Universitetet i Stavanger

# Ny løsning på antibiotikaresistens

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# Antibiotic resistance - How large is the problem?

- World wide more then >1.2 million deaths per year

-In USA more then 2 million people are infected with antibiotic resistant bacteria per year

-USA ca 23 000 deaths per year

-Europa ca 25 000 deaths per year

-WHO estimates that by 2050 10 million deaths world wide can be due to infections by antibiotic resistant bacteria

Petchiappan, A.; Chatterji, D. *ACS Omega* **2017**, *2*, 7400-7409; Murray, C. J. L. *et al*. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* **2022**, *399*, 629-655.

# From mouth to toilet to nature

# Metabolism of antibiotics in the body

- In general, 50-80% of the parent compound (antibiotic) goes through the body without being metabolized.[1] It then ends up in
  - Sewage
  - Farmland
- Sewage treatment plants are generally not made for breaking down (removing) pharmaceuticals. Partition of pharmaceuticals in water phase and solid phase (sludge)
  - Water phase is released to aquatic environments
  - Sludge is often used as fertilizer on farmland

1. Danner, M.-C.; Robertson, A.; Behrends, V.; Reiss, J. *Sci. Total Environ*. **2019**, *664*, 793-804.

# Antibiotic use in farming (food production)

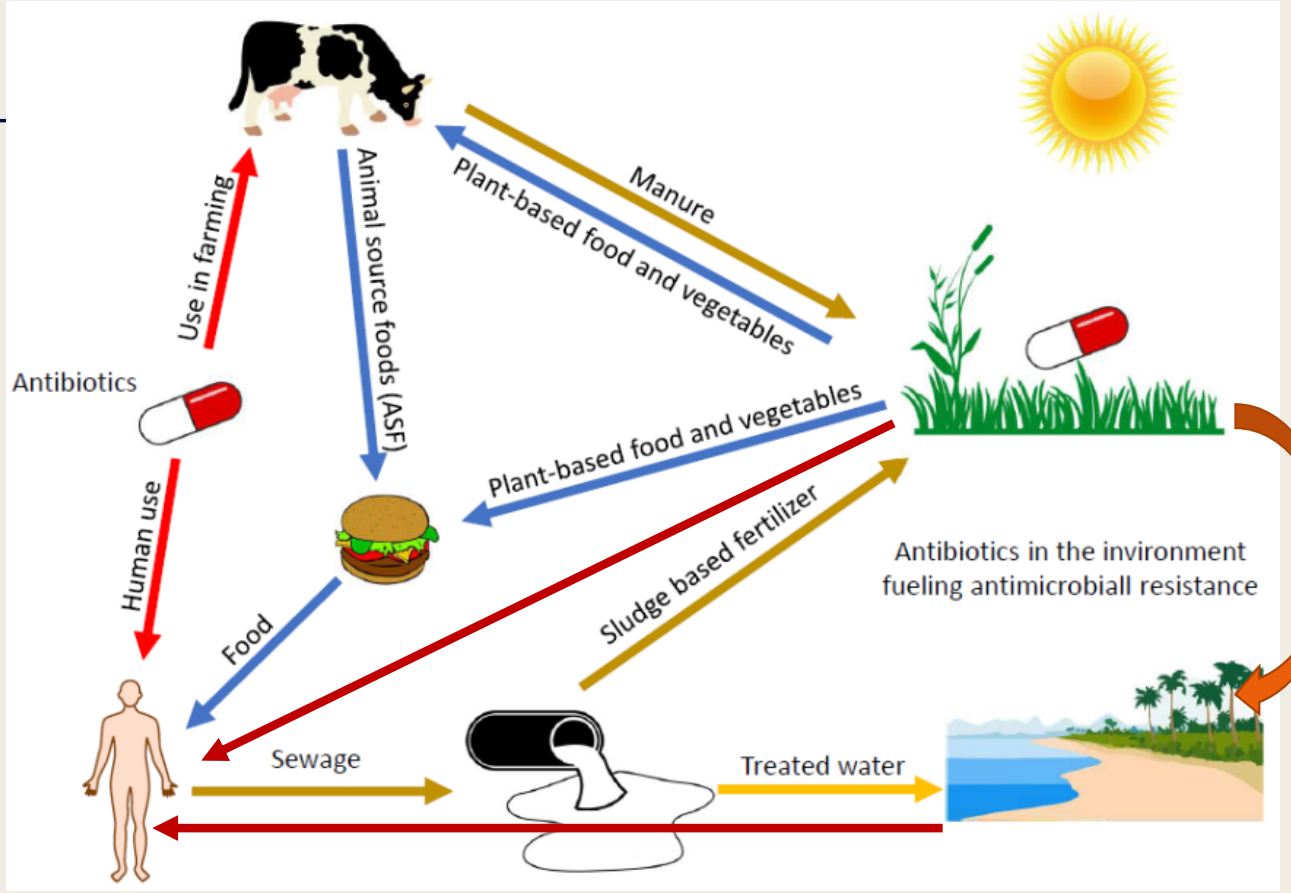
Pigs in cages, Quanzhou, China. As the largest consumer of veterinary antimicrobials, China is critical for combating antimicrobial resistance (AMR).

-China is the largest user of antibiotics in food production

-In comparison – Norway use 1/40 of the antibiotic used in Chinese farming to produce the same amount of meet.

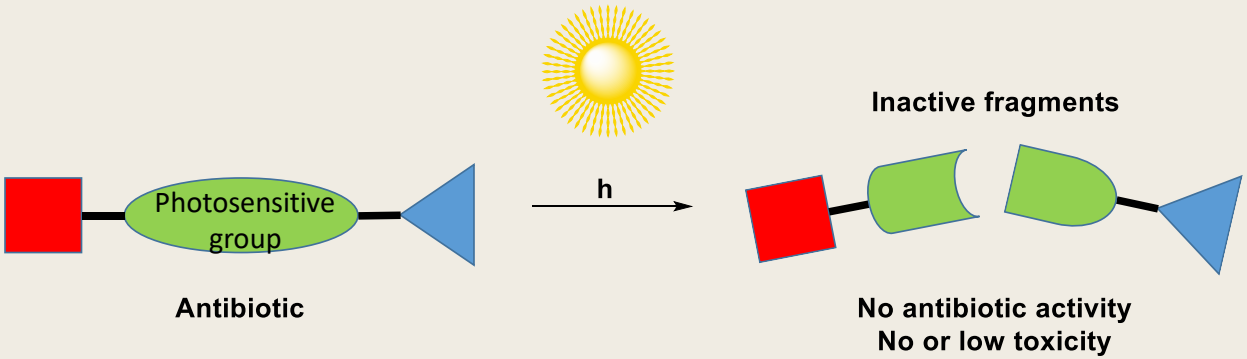
Van Boeckel, T.; Glennon, E. E.; Chen, D.; Gilbert, M.; Robinson, T. P.; Grenfell, B. T.; Levin, S. A.; Bonhoeffer, S.; Laxminarayan, R. *Science* **2017**, *357*, 1350-1352.

# Antibiotics in the environment

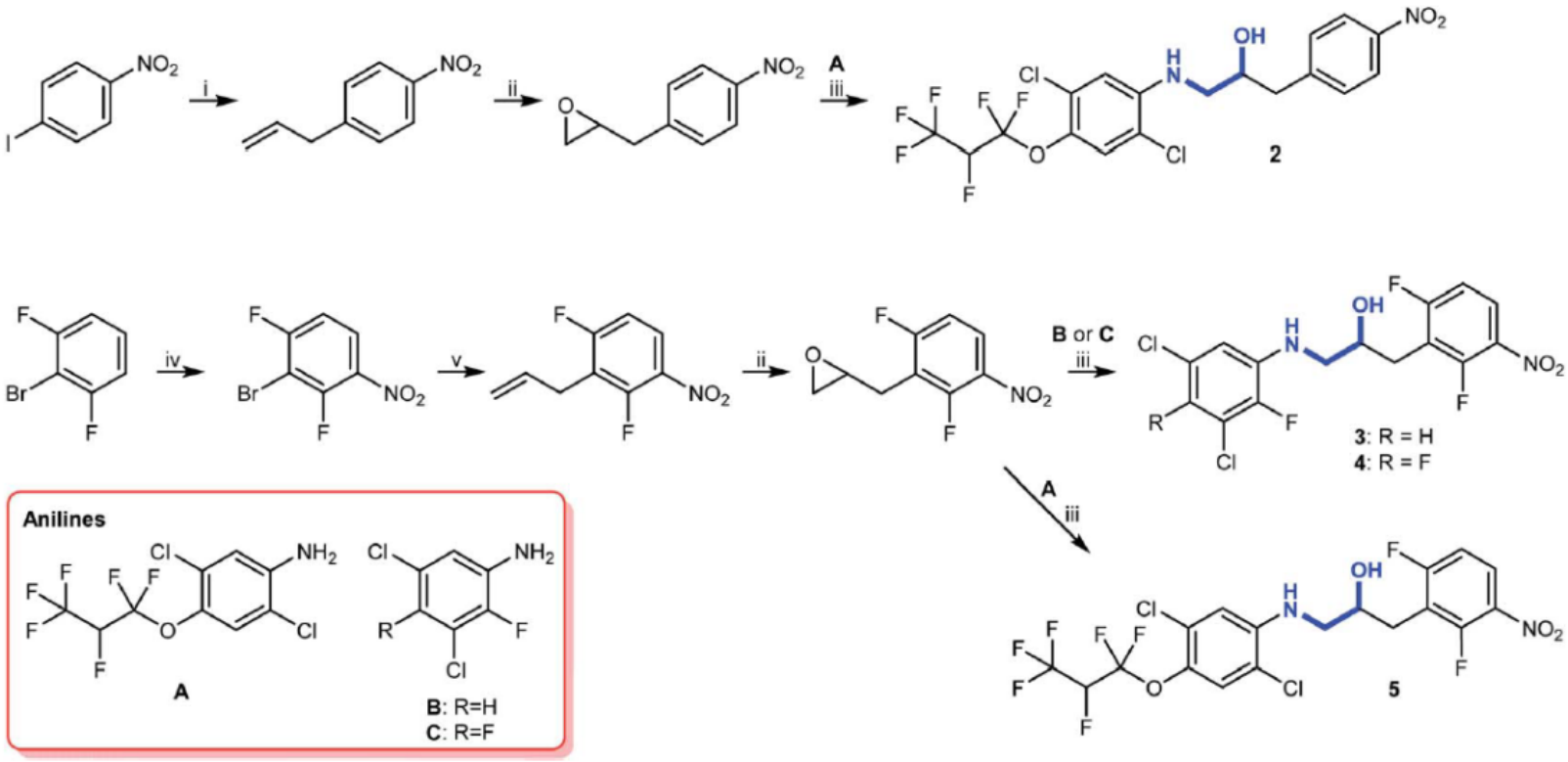


# Photobiotics
## Photodegradable antibiotics

Simple idea



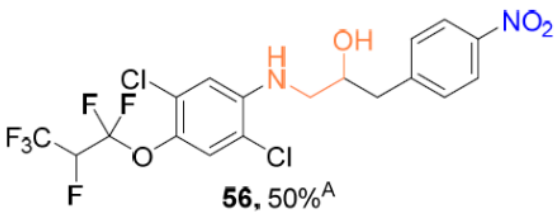
# From idea to solution



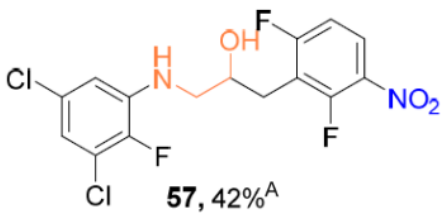

Scheme 3 Synthesis of aminols 2–5. Reagents and conditions: (i) $Pd(PPh_3)_4$, CsF, AllylBpin, THF, reflux;[27] (ii) *m*CPBA, DCM, rt; (iii) 5 M LPDE, 40 °C; (iv) $H_2SO_4$, $HNO_3$, 0 °C; (v) $Pd(PPh_3)_4$, $Bu_3SnAllyl$, DMF, 110 °C.

Eikemo, V.; Sydnes, L. K.; Sydnes, M. O. *RSC Adv*. **2021**, *11*, 32339-32345; Eikemo, V.; Holmelid, B.; Sydnes, L. K.; Sydnes, M. O. *J. Org. Chem*. **2022**, *87*, 8034-8047.

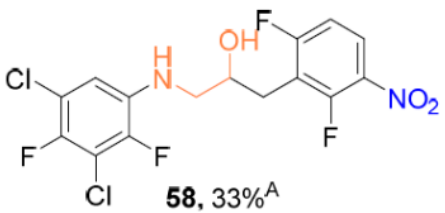
# 1st generation of active compounds



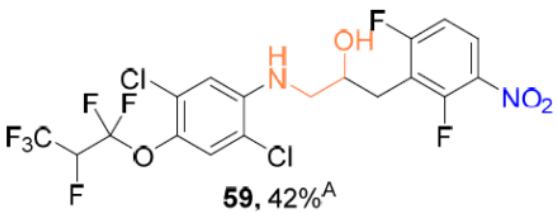
**56**, 50%[A]
***S. agalactiae* 6.3 μM**
**MRC5 50 μM, HepG2 75 μM**



**57**, 42%[A]
***S. epidermidis, S. aureus,***
***S. agalactiae* 50 μM**
**MRC5 50 μM, HepG2 75 μM**



**58**, 33%[A]
***S. aureus* 50 μM**
**MRC5 50 μM, HepG2 50 μM**

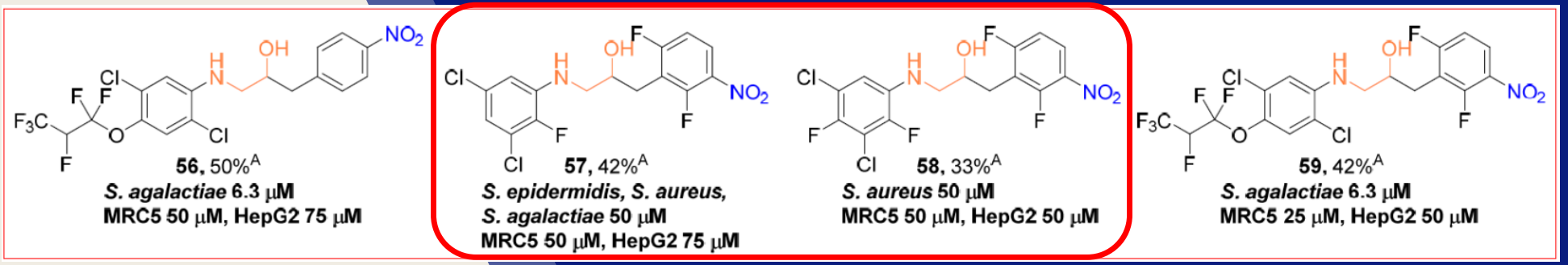


**59**, 42%[A]
***S. agalactiae* 6.3 μM**
**MRC5 25 μM, HepG2 50 μM**

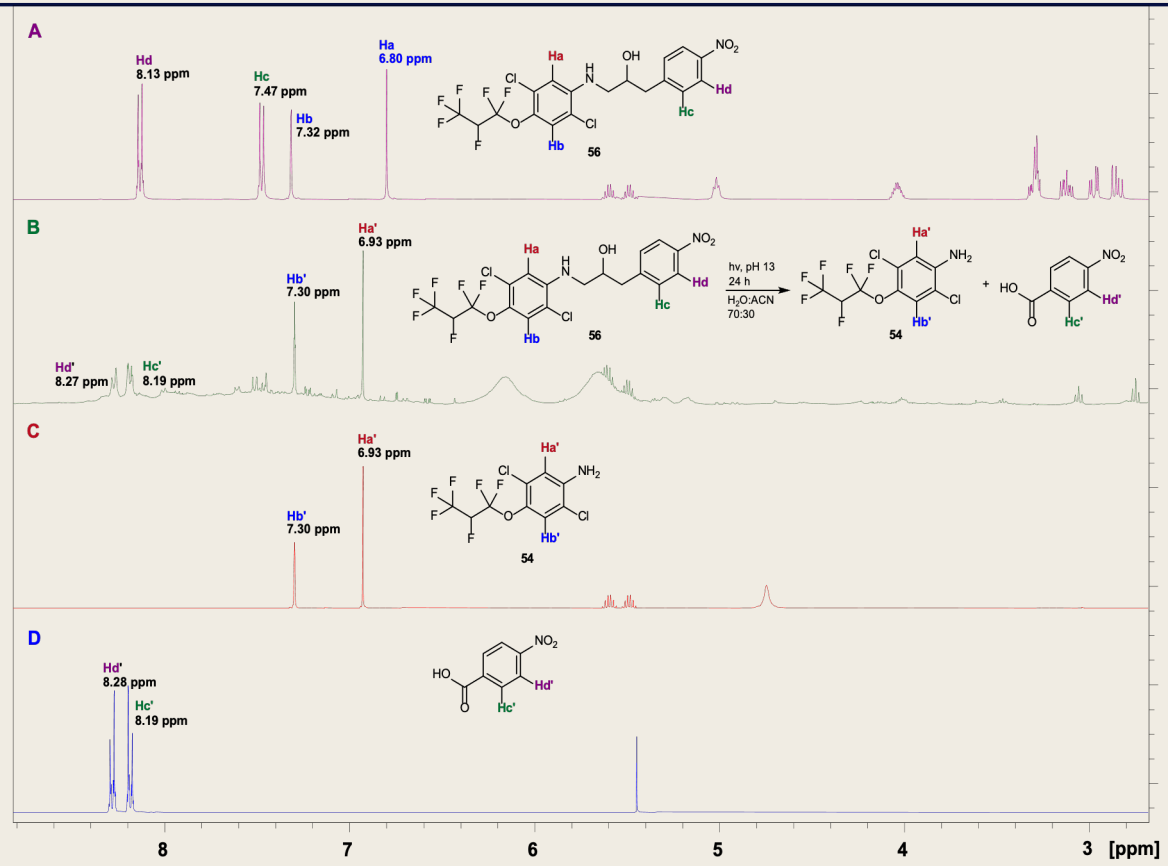
# WHO threat list of microbes

| THREAT LIST |
| --- |
| **Bacterium or bacterial family (and antibiotics it resists) ranked by threat to human health** |
| *Acinetobacter baumannii* (carbapenem) |
| *Pseudomonas aeruginosa* (carbapenem) |
| Enterobacteriaceae, extended-spectrum-β-lactamase-producing (carbapenem) |
| *Enterococcus faecium* (vancomycin) |
| *Staphylococcus aureus* (methicillin, vancomycin) |
| *Helicobacter pylori* (clarithromycin) |
| *Campylobacter* spp. (fluoroquinolone) |
| Salmonellae (fluoroquinolone) |
| *Neisseria gonorrhoeae* (cephalosporin, fluoroquinolone) |
| *Streptococcus pneumoniae* (penicillin-non-susceptible) |
| *Haemophilus influenzae* (ampicillin) |
| *Shigella* spp. (fluoroquinolone) |

SOURCE: WHO



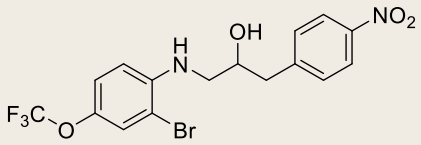
# Photodecomposition products



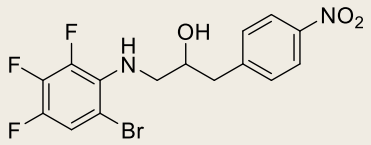

$^{1}$H NMR spectra (A) Pure compound **56**; (B) Crude degradation mixture after 24 h photolysis at pH 13; (C) Decomposition product aniline **54**; (D) Decomposition product *p*-nitrobenzoic acid. Eikemo, V.; Sydnes, L. K.; Sydnes, M. O. *J. Org. Chem.* **2022**, *87*, 8034.

# Second round – 45 new compounds

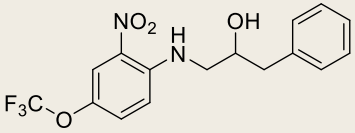
- 4 new active compounds



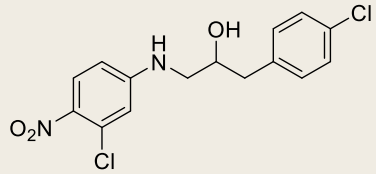

*S. agalactiae* 25 μM




*S. agalactiae* 75 μM




*S. agalactiae* 50 μM

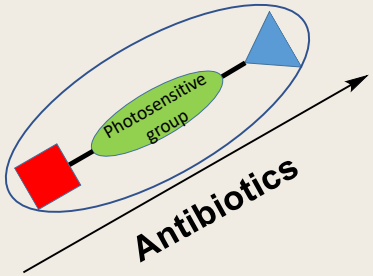



*S. agalactiae* 25 μM

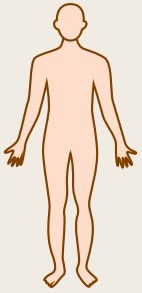
# The big picture

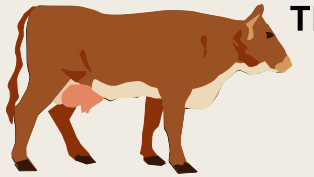
Before use

Antibiotics protected
from light
Stable and active

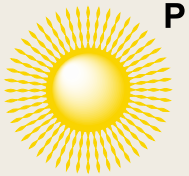



Patient on antibiotics

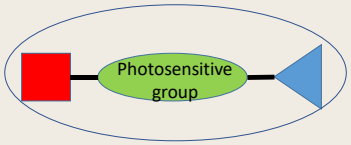




Inside the body it is dark
Antibiotics are stable
and active



Photodecomposition
with natural or
artificial light




Antibiotics pass through
the body mostly unmetabolized
The drug is as active as it was
when it went into the body

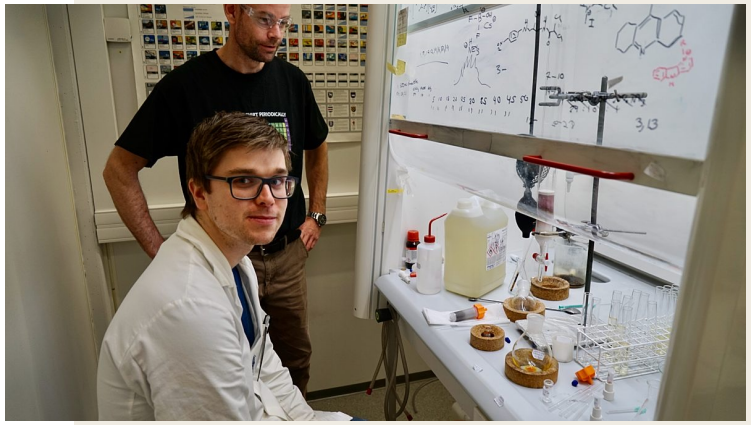
Inactive fragments

No antibiotic activity
No build up of resistance

# The future

- Stop accumulation of pharmaceuticals in the environment
- Stricter requirements to lifetime after use of pharmaceuticals
- New pharmaceuticals should have built in a “suicide” mechanism
- Photodecomposition is one such solution

# Acknowledgments

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