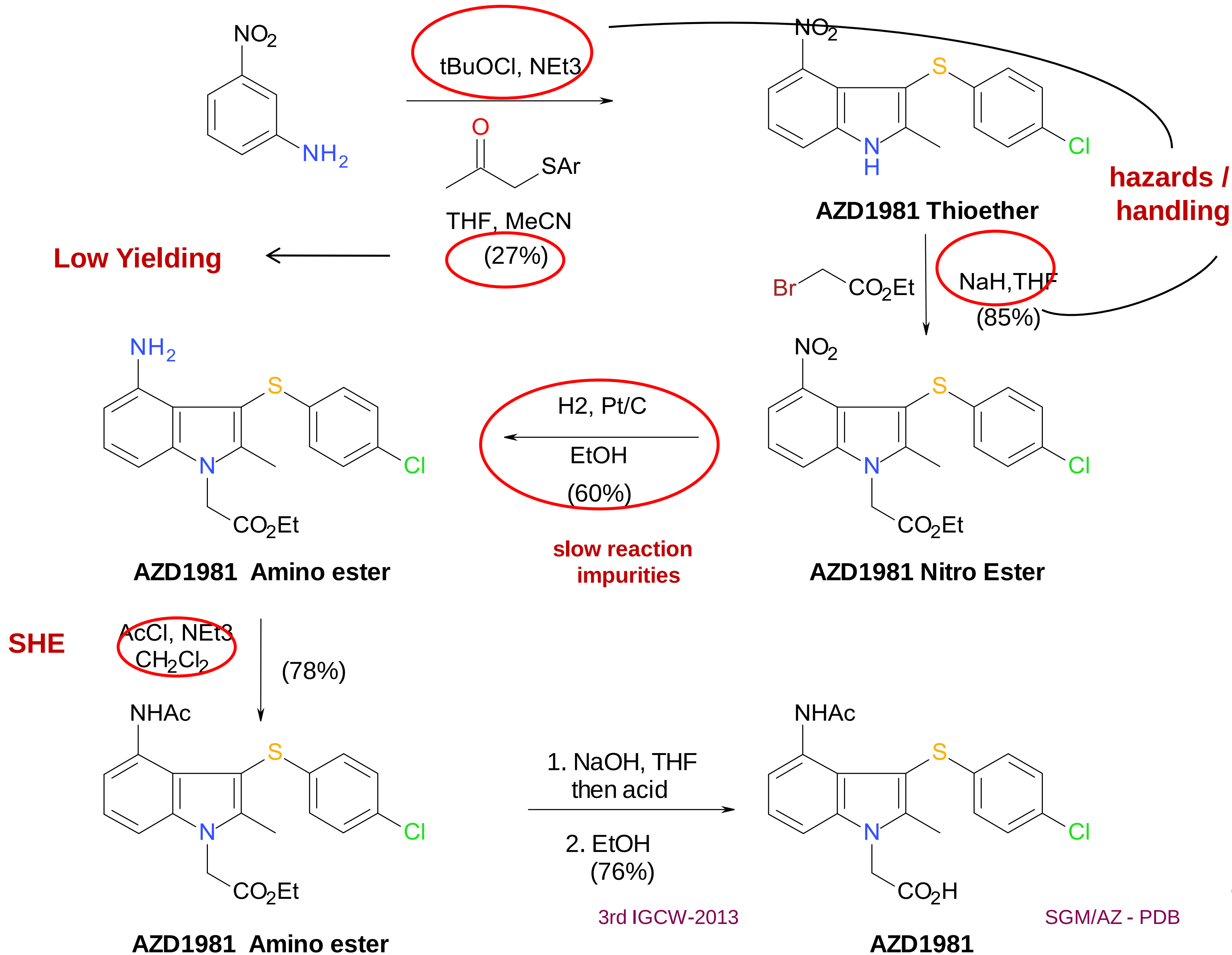
Route and Process related impurities defined.
Process optimisation is the next step

Synthetic Routes to AZD 1981

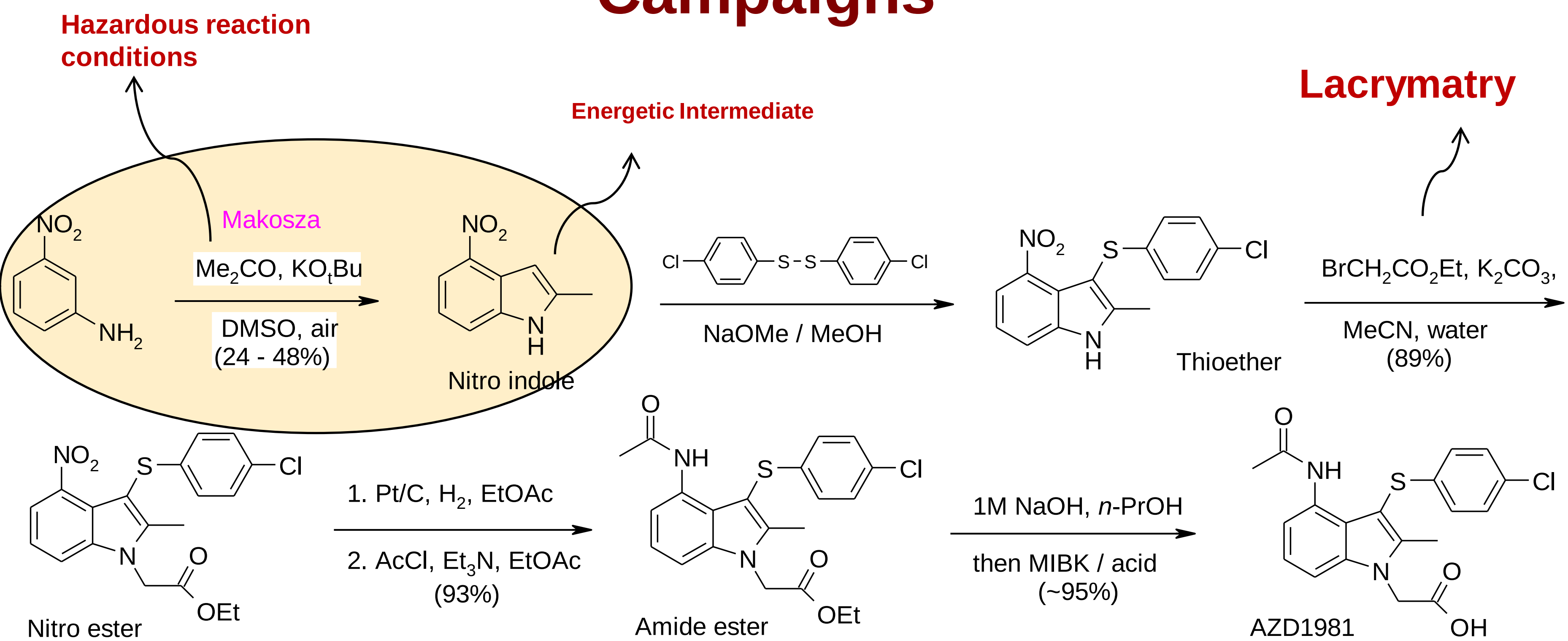


AZD1981

Discovery Route



AZD1981 Route for Pre-clinical to Phase 2b Campaigns

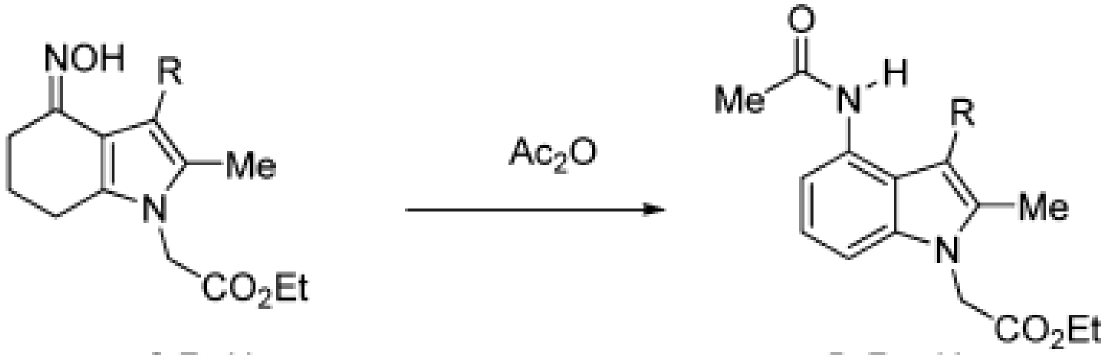


Delivered Drug Substance for clinical trials (30-500 kg)

Need for an alternate safe, efficient and sustainable process

AZD1981- Are there any better ways of making?

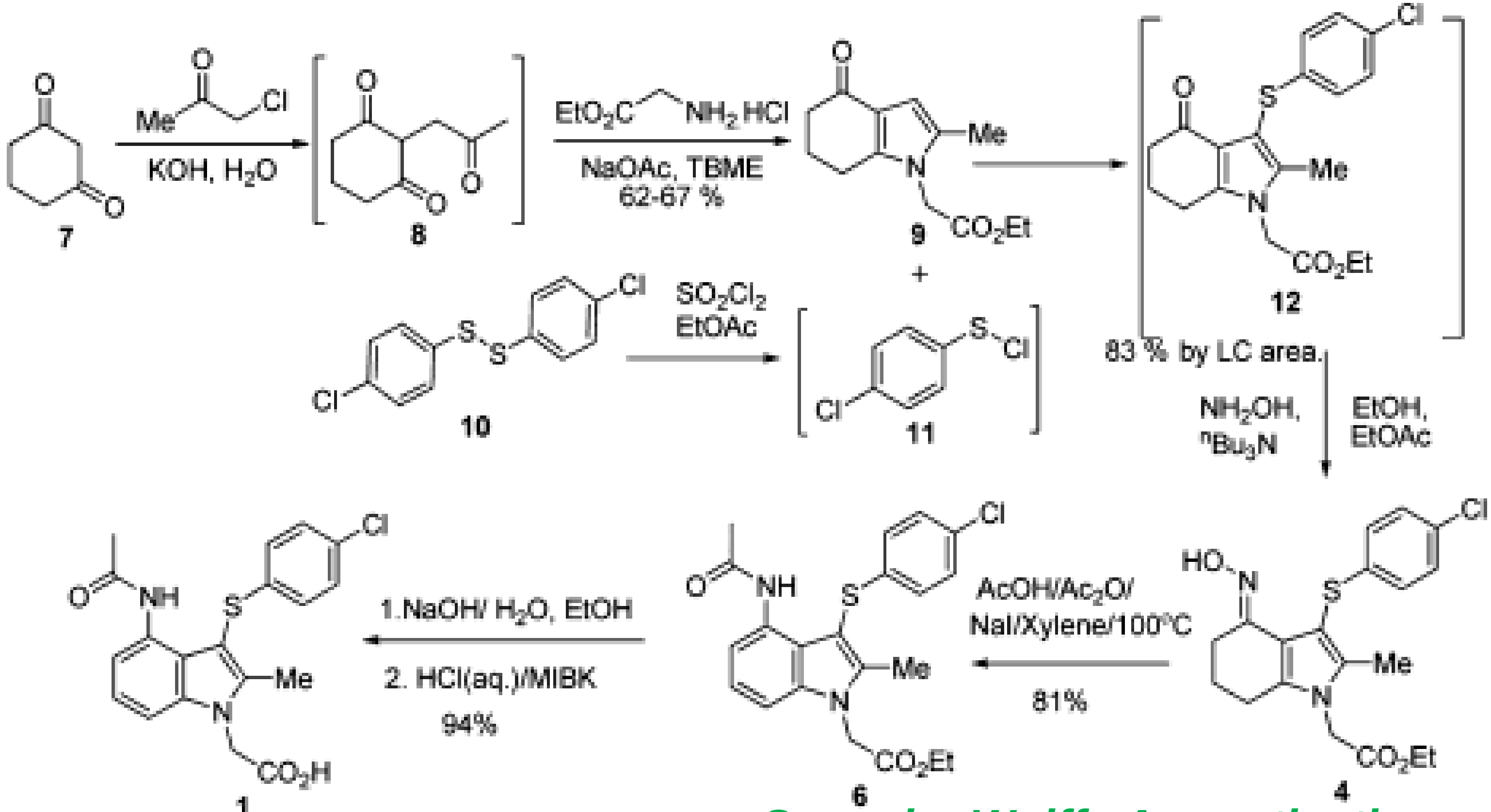
- **The Semmler-Wolff reaction**



Conversion of cyclohexenone oximes to anilines or acetanilides

- W. Semmler, Ber. Dtsch, Chem. Ges., **1892**, *25*, 3352
- L. Wolff, Annalen der Chemie, **1902**, *322*, 351

AZD 1981 – 3rd Generation Route



Semmler Wolffs Aromatisation

Overall yield:35 to 40%

New Route (Semmler - Wolff Rearrangement) - Advantages

- The Semmler - Wolff route is highly efficient, robust, and safe for the synthesis of AZD1981.
  - Safe as this does not go through energetic Nitroindole intermediate
  - Process hazard involving the synthesis of Nitroindole is also avoided

- Route goes through cheap, readily available building blocks, and is suitable for large-scale manufacture.

- Semmler−Wolff aromatisation, has been found to proceed under relatively mild reaction conditions

Org. Process Res. Dev. 2012, 16, 1746−1753

Route Selection

SELECT Guidance

Criteria	Gassman Route	Makozsa's Route	Semmler Wolff Route
Safety	Use of hazardous *tert*-butyl hypochlorite NaH – Hazardous reagent Hydrogenation reaction	Reaction in air above acetone flash point Energetic intermediate Hydrogenation reaction	Safe reactions Avoided
Environ-mental	Use of lachrymatric reagent MDC solvent	Use of lachrymatric reagent	Avoided Safe solvents
Legal	No Issues	No Issues	New oppurtunity
Economics	No issue	No Issue	No issue
Control	Less control on key reaction	Less control on key reaction	Good control
Throughput	Low yield	Low yield	High yield

CONCUSION

1. Route Design enables
    - understanding of nature of possible intermediates
    - the selection of best synthetic route with safe intermediates
    - fixes the route related impurities(RD).

2. Process Design enables selection of
    - environmental friendly solvents and reagents
    - fixes the process related impurities(PD)

3. Ensures right kind of substance for clinical and formulation studies

4. Extends right kind of supports to manufacturing and Regulatory team

5. This approach gives flexibility for the development of a sustainable manufacturing process for the drug substance

Supports the organization in reducing the carbon foot print

Managing our environmental

http://www.astrazeneca.com/Responsibility/The-environment

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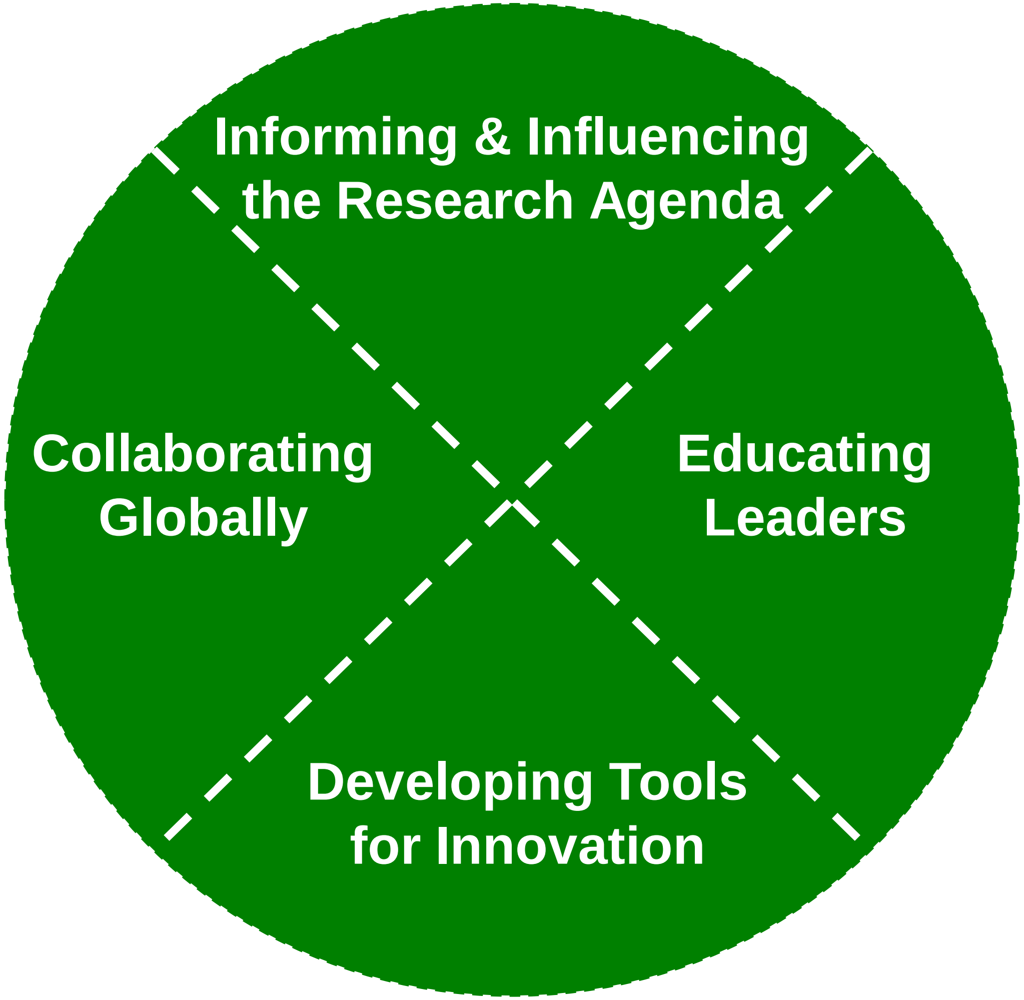

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Thank You