A new class of antibiotics

- triaromatic pleuromutilins

Value proposition and Field of application

New antibiotics with efficacy against resistant bacterial strains are urgently needed. Pleuromutilins have inherent advantages over many other antibiotics: unique mechanism of action and a slow onset of resistance.
Efficacy and safety of our compounds compare favourably with the only systemically available pleuromutilin, Lefamulin (approved 2019).

Technological description

Our new class of antibiotics, triaromatic pleuromutilins, has excellent potency against vancomycin-resistant *Enterococcus faecium* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). VRE and MRSA have the highest priority and urgency in Gram-positive antibiotic drug discovery and development (CDC, WHO, 2018).

Use of Lefamulin is contraindicated due to mild QT prolongation (hERG inhibition) and CYP3A and P-gp inhibition. Our compounds compare favourably with Lefamulin.

	MIC [µg mL^{-1}]			**Solubility** [mg mL^{-1}][c]	**Off-targets** [IC_{50}, μM]	
Compound	MRSA USA300	*E. faecalis*[a]	VRE 1[b]	HCl-salt ± SE	hERG[d]	P-gp[e]
Lefamulin (**1**)	0.12	0.12	0.12	>100 (acetate)	126 ± 14	43 ± 10
CVH-174 (**2**)	0.12 - 0.25	0.12	0.03	>10	>200	57 ± 15
CVH-88 (**3**)	0.03	0.25	0.12	0.012 ± 0.001	>200	36 ± 22

CVH-88 (**3**) is our hit compound and CVH-174 (**2**) is the optimized lead.

Using click chemistry, we have synthesized and screened >80 compounds. Our lead compound has been extensively evaluated and validated *in vitro* for drug-like properties, (solubility, P-gp inhibition, CYP3A4 inhibition, Caco-2 permeability, hERG inhibition, plasma protein binding, MIC, bacterial time-kill and cytotoxicity).

PK parameters from injection (SC and IV) in mice are on par with Lefamulin, but there are indications that oral bioavailability is poor, most likely due to poor GI solubility.

We are addressing the low solubility with more medicinal chemistry, salt screening and drug formulation strategies. A large series of fast-followers are being synthesized, and a new and extremely potent and drug-like lead has emerged. The solubility is not yet on par, so we need to make new compounds with reduced mass and increased solubility. Our structure-activity knowledge indicates that this is possible with extensive medicinal chemistry.

Current state of development

A study in pigs of the oral bioavailability of CVH-174 is ongoing. As is an *in vivo* efficacy study in mice. Medicinal chemistry is ongoing to make a series of fast-followers with reduced mass and increased solubility. Resources for screening and validating the new compounds (activity, PK and safety) are fundamental.

Team

Poul Nielsen, Professor of Chemistry, SDU

Christoffer Vogsen Heidtmann, PhD-student (Med. Chem.), SDU

Carsten Uhd Nielsen, Professor of Pharmacy, SDU

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Younger students, research assistants and lab technicians

Intellectual property rights

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International application number: PCT/EP2021/061318

Inventors: Poul Nielsen, Christoffer V. Heidtmann.

Owner: SDU

Business opportunity and Call to action

We are looking for a collaboration/partnership with a company with expertise in antibiotic development to help accelerate the further development of this new and very promising antibiotic class.

We are also looking for investors and an experienced entrepreneur who might be interested in maturing the technology in a small company.

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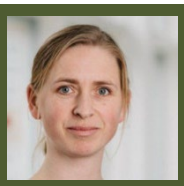

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