



New AntiBacterials with Inhibitory activity on Aminoacyl-tRNA Synthetases

FP7 theme: Health

Consortium



Spain



UK



Netherlands



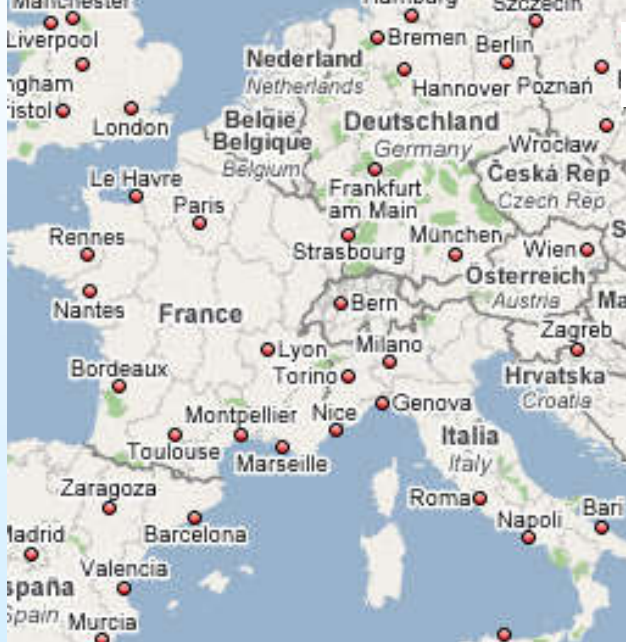
UK



Latvia

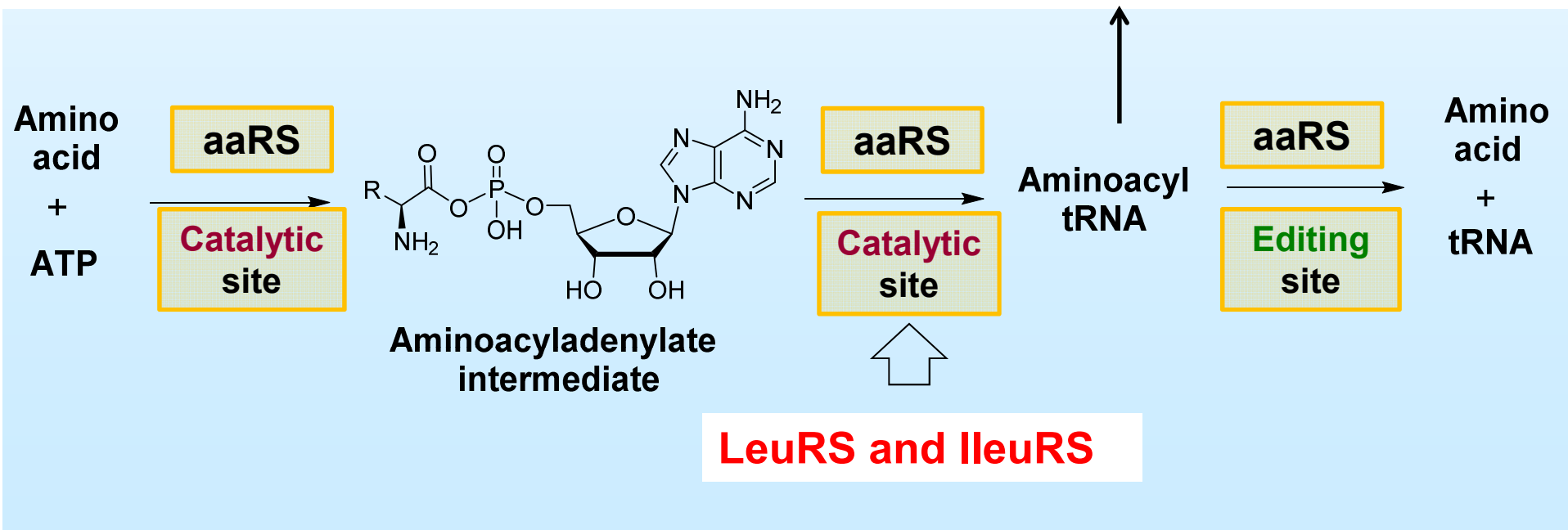
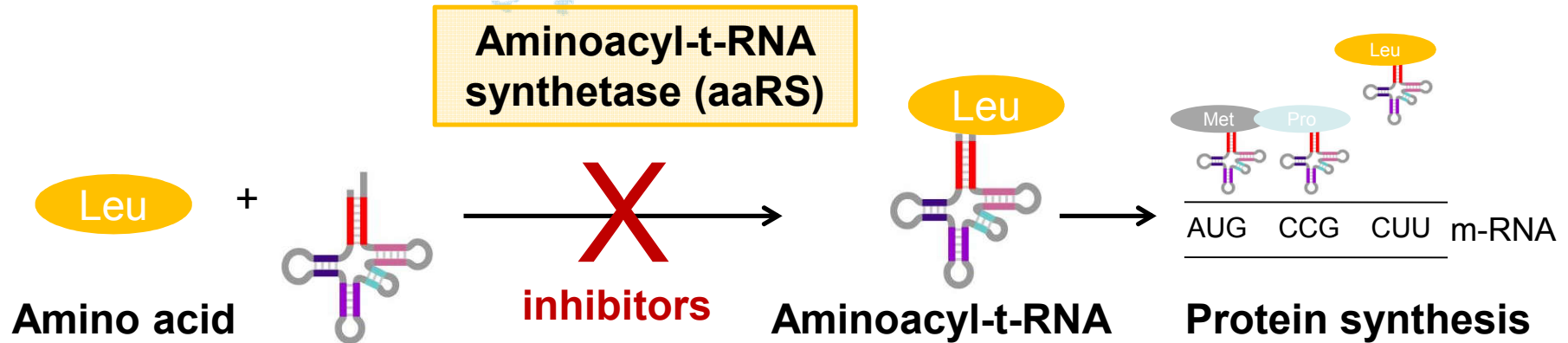


LATVIAN INSTITUTE OF ORGANIC SYNTHESIS



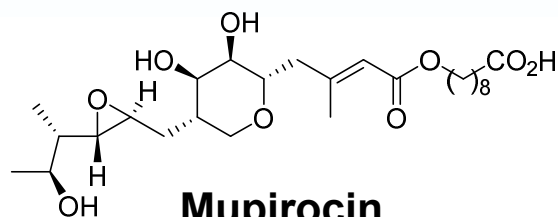
The leading drug discovery centre in the Baltics

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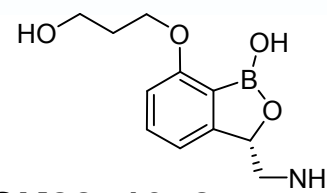




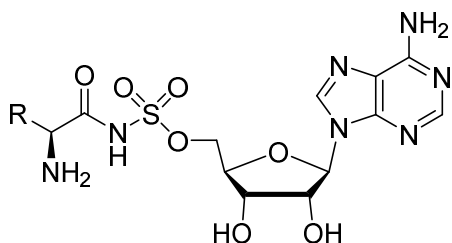
Representative IleRS and LeuRS inhibitors



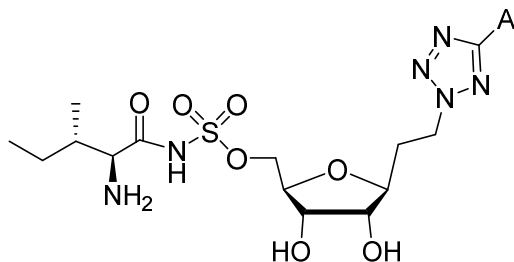
Mupirocin
IleRS (*S.Aur.*)



GSK2251052
LeuRS (*E.Coli*), editing site

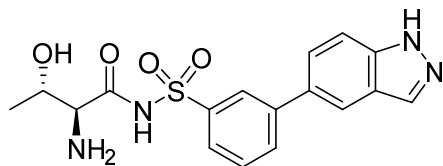


Ile-AMS (Ileu, LeuRS)

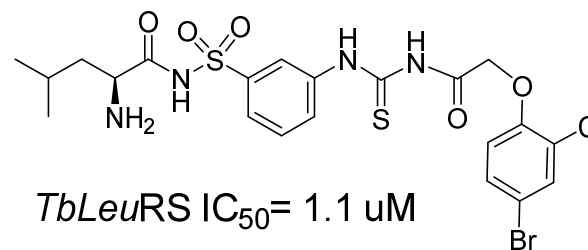


Cubist Pharmaceuticals (IleuRS)

Simplified scaffold aaRS inhibitors



E.Coli ThrRS $K_i = 0.18 \mu\text{M}$

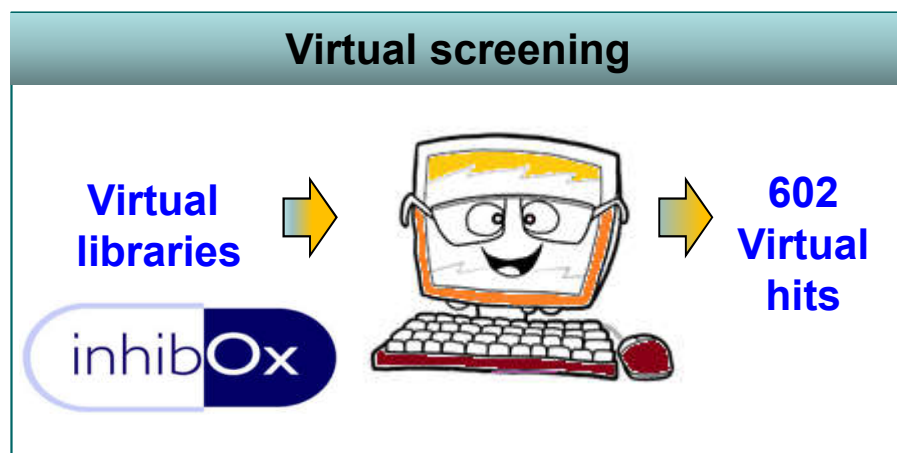


TbLeuRS $\text{IC}_{50} = 1.1 \mu\text{M}$

Medicinal chemistry approaches



1. Focused synthetic libraries



Synthesis



Testing



5 Real hits
(μM LeuRS)

HTL → Leads

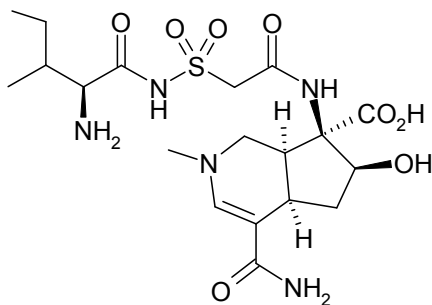
Medicinal chemistry approaches



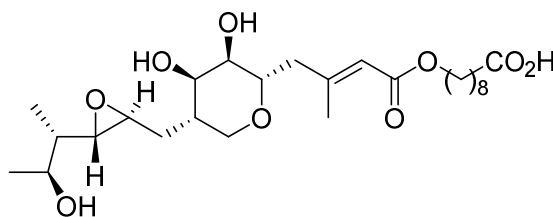
1. Focused synthetic libraries

2. Simplified analogues of natural products

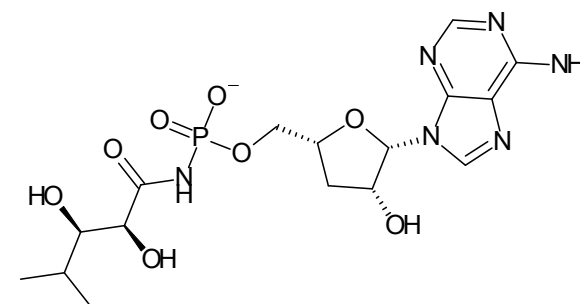
SB203207



Mupirocin



Agrocin TM 84

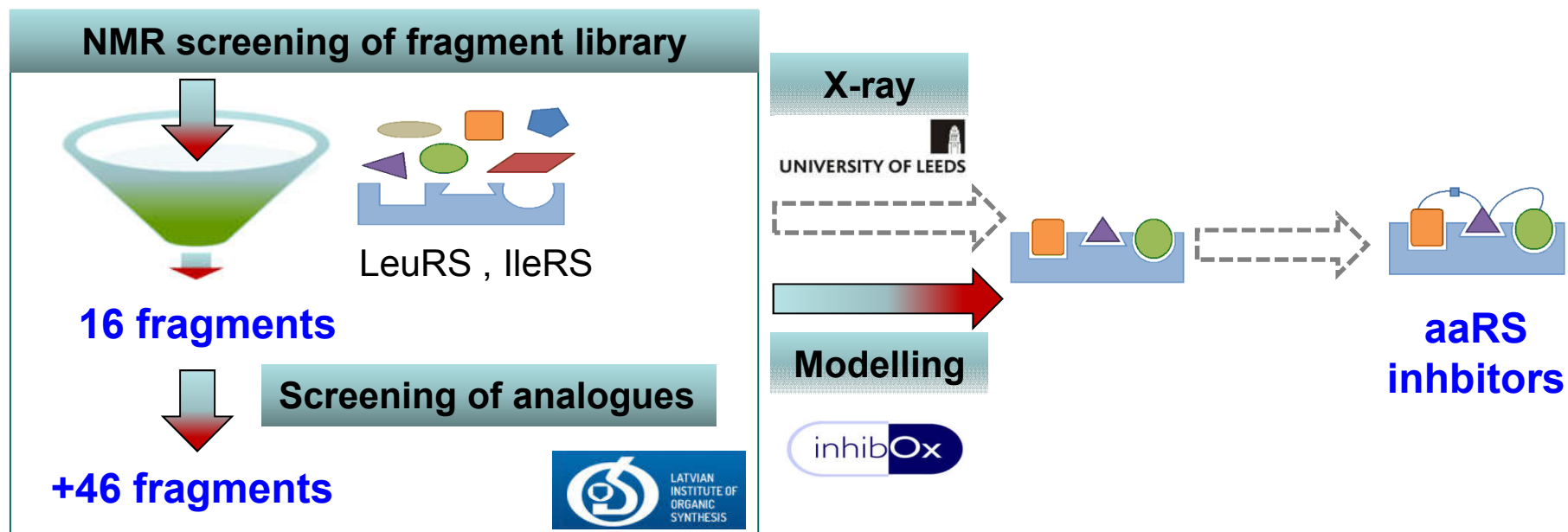


4 hits
(μM LeuRS) $\xrightarrow{\text{HTL}}$ **Leads**

Medicinal chemistry approaches



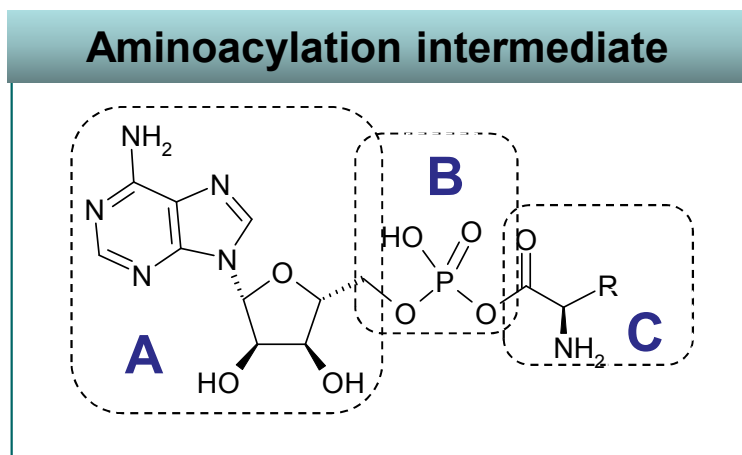
1. Focused synthetic libraries
2. Simplified analogues of natural products
3. Fragment based lead discovery



Medicinal chemistry approaches



1. Focused synthetic libraries
2. Simplified analogues of natural products
3. Fragment based lead discovery
4. Rational design of inhibitors



Bioisosteric
replacements
of A, B, C



**2 series of LeuRS
inhibitors (nM activity)**



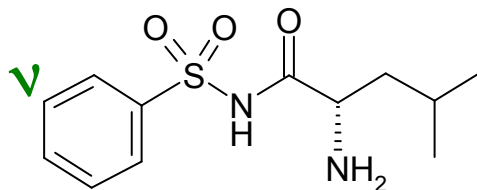
PCT patent application

N-Acyl benzenesulfonamide LeuRS inhibitors



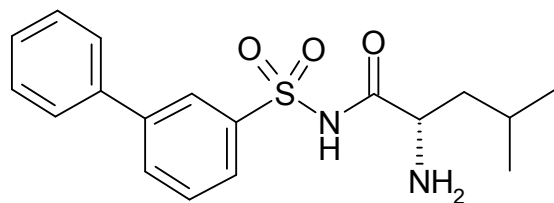
(72 analogues prepared)

SAR investigation

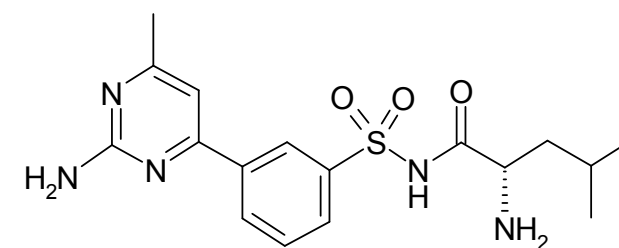
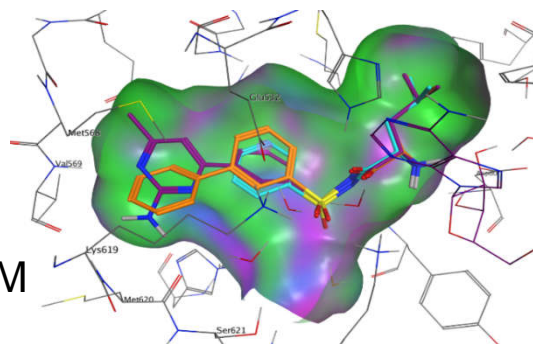


IK-698, IC_{50} E.Coli LeuRS = 49 nM;
 IC_{50} S. Aur. LeuRS = 1.1 μ M
 IC_{50} Human LeuRS = 1.1 μ M

K_D E.Coli LeuRS = 93 nM (ITC)
 ΔH = -13.5 kcal/mol;
 $-T\Delta S$ = 3.9 kcal/mol



IK-681, IC_{50} E.Coli LeuRS = 32 nM
 K_D E.Coli LeuRS = 10 nM (ITC)
 ΔH = -8.1 kcal/mol;
 $-T\Delta S$ = -2.8 kcal/mol



IK-580, IC_{50} E.coli LeuRS = 41 nM
 K_D E.Coli LeuRS = 10 nM (ITC)
 ΔH = -12.5 kcal/mol;
 $-T\Delta S$ = 1.6 kcal/mol

IK-698, IK-681, IK-580 no growth inhibition of wild type *E. Coli*

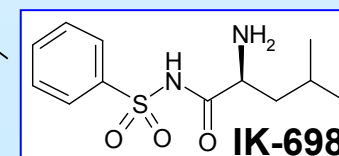
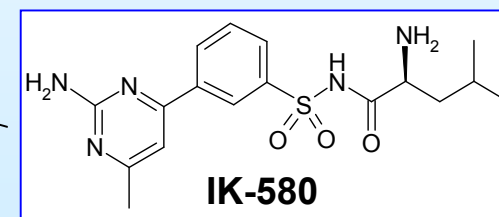
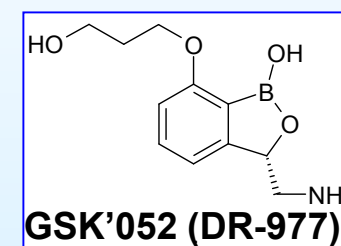
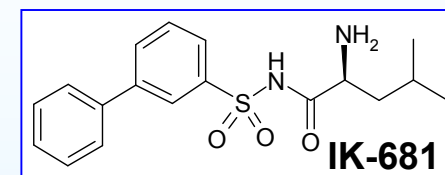
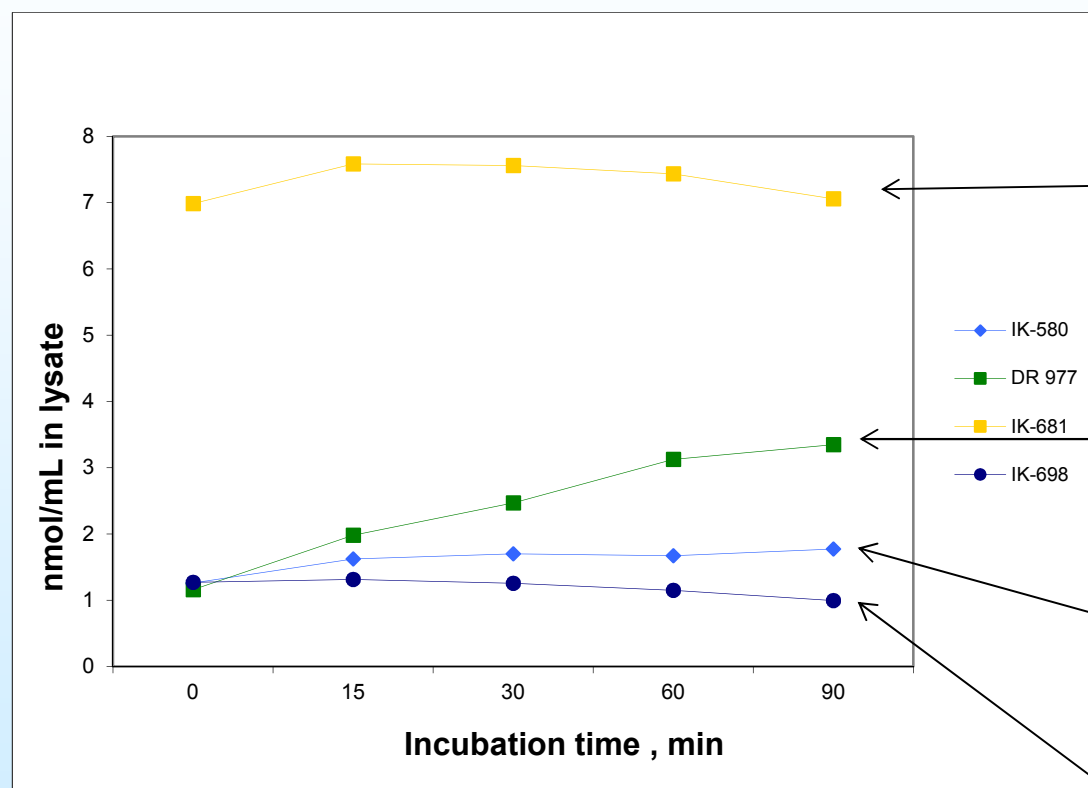
- amine prodrugs **X**
- siderophore conjugate **X**





Bacterial concentration

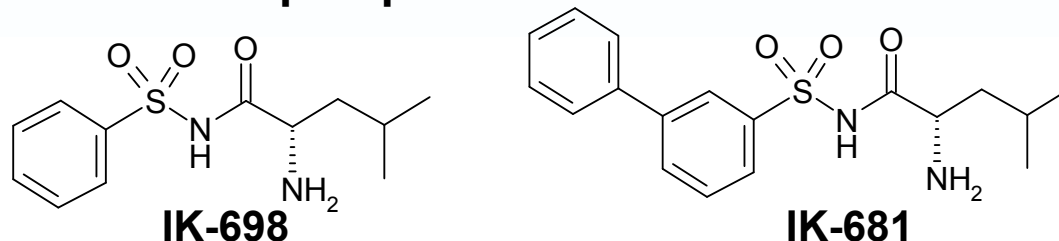
Determined by LC/MS in E.Coli



Reaching antibacterial activity



Activity on *E. Coli* efflux pump mutant strains



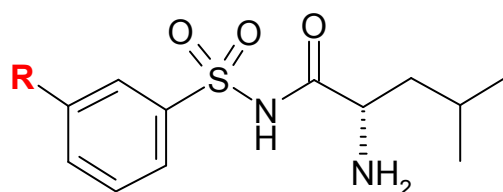
Strains	IK-698 MIC, ug/mL	IK-681 MIC ug/mL
<i>E. coli</i> BW25113	>128	>128
BW25113 Δ tolC	16	>128
BW25113 Δ acrA	>128	128
BW25113 Δ acrB	>128	128

Group of
prof. A. O'Neill



UNIVERSITY OF LEEDS

Analogue
generation



NAB-1

E. Coli LeuRS: IC₅₀ = <100 nM

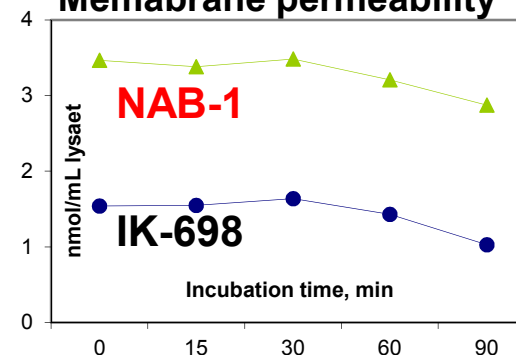
***E. coli* BW25113, MIC= 16 ug/mL**

MRSA: inactive

(-) membrane damaging assay



Membrane permeability





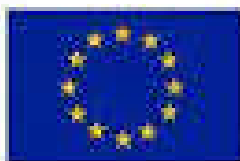
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Thank you for your attention!