Novel Desosamine-Modified 14- and 15-Membered Macrolides Without Antibacterial Activity

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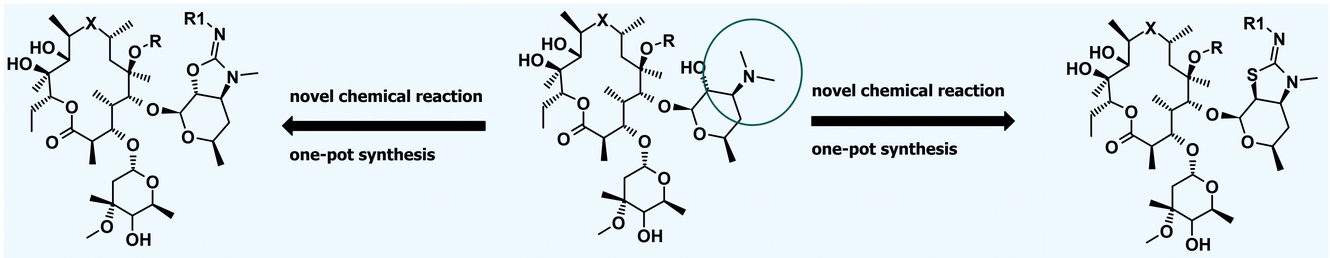
Introduction

Macrolide antibiotics have been used for treatment of bacterial infections for more than 50 years.[1] However, it seems that broad potential of macrolides has not been fully explored yet. Most recently antibacterial macrolides have attracted considerable attention for two main reasons: (a) as with other antibiotics, active use of macrolides resulted in development of macrolide resistance that fuels a search for novel types of macrolides having better antibacterial activity, pharmacokinetic properties, and safety profiles (b) macrolide derivatives, especially 14- and 15-membered classes, have also become interesting for treating important chronic diseases, that is, asthma, chronic sinusitis, diffuse panbronchiolitis, cystic fibrosis, etc.

Novel anti-inflammatory macrolides - Rational design

- Long-term treatment with macrolide antibiotics presents a considerable risk for promotion of bacterial resistance.
- N,N-dimethylamino group of the desosamine ring - essential for antibacterial activity – bridging of the ring should diminish antibacterial activity.



Objective

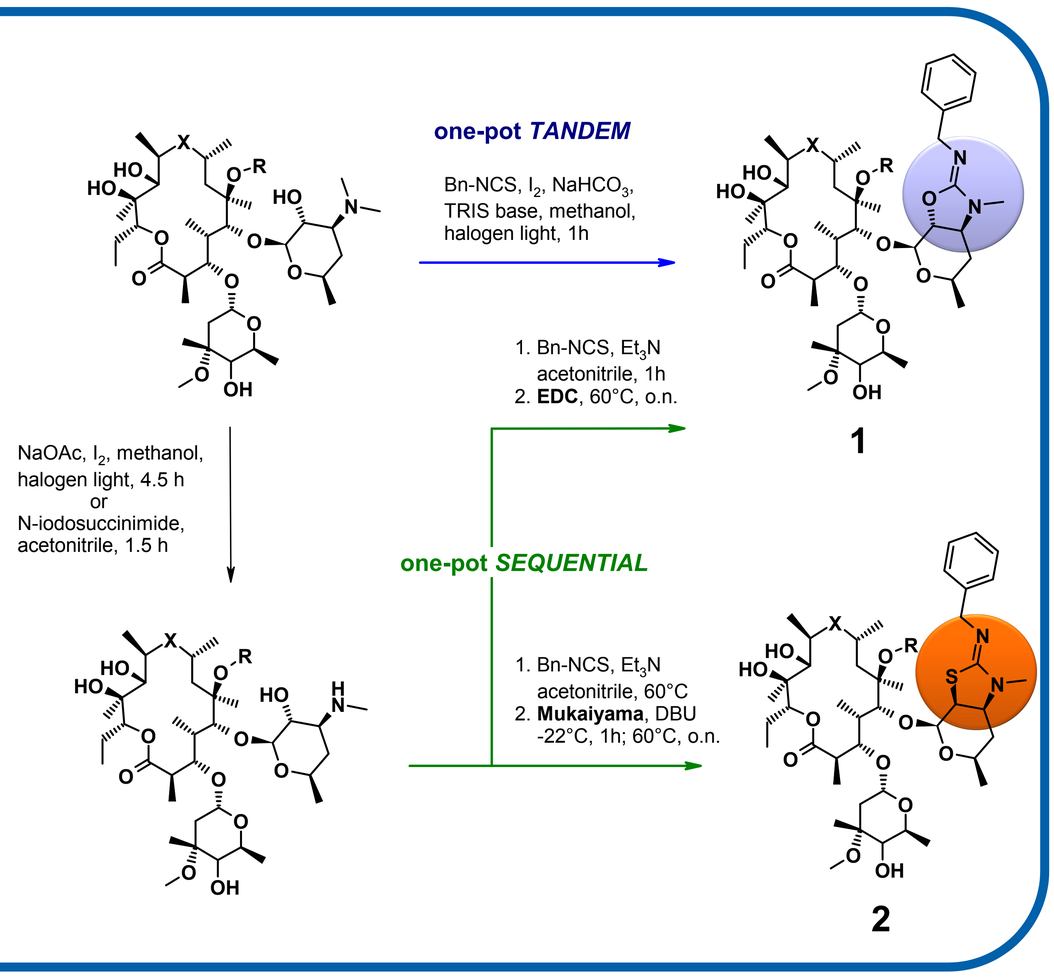
- **First-in-class, antimicrobially inactive, anti-inflammatory macrolide for treatment of neutrophil dominated chronic inflammatory lung diseases with once daily oral dosing**
  - ➢ removal of antimicrobial activity with retention of anti-inflammatory activity and favourable PK properties characteristic for azithromycin
  - ➢ design of screening cascade

Challenge

- Development of robust method for larger-scale production of differently **R1** substituted oxazolidines **A** and thiazolidines **B** on various macrolide scaffolds.
- No reported example of the bridging of desosamine ring that would allow easy incorporation of various substituents.

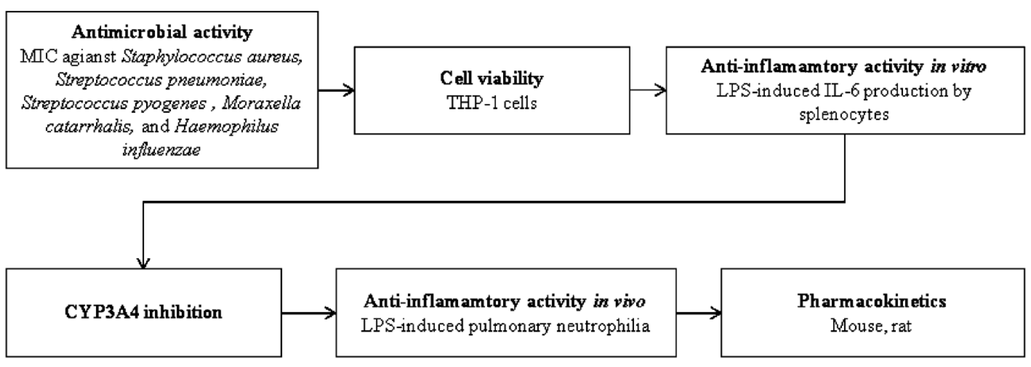
Chemistry

- A novel, mild, one-pot methods, **sequential** and **tandem**, for annelation of N-substituted 2-imino-1,3-oxazolidine (**1**) and N-substituted 2-imino-1,3-thiazolidine **(2)** moiety to the 2′,3′-positions of the desosamine sugar of 14- and 15-membered antibacterial macrolides were developed.[2,3]
- Particularly interesting is the **tandem** reaction that involves dealkylation, thiocarbamoyl intermediate formation and final cyclization to yield target structure **1**.[2]
- Fine tuning of reaction conditions enables chemoselectivity towards structure **1** or **2** due to influence on equilibrium between deprotonated **2-OH** and **thiocarbamoyl** moieties.[3]
- A reaction of thiophilic reagent with deprotonated thiocarbamoyl moiety forms **oxazolidine ring** (**1**), while reaction with deprotonated 2-OH leads to formation of **thiazolidine ring** (**2**) with oposite stereochemistry at position C-2′.
- Method is suitable for introduction of various R1 substituents and large scale synthesis of potential drug candidates – **opportunity for early SAR exploration on diverse sensitive scaffolds!**

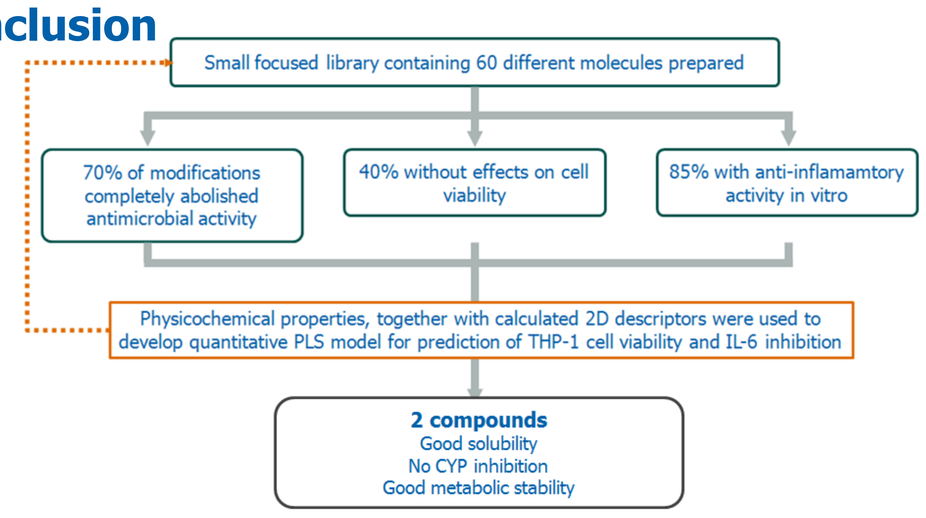


Biological profiling

- Screening cascade was designed to select compounds that inhibit IL-6 production without antibacterial activity and effects on THP-1 cell viability.[4]



Conclusion



In vivo activity and pharmacokinetics of selected compound proved comparable to azithromycin.

References

1. Macrolide Antibiotics, Birkhäuser, Basel, 2002
2. Eur. J. Org. Chem. 2011, 2507–2518
3. Eur. J. Org. Chem. 2013, 4666–4673
4. J. Med. Chem. 2012, 55, 6111−6123

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