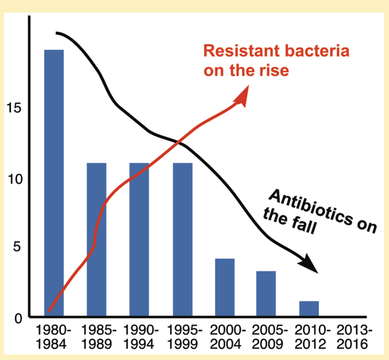
# New antibiotics against MRSA

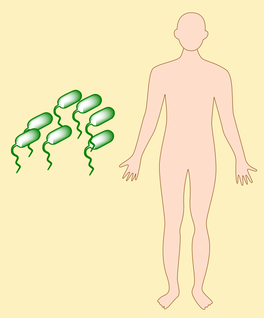
## -Piperazine Inhibitors of Bacterial Gyrase and Topoisomerase IV

**Biotech and Health Care**

## The problem

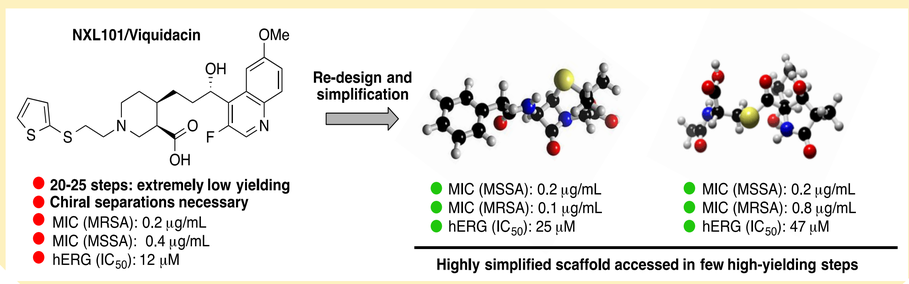
The extensive use of penicillin derivatives has resulted in development of resistance among bacteria such as MRSA. The mortality rate for humans infected is 15-60% and in Europe 25,000 people die every year from infections caused by multidrug-resistant bacteria.



## The invention

Compared with NXL101 the compounds of the present invention contain a piperazine core and not a piperidine core. By changing the piperidine core with a piperazine core in general does not affect the antibiotic activity, however, it is important for the reduction in hERG activity.




NXL 101: Discontinued compound from the biotech company, Novexel, that was acquired by Astra Zeneca in March 2010

## Antibiotic activity

MIC determination of our compound benchmarked with Ciprofloxacin, NXL101 and GSK210944. Ciprofloxacin is a widely used of the second-generation quinolones antibiotic.

| | Bacterial pathogens | Our compound | GSK210944 | NXL101 | Ciprofloxacin |
|---|---|---|---|---|---|
| Gram P | *Staphylococcus aureus* | 0.4 | 0.8 | 0.4 | 0.4 |
| | *MRSA*, CC398 | 0.4 | 0.8 | 0.4 | 0.4 |
| | *Enterococcus faecium* | 1.6 | 3.2 | 1.6 | ≤0.1 |
| | *Enterococcus faecium*, (VRE) | 3.2 | 12.5 | 1.6 | >50.0 |
| Gram N | *Pseudomonas aeruginosa* | >50.0 | 12.5 | >50.0 | 0.1 |
| | *Enterobacter cloacae* | >50.0 | >50.0 | >50.0 | 0.1 |
| | *Klebsiella pneumoniae* | >50.0 | >50.0 | >50.0 | 0.1 |

*Minimal Inhibitory Concentration (MIC) values (µg/ml)*

## Our new antibiotic

- Excellent MRSA activity
- Slow resistance development
- Highly cost-efficient synthesis
- Good results vs known drugs
- Early hERG data promising
- Preliminary SAR established
- Target-based enzymatic assay
- Administration: topical/peroral/IV

| Compound | Our compound | GSK210944 | NXL101 | Other Pharma |
|---|---|---|---|---|
| Development stage | Early | Phase II | Discontinued | Early |
| Potency | ✓ | ✓ | ✓ | ✓ |
| Safety profile | ✓ | ✓ | ✗ | ✓ |
| Cost of synthesis | ✓ | ✗ | ✗ | ✗ |
| Patent | ✓ | ✓ | ✓ | – |

**Value proposition/USP**

A new class of synthetic antibiotics with excellent activity against Gram-positive bacteria and especially methicillin-resistant *Staphylococcus aureus* (MRSA) with slow resistance development compared to current drugs and promising hERG data. This new class of antibiotics possesses a simple chemical structure, which facilitates its rapid non costly preparation via chemical synthesis.

**Business Opportunity/Objective/commercial perspectives**

The cost of health-care related bacterial infections in Europe amounts to ~5% of the total EU health-care budget, and *Staphylococccus* infections are by far the most prevailing. Among these, there are approximately 2.000 patients annually with MRSA in DK (150.000 in EU). The use of antibiotics are increasing worldwide simultaneously with the increase in drug resistant bacteria with MRSA being one of the most prevalent.

Technology description/technology Summary

The new class of antibiotics is constituted by a piperazine core that links to a fluoroquinoline and a hydrophobic moiety. The antibiotics target bacterial type II topoisomerase with mode of action, which is distinct from the one of currently approved drugs. The antibiotics inhibit bacterial gyrase and topoisomerase IV and hamper DNA transcription and replication in living bacterial cells.

Development phase/current state

We have a number of promising lead compounds that have excellent antibiotic properties against MRSA and other Gram-Positive strains in a similar range as NXL-101 and GSK2140944, a novel piperidine antibiotic in the pipeline at GSK. NXL101 was a lead compound from Novexel but it was discontinued due to unfavorable route of synthesis and hERG profile discovered in a Phase I trial. We have performed some lead optimization and are now approaching preclinical testing of these leads.


The inventors

Prof. Michael Givskov
Prof. Thomas E. Nielsen
Prof. Tim Tolker-Nielsen
Assistant Prof. Tim Holm Jakobsen
Associate Prof. Jens Bo Andersen, + *et al*.

Contact information

Peter Stein Nielsen
Commercial Officer
peter.nielsen@adm.ku.dk
+45 2164 7447


Intellectual property rights: PCT patent application filed on March 2, 2016

UNIVERSITY OF COPENHAGEN

DTU Technical University of Denmark

DANISH IP FAIR
Inventions from Danish Research Institutions