PROEXP PHARMA PVT LTD

SIMPLE METRICS TO MEASURE PROCESS GREENNESS

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Presentation Outline

- Introduction
- Metrics in Green Chemistry
- Metrics for Route Selection

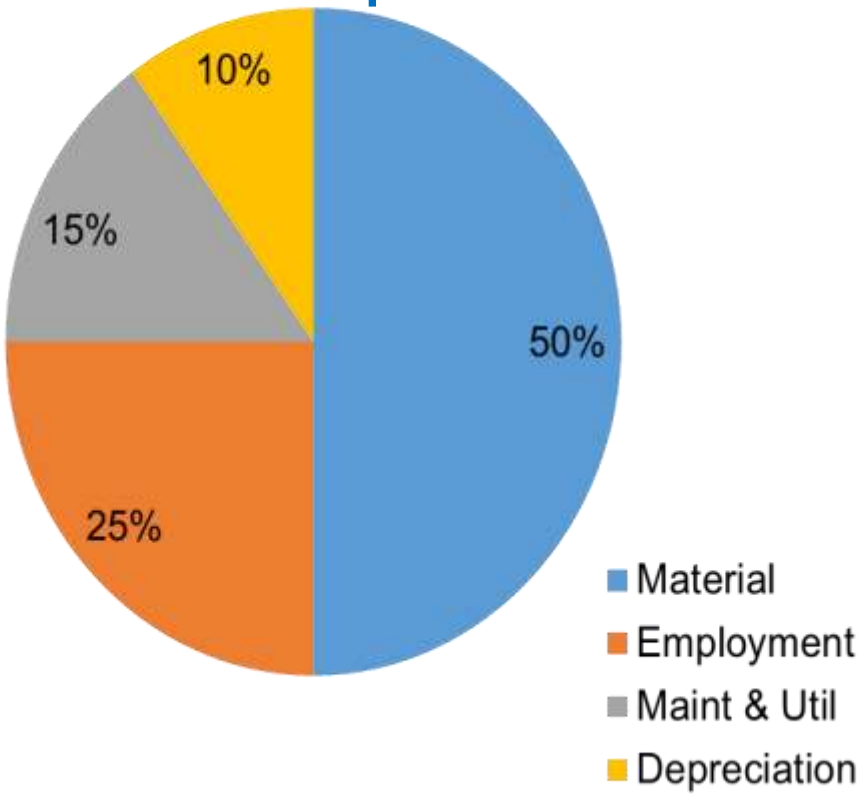
INTRODUCTION

Green Chemistry & Pharmaceutical Industry

- Green/Sustainable chemistry is the design of chemical ***products and processes*** that reduce or eliminate the use or generation of hazardous substances.
- Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, use, and ultimate disposal.
- Manufacturing of pharma products is more complex in nature and need to meet stringent quality requirements.
- E-Factor in pharmaceutical industry is much higher as compared to other chemical manufacturing.
- Greener processes are invariably more cost competitive

Challenges Facing Generic Pharma

Average API Manufacturing Cost Breakup



- Excessive amount of product non- conformances – market recalls, regulatory & quality compliance
- Changing regulatory landscape (GDUFA requirement, QbD, etc)
- Longer product development cycle time
- Large inefficient batch equipment with lower utilization
- Capital and labor intensive
- High inventories and excessive warehouse space

Green Chemistry Principles & Reg Guidelines

Green Chemistry Principles
▪ Prevent waste instead of treating it.
▪ Design atom-efficient synthetic methods.
▪ Choose synthetic routes using nontoxic compounds were possible.
▪ Design new products that deserve functionality while reducing toxicity.
▪ Minimize the use of auxiliary reagents and solvents.
▪ Design processes with minimal energy requirements.
▪ Preferable use renewable raw materials.
▪ Avoid unnecessary derivatization.
▪ Replace stoichiometric reagents with catalytic cycles.
▪ Design new products with biodegradable capabilities.
▪ Develop real-time and on-line process analysis and monitoring methods.
▪ Choose feedstocks and design processes that minimize the chance of accidents.

Regulatory Guidelines
▪ ICH Q11: Development and manufacture of drug substances[20]
▪ ICH Q3C: Residual solvents[20]
▪ ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk[20]
▪ ICH Q8: Pharmaceutical development[20]
▪ Cleaning procedures to avoid cross contamination: EMA guideline on setting health-based exposure limits[21,22]
▪ FDA Guidance Advancement of Emerging Technology Applications[23]
▪ ICH Q3A/B Impurities in new drug substances/products[20]
▪ ICH Q6A specification and acceptance criteria for new drug substances and new drug products: chemical substances[20]
▪ ICH Q1A-F: Stability of drug substances and drug product[20]
▪ FDA Guidance Quality Considerations for Continuous Manufacturing[24]
▪ ICH Q9: Quality Risk Management[20]

- Alignment of Green Chemistry principles and ICH regulatory guidelines

Curr Opn Green Sus Chem. **2022**, *33*, 100562

METRICS IN GREEN CHEMISTRY

Metrics in Green Chemistry

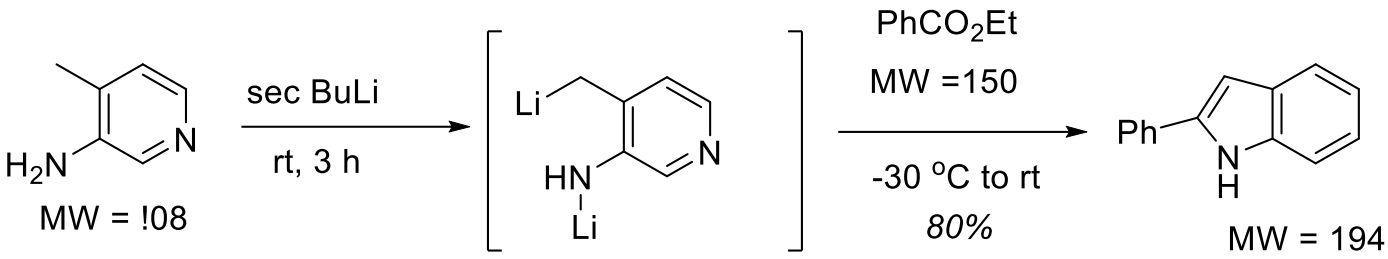
- Metrics are important to drive efficiency in any process
- Early metrics used in synthetic chemistry were limited to only yield and cost.
- Atom economy and E-Factor were two early measurements.
- Green chemistry metrics describe aspects of a chemical process relating to the principles of green chemistry. The metrics serve to quantify the efficiency or environmental performance of chemical processes, and allow changes in performance to be measured.
- Green chemistry metrics give more insights to understand process efficiencies expressed in various ways.

Green Chemistry Metrics

$Atom\ Economy = \frac{\text{MW of the Product}}{\text{Total MW of Reactants}} \text{ x } 100$	$Volume\ Time\ Output\ (VTO) = \frac{\text{Nominal vol of all reactors [m3]X time per batch [h]}}{\text{Output per step [kg]}}$
$Atom\ Efficiency = Atom\ Economy\ X\ Yield$	$Process\ Mass\ Intensity\ (PMI) = \frac{\text{Total Mass used in Process [kg]}}{\text{Mass of product [kg]}}$
$E - Factor = \frac{\text{total mass of waste [kg]}}{\text{Mass of product[kg]}}$	$E - Factor = PMI - 1$

Org. Process Res. Dev . **2013**,*17*, 912

Green Chemistry Metrics

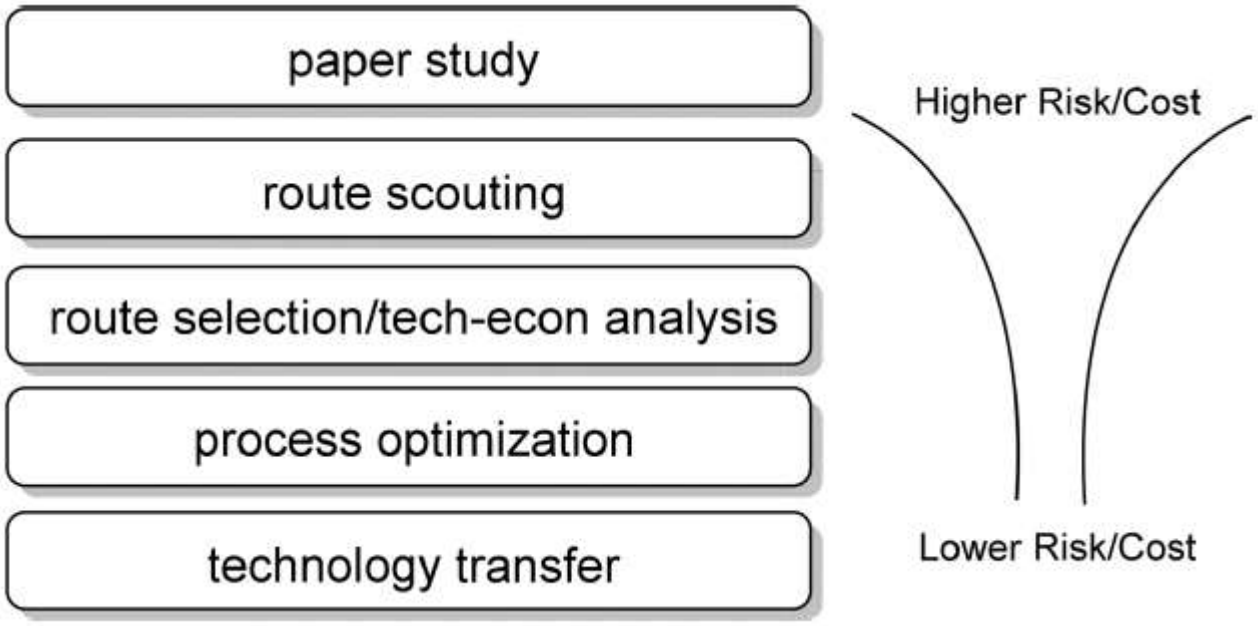


$Atom\ Economy = \frac{194}{108 + 150} \text{ x } 100$ = 75%	$Volume\ Time\ Output\ (VTO) = \frac{(3+3)\ [\text{m3}]\text{X } 24\ [\text{h}]}{250\ [\text{kg}]}$ = 0.58 m^3h/kg
$Atom\ Efficiency = 75\ \%\ x\ 0.8$ = 64%	$Process\ Mass\ Intensity\ (PMI) = \frac{3000\ [\text{kg}]}{250\ [\text{kg}]}$ = 12
$E - Factor = \frac{2750\ [\text{kg}]}{250\ [\text{kg}]}$ = 11	$E - Factor = 12 - 1$ = 11

Org. Process Res. Dev . **2012**, *16,* 1697

METRICS FOR SYNTHETIC ROUTE SELECTION

Typical Product Development Approach



Org. Process Res. Dev . **2019**, *23,* 711

Synthetic Route

- Starting point for any process
- Dictates starting materials, safety, cost and impurity profile of the product.
- Choice of synthetic route in pharma industry is governed by IP landscape, cost, impurities, supply chain, etc.
- Convergent routes are more efficient than linear.
- Metrics based synthetic route evaluation helps in making a informed decisions.

Synthetic Route: SELECT APPROACH

- **S**afety: Process Safety and Exposure to personnel
- **E**nvironmental: Minimize environmental impact
- **L**egal: Intellectual property and Regulatory aspects
- **E**conomics: Cost of goods and production cost
- **C**ontrol: Consistently meeting quality specifications
- **T**hroughput: Maximizing space-time yield

BI Metrics for Route Selection

- Material cost
- Process efficiency
- Yield
- Volume-time-output (VTO)
- Environmental factor (E factor/process mass intensity)
- Quality service level
- Process excellence index (yield and cycle time)
- Modified EcoScale

Org. Process Res. Dev . **2012**,*16*, 1697

Modified Metrics for Desktop Screening

- Based on key aspects in product development.
- Provide a simple and easy tool for desk top synthetic route screening.
- Conversion of qualitative parameters to numbers
- In desktop screening Reaction Mass Intensity (RMI): ratio of the total MW of reactants to that of MW of product is considered.
- Solvents and reagents that do not contribute atoms to product are not considered in analysis.

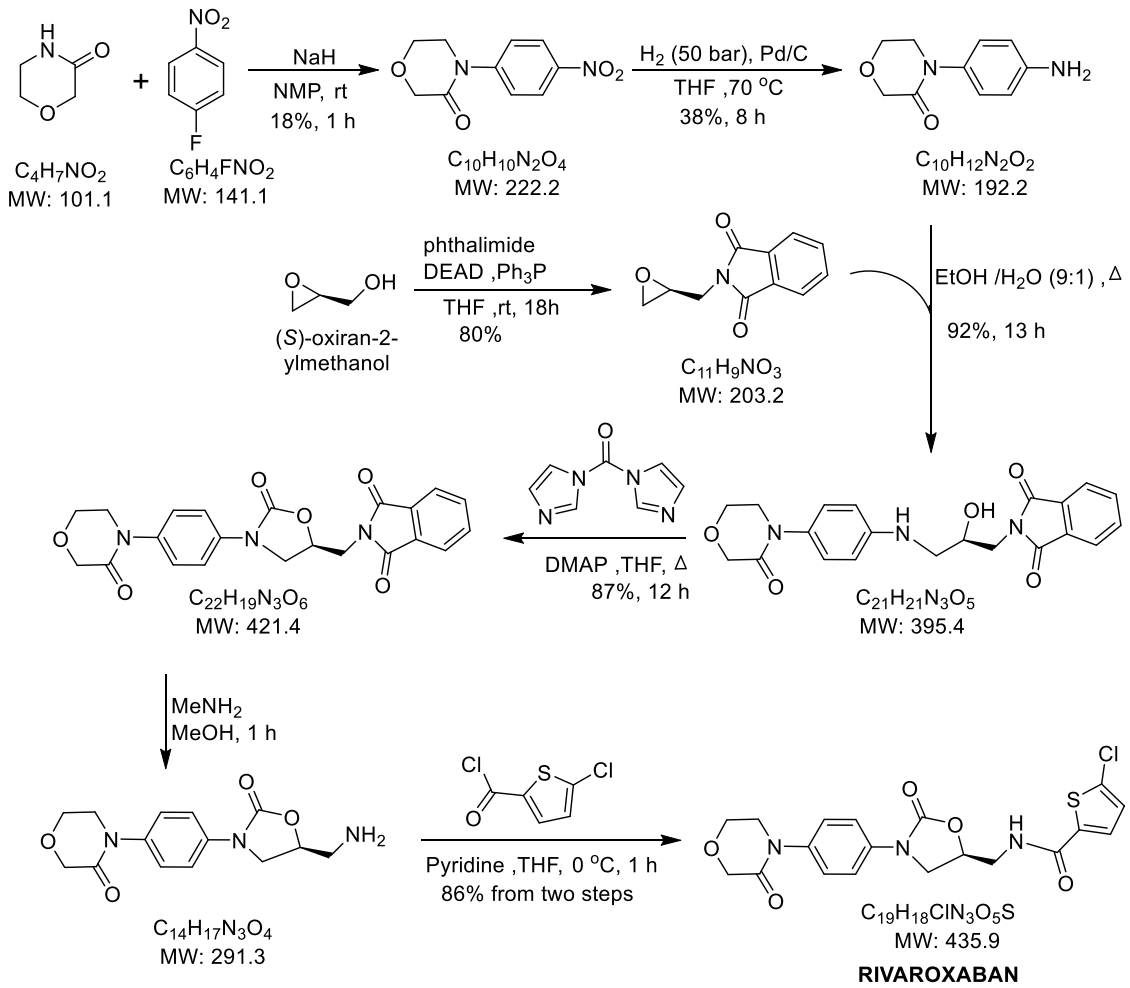
Desktop Route Selection Metrics

No.	Parameter	Variable	Criterion	Points
1	Reaction Mass Intensity (Total MW of reactants/MW of product)	Does any stages have RMI greater than 3?	No/Yes	10/7
2	Number of Steps	10 (shortest)/ 8 (1 step more)/ 6 (two steps more)/ 4 (3 steps more)		10/8/6/4
3	Yield	Any stages have yield less than 80% ?	No/Yes	10/7
4	Starting Materials	Are all raw materials readily available and inexpensive (individual contribution of less than 20% to total RMC)?	Yes/No	10 /7
5	Use of Hazardous Reagents	Any hazardous reagents used?	No /Yes	10/7
6	Intermediates physical properties	Does route involves intermediates with poor physical and hazardous chemical properties?	Yes/No	10/7

Desktop Route Selection Metrics

No.	Parameter	Variable	Criterion	Points
7	Use of Hazardous Solvents (ICH Class I)	Any hazardous solvents used?	No/Yes	10/7
8	Extreme reaction temperature or pressures	What is the reaction temperature or pressure	No extremes / > 150 °C / < -30 °C Or pressure >5 bar	10/7/7/7
9	Reaction time	What is the time required for reaction?	<12 h/>12h	10/7
10	Safety	Highly exothermic reaction or other safety considerations?	No/Yes	10/7
11	Impurities	Does route produce any genotoxic impurities or other impurities that are potentially difficult to remove in API stage?	No/Yes	10/7
Total				

Rivaroxaban: Route-A



- Convergent synthesis with 6 linear steps
- Two relatively expensive building blocks required
- Two low yielding steps
- Caution: Use of NaH and 50 bar pressure

WO 2000147919

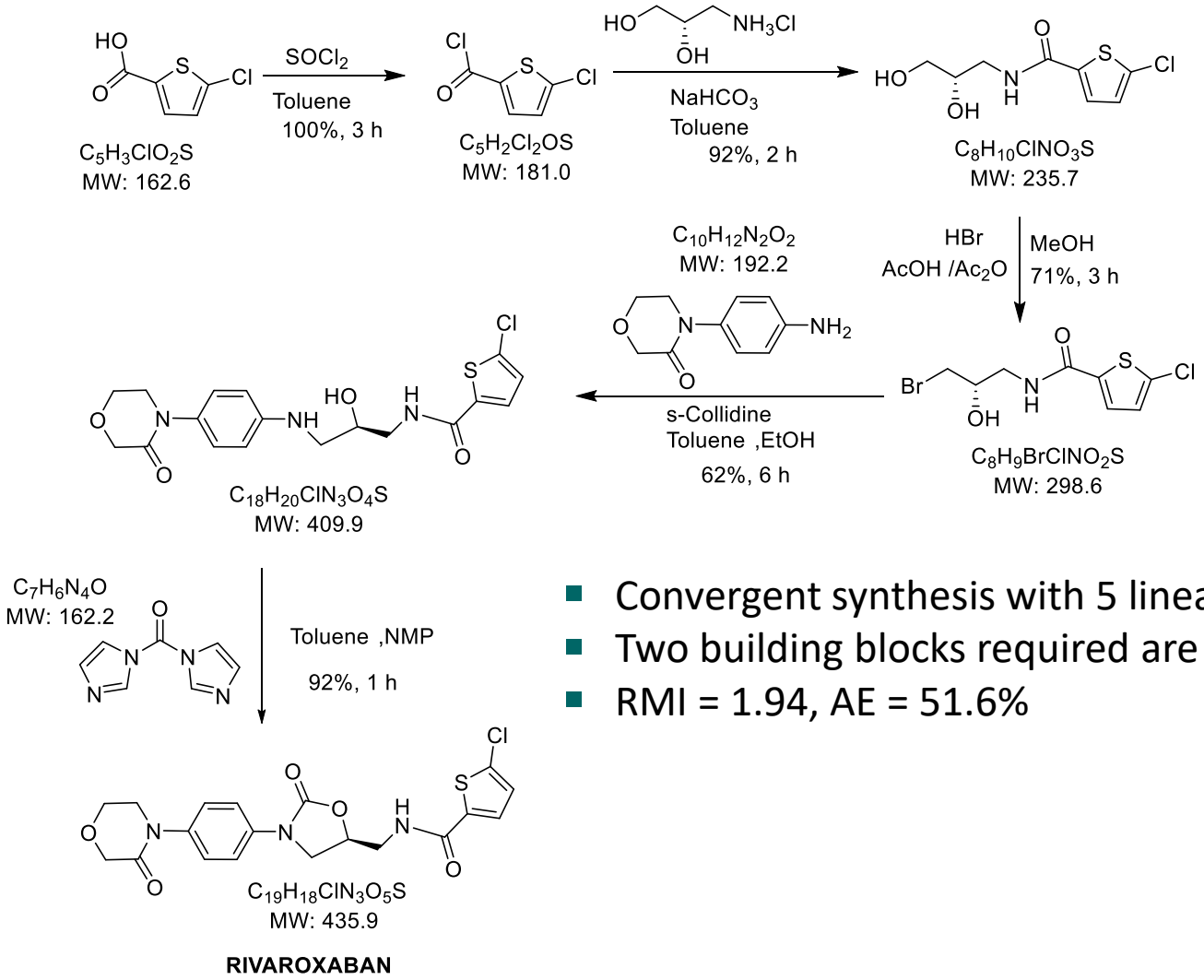
Rivaroxaban: Route-A

S. No.	Reactants		Product		Waste	
	Empirical formula	MW	∑Atoms utilized	MW	Atoms unutilized	MW
1	$C_{10}H_{11}FN_2O_4$	242.2	$C_{10}H_9N_2O_2$	189.2	FO_2	51.0
2	$3H_2$	6.0	H_2	2.0	$2H_2$	4.0
3	$C_{11}H_9NO_3$	203.2	C_3H_5NO	71.1	$C_8H_4O_2$	132.1
4	$C_7H_6N_4O$	162.1	CO	28.0	$C_6H_6N_4$	134.1
5	$C_2H_{10}N_2$	62.1	--	--	$C_2H_{10}N_2$	62.1
6	$C_5H_2Cl_2OS$	181.0	C_5H_2ClOS	145.6	Cl	35.4
Total	$C_{35}H_{42}Cl_2FN_9O_9S$	854.7	$C_{19}H_{18}ClN_3O_5S$	435.9	$C_{16}H_{24}ClFN_6O_4$	418.8

RMI (Reaction Mass Intensity) $= \frac{\sum MW\ of\ Reactants}{MW\ of\ Product}$ = *845.7/435.9* **= *1.96***

Atom Efficiency $= \frac{MW\ of\ Product}{\sum MW\ of\ Reactants}$ *x 100 = 435.9/854.7* **= *51.0%***

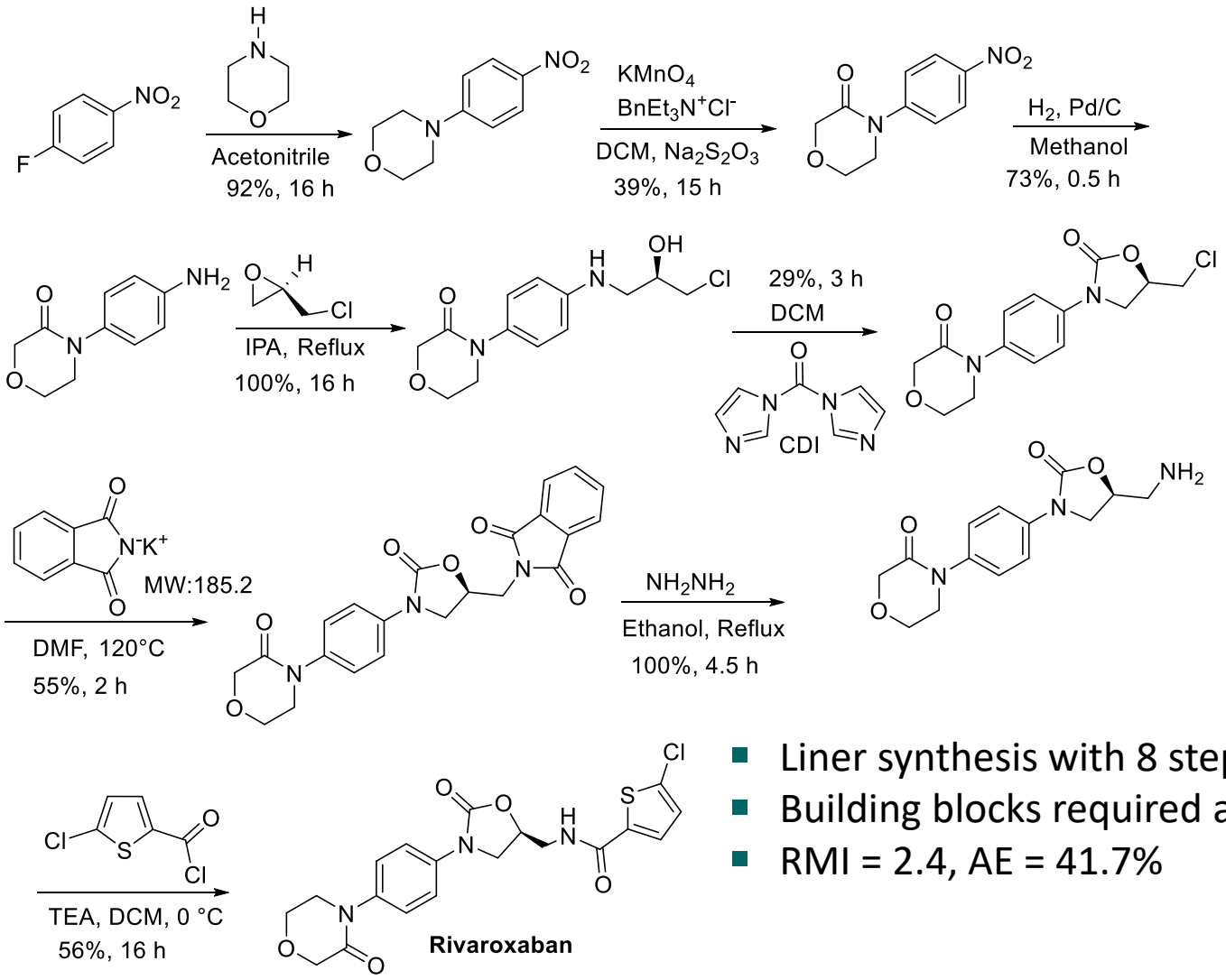
Rivaroxaban Route-B



- Convergent synthesis with 5 linear steps
- Two building blocks required are relatively expensive
- RMI = 1.94, AE = 51.6%

US 20070149522

Rivaroxaban Route-C



- Liner synthesis with 8 steps
- Building blocks required are relatively inexpensive
- RMI = 2.4, AE = 41.7%

US 20090137535

Desktop Screening of Rivaroxaban Routes

No.	Parameter	Variable	Criterion	Points	Route A	Route B	Route C
1	Reaction Mass Intensity (Total MW of reactants/MW of product)	Does any stages have RMI greater than 3?	No/Yes	10/7	10	10	10
2	Number of Steps	10 (shortest)/8 (1 step more)/6 (two steps more)/4 (3 steps more)			8	10	6
3	Yield	Any stages have yield less than 80% ?	No/Yes	10/7	7	7	7
4	Starting Materials	Are all raw materials readily available and inexpensive (individual contribution of less than 20% to total RMC)?	Yes/No	10 /7	7	7	7
5	Use of Hazardous Reagents	Any hazardous reagents used?	No /Yes	10/7	7	10	10
6	Intermediates	Does route involves intermediates with poor physical and hazardous chemical properties?	Yes/No	10/7	10	10	10

Desktop Screening of Rivaroxaban Routes

No.	Parameter	Variable	Criterion	Points	Route A	Route B	Route C
6	Use of Hazardous Solvents (ICH Class -I)	Any hazardous solvents used?	No/Yes	10/7	10	10	10
7	Extreme reaction temperature or pressures	What is the reaction temperature or pressure	No extremes/> 150° C / < -30 C Or pressure >5 bar	10/7/7/7	7	10	10
8	Reaction time	What is the time required for reaction?	<12 h/>12h	10/7	7	7	7
9	Safety	Highly exothermic reaction or other safety considerations?	No/Yes	10/7	7	10	7
10	Impurities	Does route produce any genotoxic impurities or other impurities that are potentially difficult to remove in API stage?	No/Yes	10/7	7	10	10
Total Points (Out of 110)					87	***101***	94

Route B has highest score as compared to Route A & B

DESKTOP EVALUATION: Step by Step Approach

- Andrao's metrics: Reaction mass efficiency depends reaction yield, atom economy, and stoichiometric factor. Based on these factors waste generated can be calculated.
- Write step wise balances equation to account all reactants
- Prepare tables from step wise balanced chemical equation.
- Calculate stepwise Andrao's metrics: Emw (E-Factor based on MW), Stoichiometry factor (SF), Atom economy (AE), Em (E-factor based on mass) and Waste factor.

Org. Process Res. Dev . **2005**, *9,* 149; *Org. Process Res. Dev* . **2007**,11*,* 470;

Andrao's Metrics

$$E_{mw} = \frac{\Sigma \text{Molecular weights of the byproducts}}{\text{Molecular weight of the product}} \qquad \text{Atom Economy (AE)} = \frac{1}{1 + E_{mw}}$$

$$\text{Stoichiometric Factor (SF)} = 1 + \frac{\Sigma \text{Mass of excess reagents}}{\text{MW of product} + \Sigma \text{MW of reagents}}$$

$$\text{Reaction Mass Efficiency (RME)} = \frac{\varepsilon\,(\text{AE})}{\text{SF}} \quad \text{where } \varepsilon = \text{Yield}$$

$$E_m = \frac{1}{\text{RME}} - 1$$

$\bar{\omega}_j$ = Cumulative waste for each step$_j$ for x moles of final target product

$$= p_j(Em)_j\left(\frac{x}{\prod \varepsilon_k}\right)$$ where x = 1 for 1 mole of final target product and

$\prod \varepsilon_k$ = multiplicative chain of reaction yields connecting the product from step j to the final target product

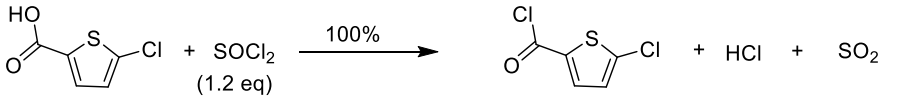
$$(E_{mw})_{overall} = \frac{\Sigma \text{MW of byproducts}}{\text{MW of final target product}} \qquad AE_{overall} = \frac{1}{1 + (E_{mw})_{overall}}$$

$$(E_m)_{overall} = (E_m)_{overall} = \frac{\Sigma \bar{\omega}_j}{p_j x}$$

Org. Process Res. Dev . **2005**, *9,* 149; *Org. Process Res. Dev* . **2007**,11, 470;

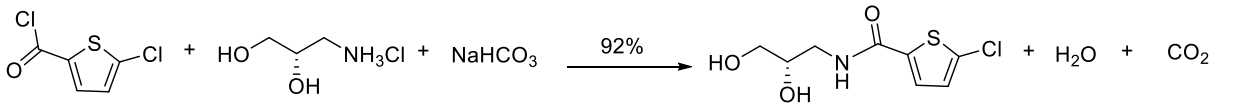
Desktop Evaluation of Route-B

Step-1



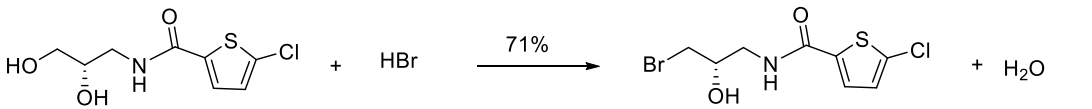
MW: 162.6 MW: 119.0 MW: 181.0 MW: 36.5 MW: 64.1

Step-2



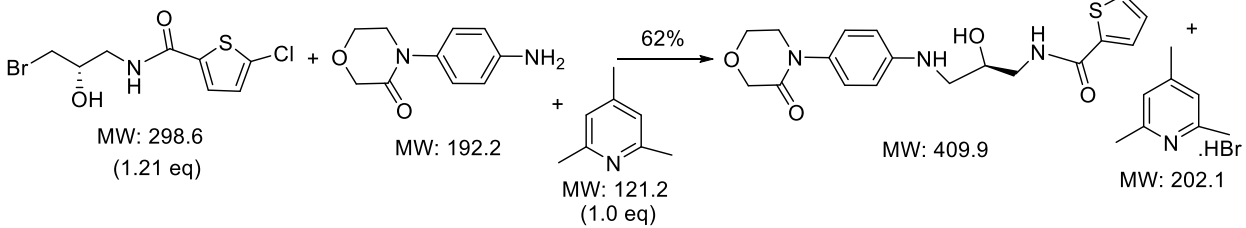
MW: 181.0 MW: 127.6 (1.08 eq) MW: 84.0 (1.85 eq) MW: 235.7 MW: 18.0 MW: 44.0

Step-3



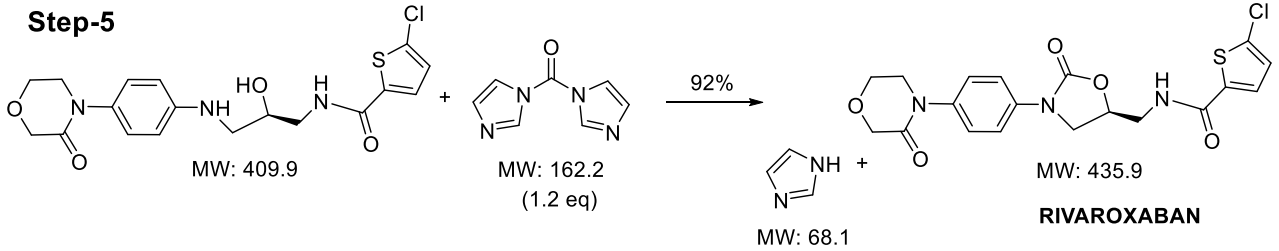
MW: 235.7 MW: 80.9 (2.9 eq) MW: 298.6 MW: 18.0

Step-4



MW: 298.6 (1.21 eq) MW: 192.2 MW: 121.2 (1.0 eq) MW: 409.9 MW: 202.1

Step-5



MW: 409.9 MW: 162.2 (1.2 eq) MW: 68.1 MW: 435.9

RIVAROXABAN

Desktop Evaluation of Route-B

Step	By products	MW By products	MW (product) (pi)
1	SO_2, HCl	100.6	181.0
2	H_2O, CO_2, NaCl	120.5	235.7
3	H_2O	18.0	298.6
4	s-Coll HBr	202.1	409.9
5	2x Imidazole	136.2	435.9

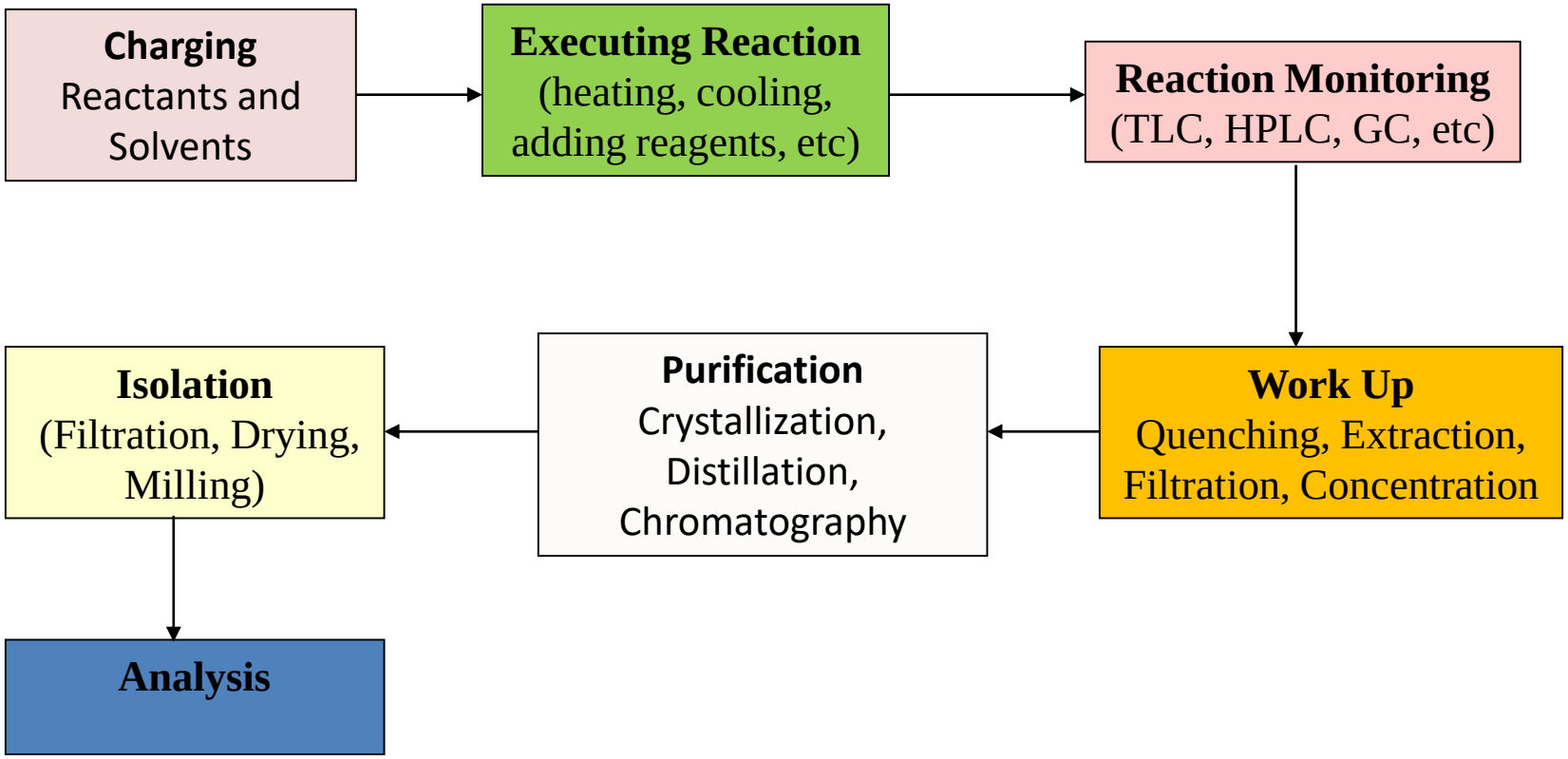
Step	Compound	Equiv Mass	Excess Equiv	Excess Mass	Yield (%)
1	Thionyl chloride	119.0	0.2	23.8	100
2	Amine HCl $NaHCO_3$	127.6 84.0	0.08 0.85	10.2 71.4	92
3	HBr	80.9	1.9	153.7	71
4	Bromide	298.6	0.21	62.7	62
5	CDI	162.2	0.2	32.4	92

Desktop Evaluation of Route-C

Step	MW(pi)	Yield (ε)	SF	E_{mw}	AE	RME	E_m	Mass waste (g)
1	181.0	1.0	1.08	0.56	0.64	0.59	0.69	333.5
2	235.7	0.92	1.18	0.51	0.66	0.59	0.69	403.4
3	298.6	0.71	1.40	0.06	0.94	0.56	0.78	407.3
4	409.9	0.62	1.09	0.49	0.67	0.32	2.16	962.9
5	435.9	0.92	1.05	0.31	0.76	0.64	0.55	240.7
Overall		0.37		1.33	0.43	0.16	5.39	2347.8

- For one mole of Rivaroxaban (435.7 g) waste generated is 2347.8 g (5.39 kg/kg of API)
- Maximum waste is generated in step-4 (coupling step)
- Calculations do not consider solvents or water used in process.

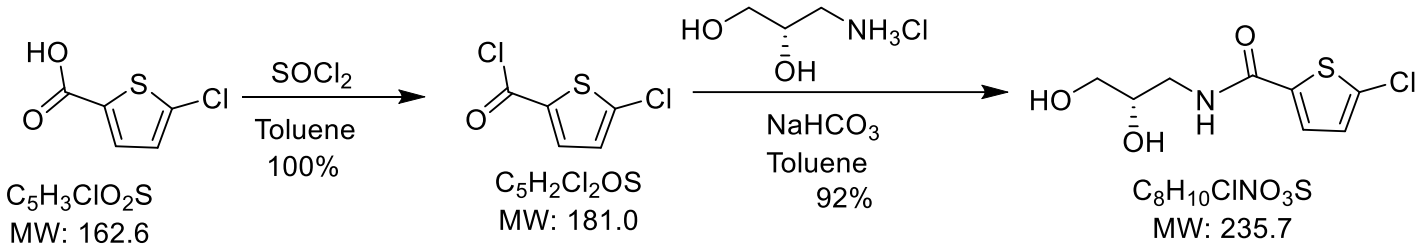
Typical Chemical Reaction Flow



Chemical Reactions For API Synthesis

- Route Selection
- Understand physicochemical properties of reactants, product and impurities
- Select right Reagent and Solvent selection for transformation
- Process Optimization of reaction parameters: Maximize in solution yield (Use of OVAT or DoE approach): Optimization of solvent, reagent, temperature, addition modes, etc.
- Design work up to minimize waste generation and solvent usage while still targeting highest yield and quality.

Metrics to be Tracked During Development



	Chemical	Yield (%)	Qty Used (g)	Amt Rec (g)	Qty After Rec (g)	Prdt Output Wt (g)	PMI
Step-1	Thiophene acid		100.0	0.0	100.0		
	Thionyl chloride		88.3	0.0	50.0		
	Toluene		344.0	275.2	68.8		
	Step-1 Output (Acid chloride)	**100.0**				**120.0**	**1.82**
Step-2	Acid chloride		100.0	0.0	100.0		
	Amine hydrochloride		65.4	0.0	65.4		
	Sodium carbonate		86.1	0.0	86.1		
	Water		392.0	0.0	392.0		
	Methyl THF		151.6	0.0	151.6		
	Toluene		196.0	156.8	39.2		
	Step-2 Output (Amide)	**92.0**				**110.0**	**7.58**

- Metrics for Step Optimization:
  - Yield, Purity/Assay, Cost
  - PMI
  - Throughput: Kg product/Kg of solvent

Summary

- Need to develop a mindset for greener and simpler processes: Use readily available Green Chemistry tools like route selection, solvent selection and reagent selection guides from ACS GCI web site.

- Telescoping reactions greatly reduces cycle time and labour costs

- Focus on solvents & water usage which contributes to about 90% waste in pharma manufacturing.

- Chemistry and technology is changing rapidly – Need to try newer approaches to solve problems

Green Chemistry & Engineering principles provide a strong framework in developing greener processes

Proexp Pharma Pvt Ltd

- Mission: Inspired by “Make in India” initiative, we develop and implement greener and novel technologies to enable efficient manufacturing of Intermediates and Drug substances.

- Focus on developing greener routes to older API’s and intermediates.

- Contract Research, custom synthesis and Develop and transfer greener technologies.

Acknowledgment