Fidelta
A Galápagos Company

We make the difference in efficacy and safety

www.fidelta.eu

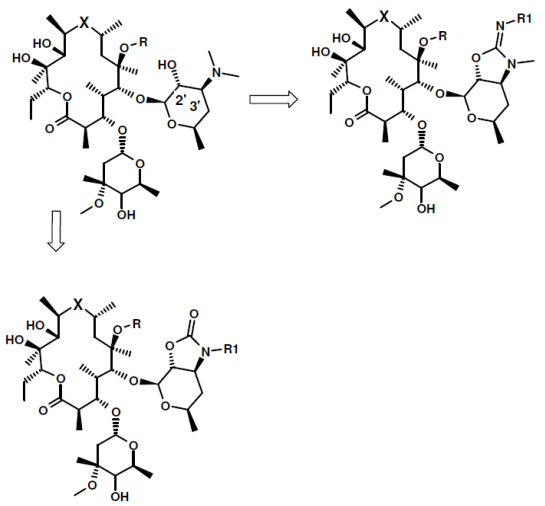
Medicinal Chemistry Case Study: Novel Desosamine-Modified 14- and 15-membered Macrolides without Antibacterial Activity

Objective:

- First-in-class, antimicrobially inactive anti-inflammatory macrolide for the 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

Chemistry:

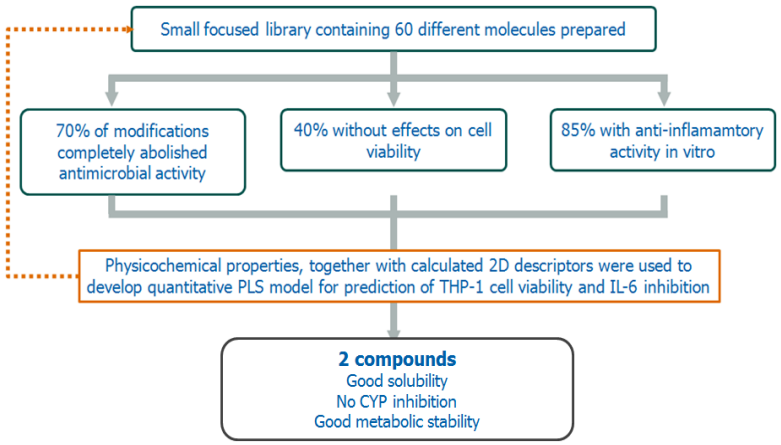
- In order to completely suppress antibacterial activity, Fidelta's scientists developed novel methods for modifications of the desosamine sugar of 14- and 15-membered antibacterial macrolides
- Included was annelation of *N*-substituted 2-imino-1,3-oxazolidine 1 and 1,3-oxazolidin-2-one 2 moiety to the 2',3'-positions of desosamine
- The method is suitable for introduction of various R1 substituents and large scale synthesis of prospective drug candidates



Modifications that provide complete suppression of antibacterial activity with minor alterations to the macrolide structures and/or physico-chemical properties are of great interest.

Biological profiling:

- The screening cascade was designed to select compounds that inhibit IL-6 production without antibacterial activity and effects on THP-1 cell viability
- Pharmacokinetic studies in rodents revealed compounds with good oral bioavailability and a half-life that supports once-daily dosing in humans



References

1. I. Vujasinovic et al, Eur. J. Org. Chem. 2011, 2507–2518,
2. I. Palej Jakopovic et al, Bioorg. Med. Chem. Lett. 2012, 22, 3527–3530
3. M. Bosnar et al., J. Med. Chem. 2012, 55, 6111−6123

Contact us:

Adrijana Vinter, Business Development
adrijana.vinter@glpg.com
+385 91 265 5527

Mila Vrančić, Business Development
mila.vrancic@glpg.com
+385 91 265 5528