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Medicinal Chemistry Case Study: Novel Macrolide Antibiotics

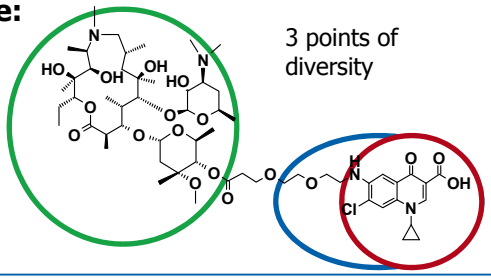
Objective:

- Synthesis of new macrolides active towards resistant bacterial strains
- Design and implement synthesis of new macrolide analogues
- Preparation of macrolide derivative for *in vivo* studies (0.1 g scale, purity > 95.0 %, 50 g scale, purity > 98.5 %)

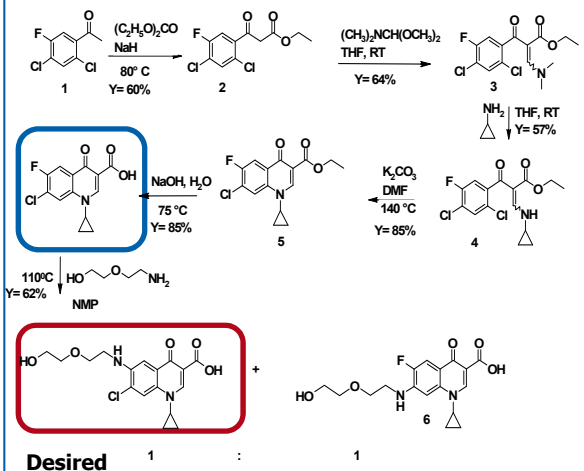
Challenge:

- Develop suitable synthetic route for industrial production in given timeframe (3 months)

Target molecule:



Synthesis of quinolone intermediate



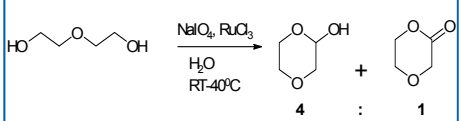
Desired compound 1 : 1

Small scale synthesis:

- 0.1 g scale
- 50% of desired product in the reaction mixture
- Not suitable for scale up
- Desired compound: 6 steps & 5% overall yield

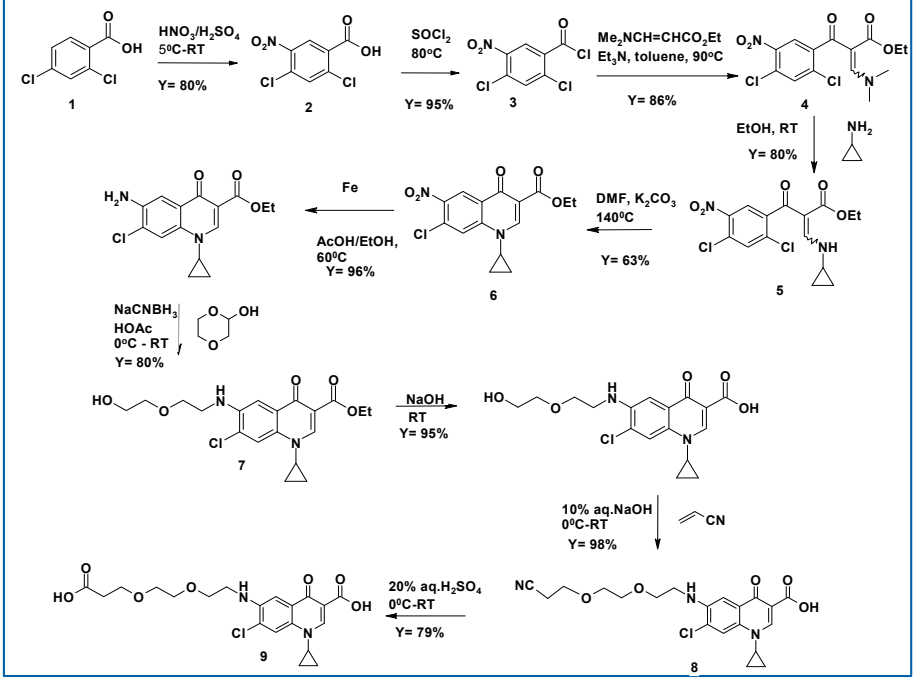
Optimized procedure for chloroquinolone synthesis-summary

- Scale up synthesis:
- 50 g scale
- Suitable for further scale up
  - overall yield ~ 19%/10steps



New method for selective diethyleneglycol oxidation was developed

Quinolone intermediate - optimized synthetic route:



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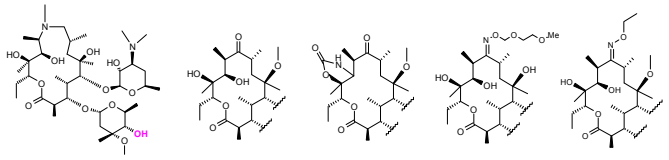
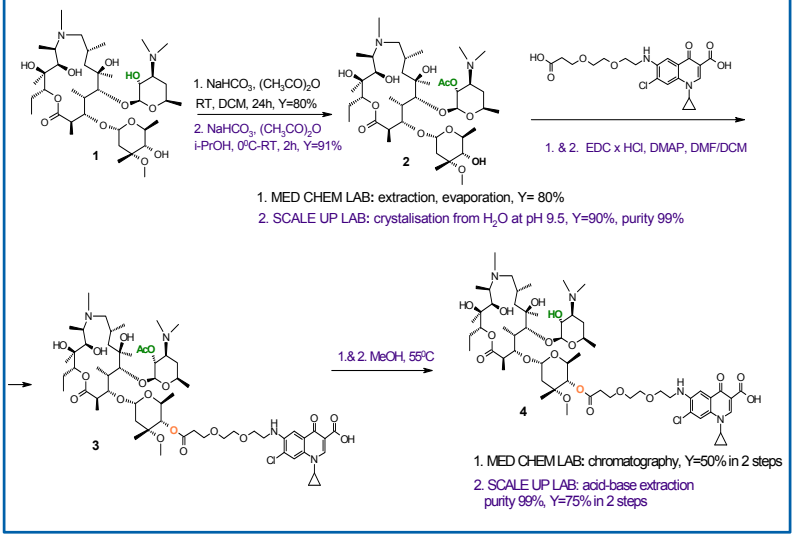
Synthesis of macrolide derivatives



Macrolides used

Scale up of Azithromycin analogue



Large scale vs small scale synthesis:

- Low b.p. solvents avoided, i-PrOH used instead of DCM
- Used isolation techniques more suitable for industrial production
- Crystallization instead of extraction
- Acid-base extraction instead of column chromatography
- Improved overall yield; 61% large scale vs 32% small scale for 3 steps

Summary:

- A new macrolide antibiotic was designed and synthesised
- Synthesis of each step optimised for large scale
- Innovative chemistry of diethylenglycol oxidation

In vitro antibacterial activity

	S.aureus	*S. pneumoniae*	*S. pyogenes*	*S.aureus*	*S.pneumoniae*	*S. pyogenes*	*S.aureus*	*S.pneumoniae*	*S.pyogenes*	*H.influenzae*
	eryS	M	M	M	iMcLS	iMLS	iMLS	cMLS	cMLS	
CMPD	0,25	≤0,125	≤0,125	0,25	≤0,125	≤0,125	0,25	≤0,125	≤0,125	0,5
azithro mycin	0,5	8	8	>64	>64	16	>64	>64	>64	1
telithro mycin	≤0,125	0,25	0,5	≤0,125	0,25	≤0,125	≤0,125	0,25	16	2

References

1. A.Fajdetić, et al., *Eur. J. Med. Chem.* 46 (2011) 3388–3397
2. S. Alihodzic, et al., WO2005/108412
3. A. Vinter, et al. , *Synthesis*, 2 (2010) 255-258;

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