

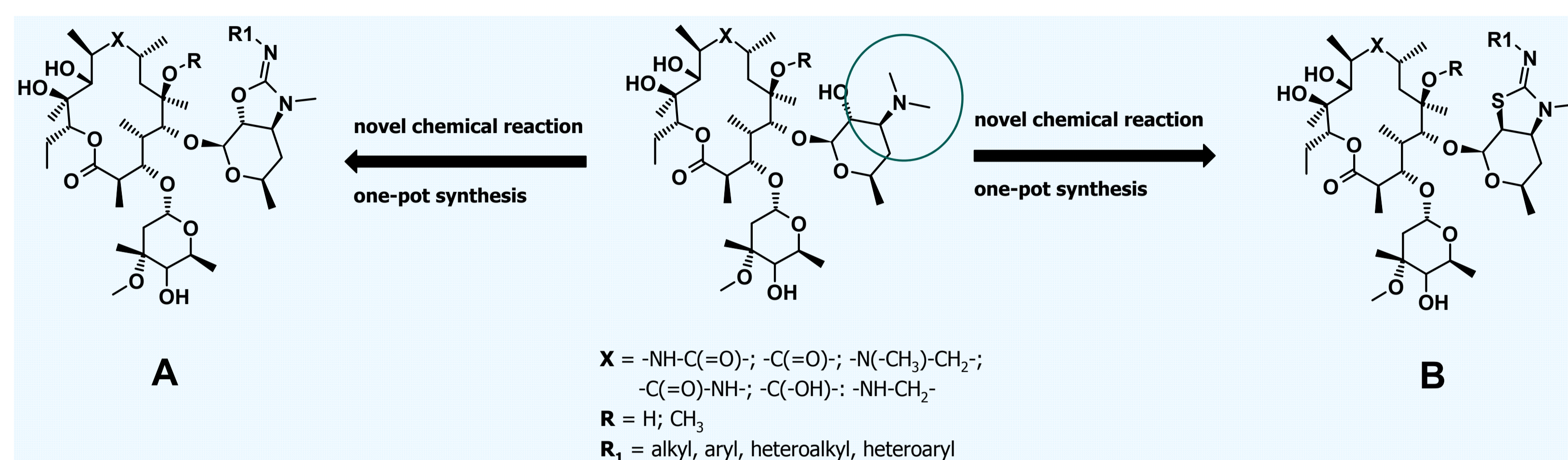


Introduction

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

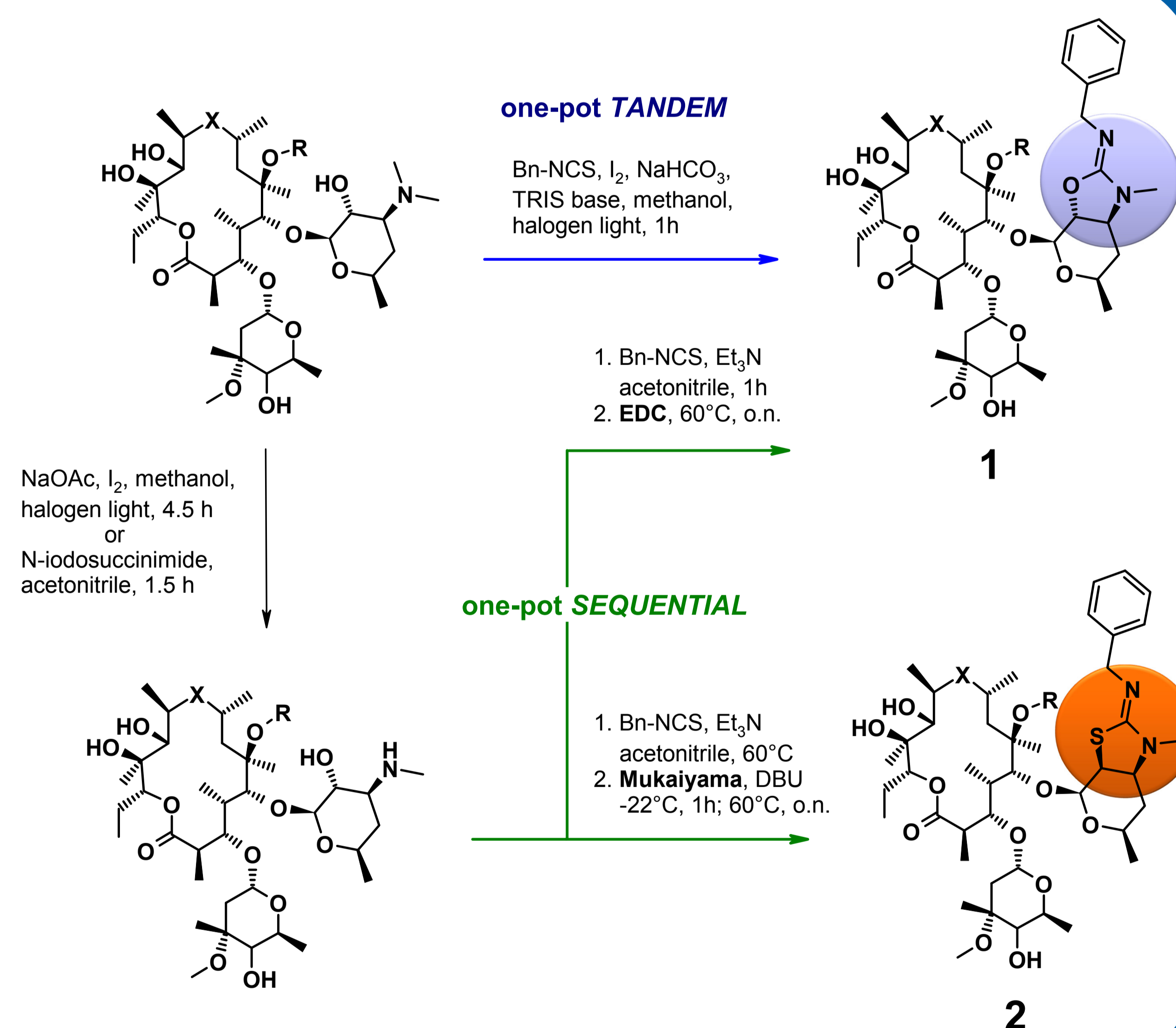
- First-in-class, antimicrobially inactive, anti-inflammatory macrolide for treatment of neutrophil dominated chronic inflammatory lung diseases with once daily oral dosing**
 - removal of antimicrobial activity with retention of anti-inflammatory activity and favourable PK properties characteristic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

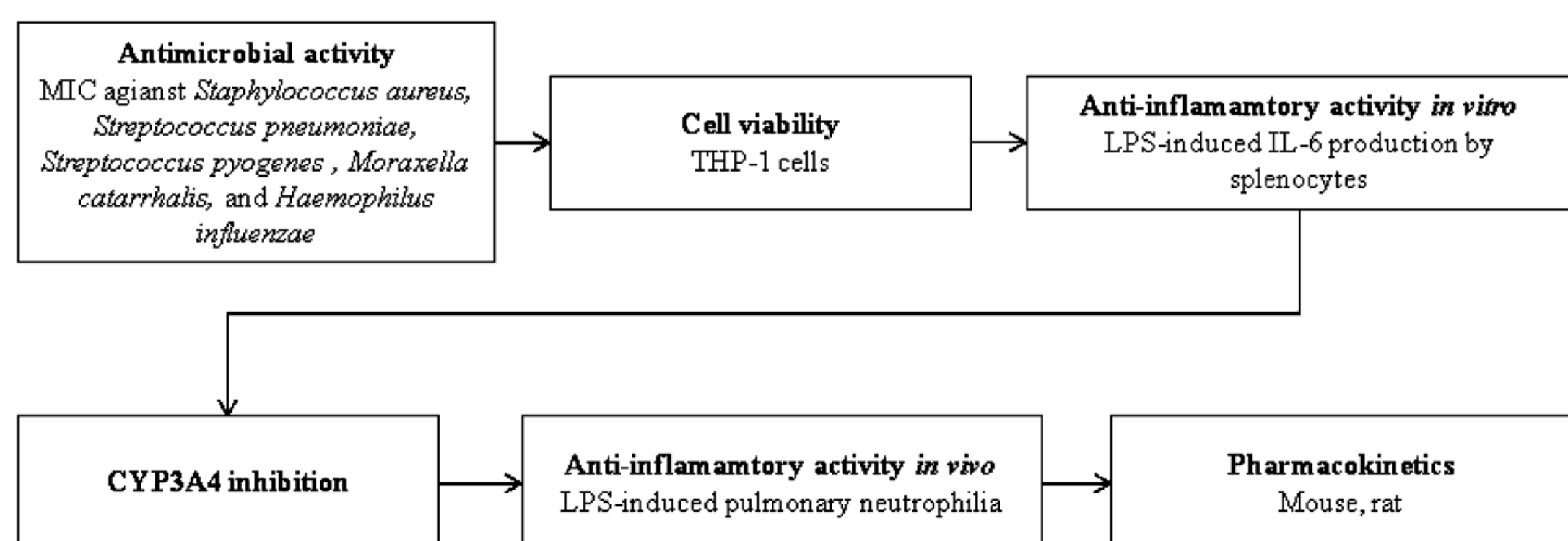
Chemistry

- 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 opposite 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!**

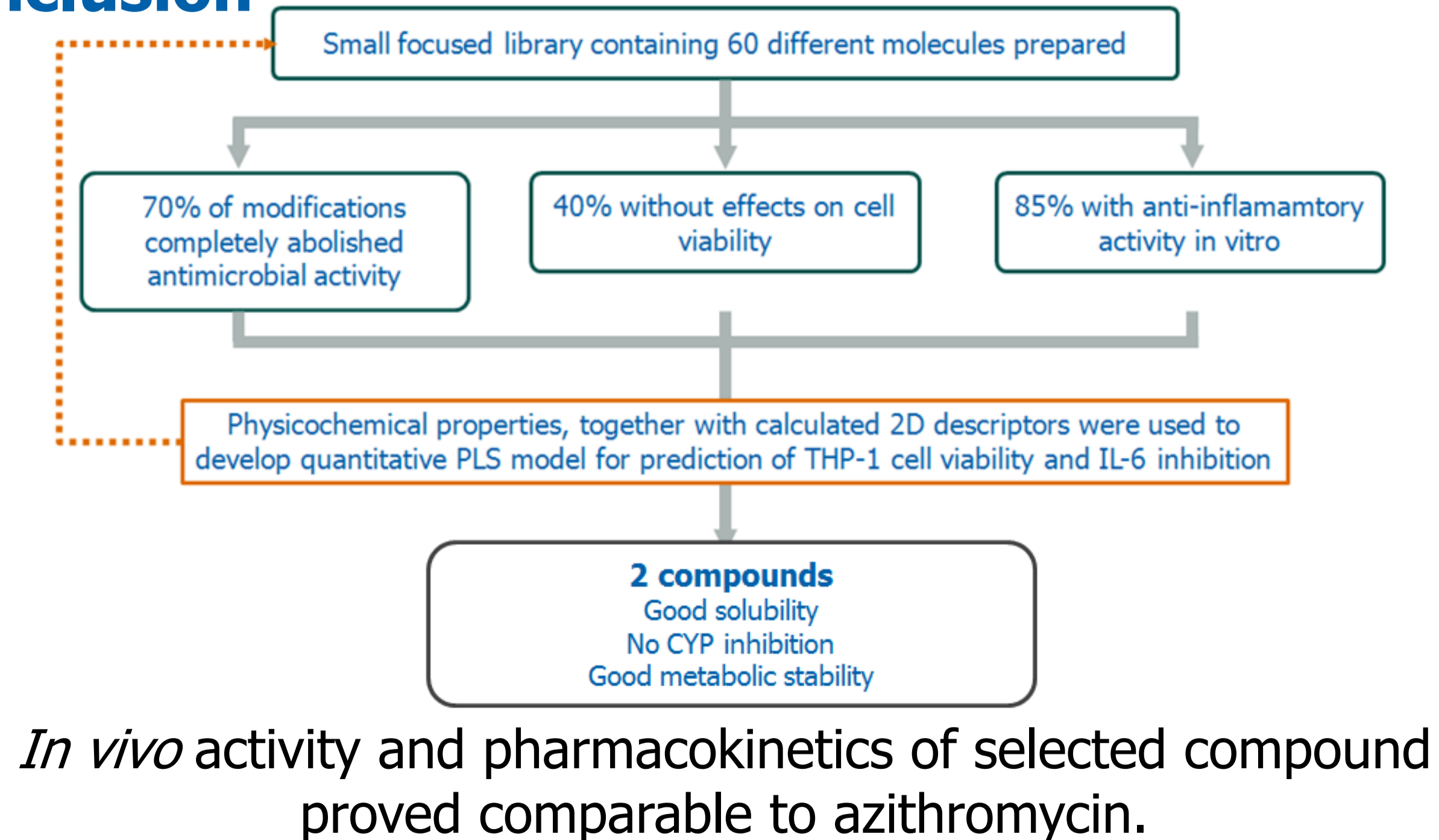


Biological profiling

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



Conclusion



References

- Macrolide Antibiotics, Birkhäuser, Basel, 2002
- Eur. J. Org. Chem. 2011, 2507–2518
- Eur. J. Org. Chem. 2013, 4666–4673
- J. Med. Chem. 2012, 55, 6111–6123