Minor Groove Binders at Strathclyde

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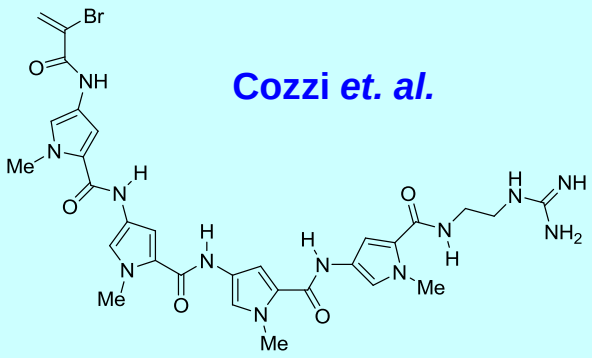
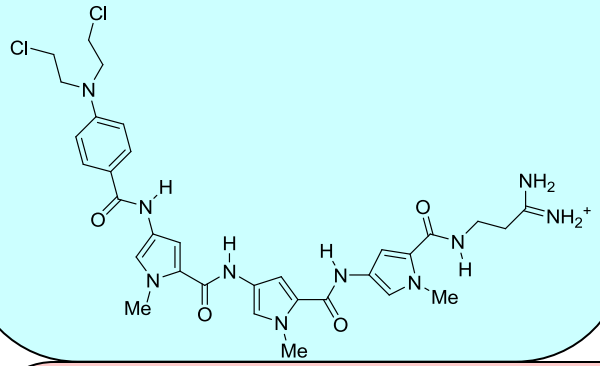
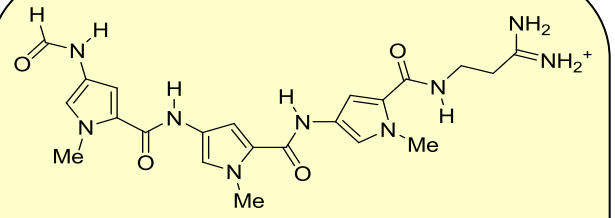
Polyamide MGBs

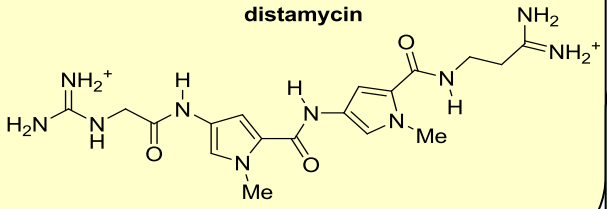


Cozzi *et. al.*

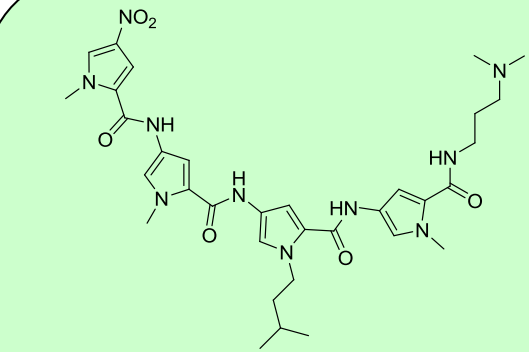


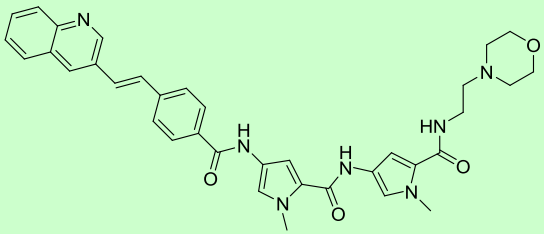


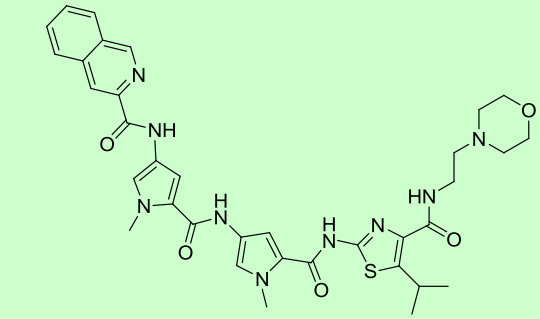
distamycin



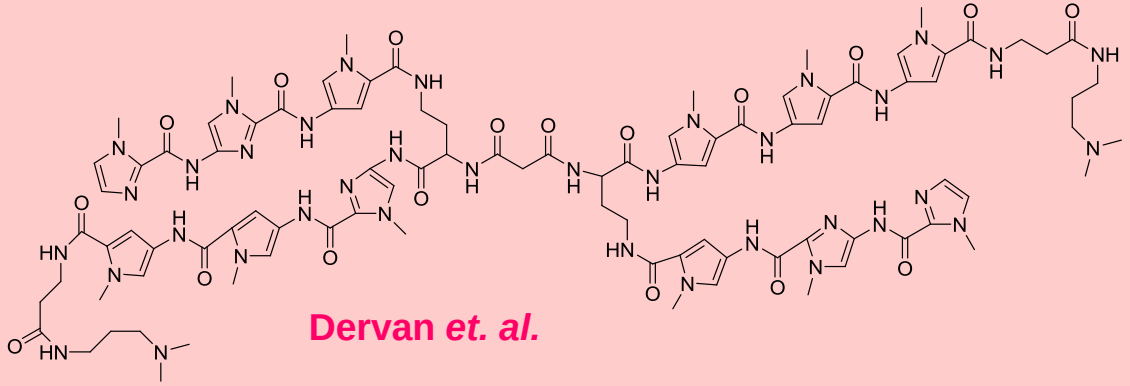
netropsin





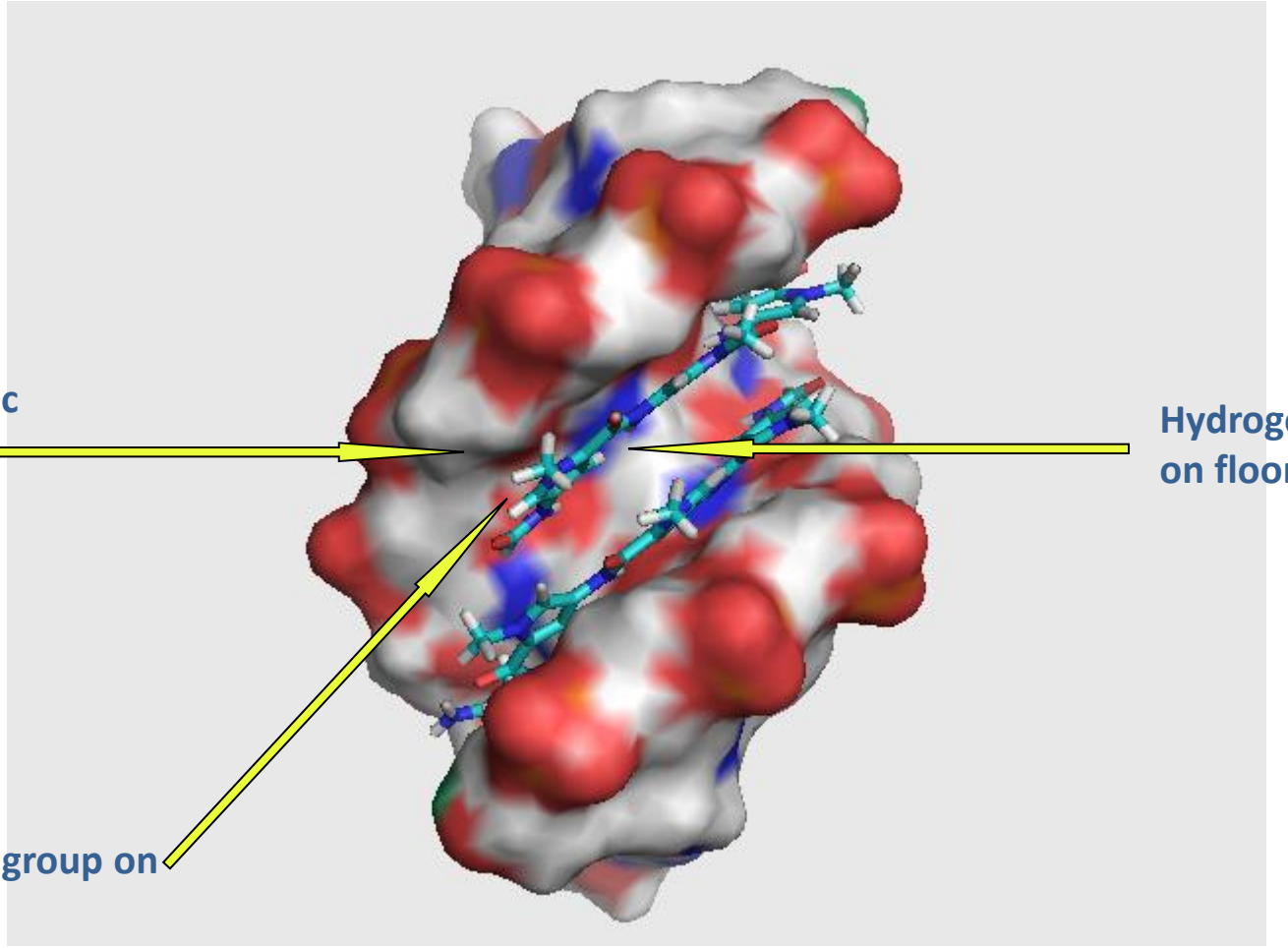


Strathclyde



Dervan *et. al.*

Primary design concept at Strathclyde



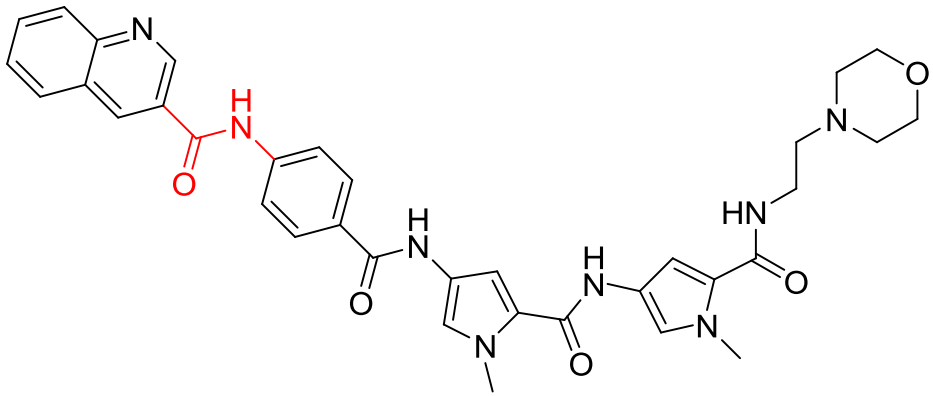
An amide isostere – the key structural change

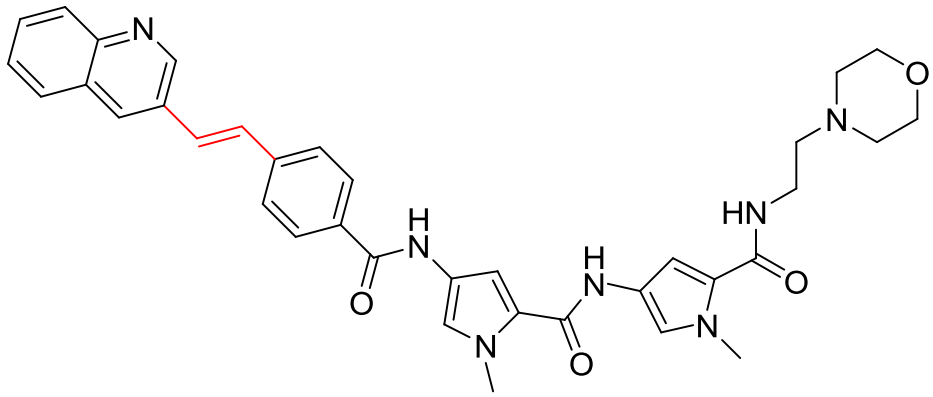
Amide: planar, H-bond donor and acceptor, hydrolysable.

Alkene: planar, non-polar, stable to hydrolysis.

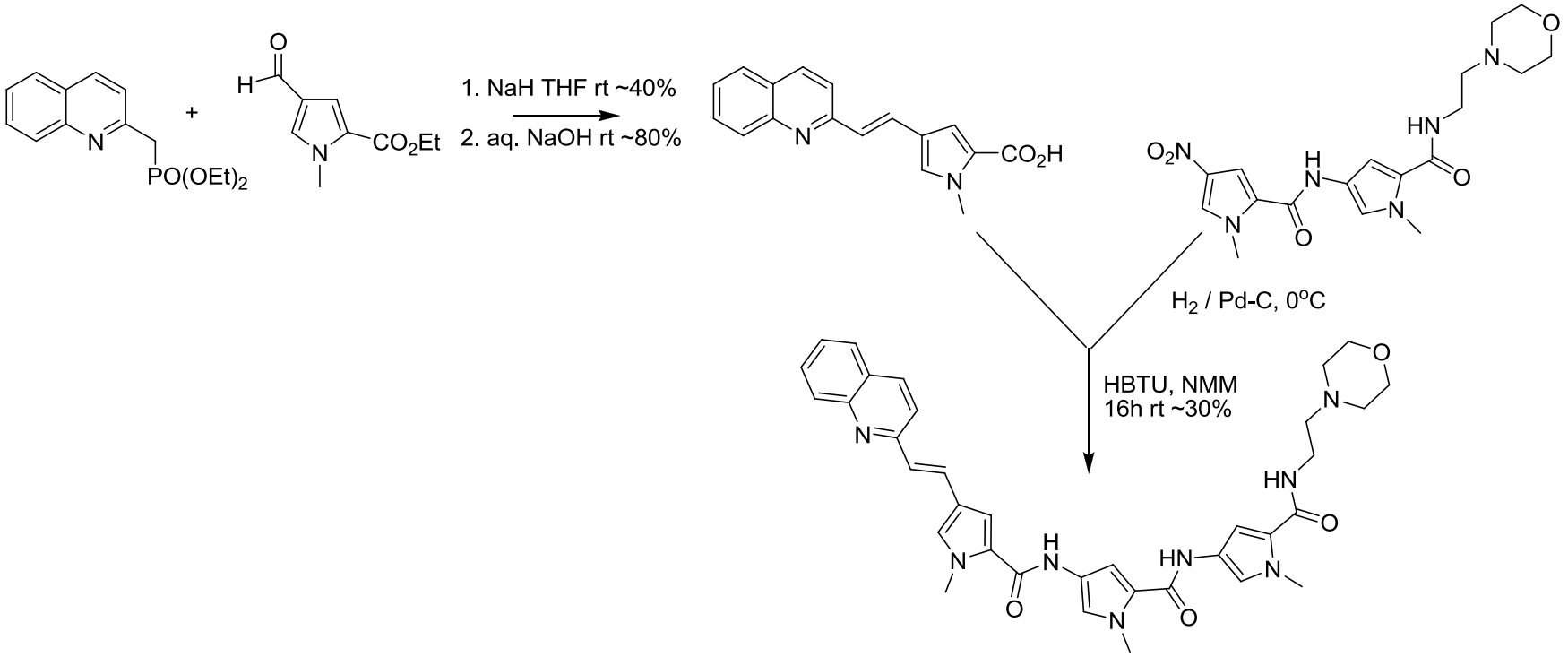
One hydrogen bond lost.

T_m measurements show that loss of a hydrogen bond does not weaken binding to DNA oligos in this group of compounds.

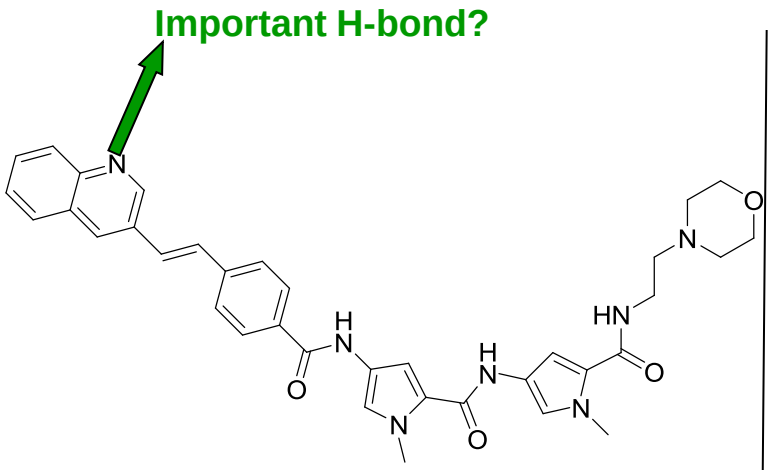




Synthesis is modular and flexible

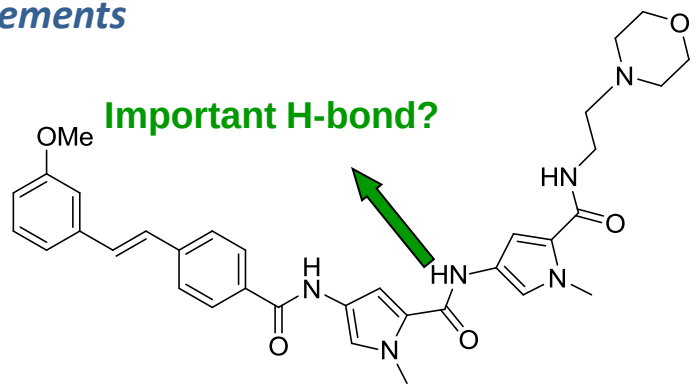


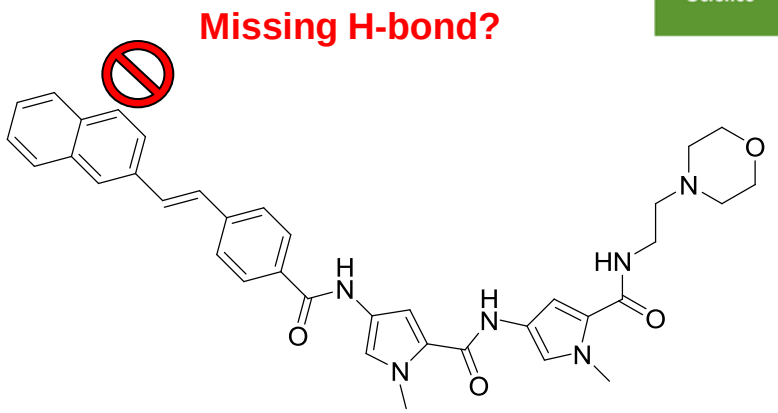
Molecular recognition in antibacterials



Active antibacterial compounds.

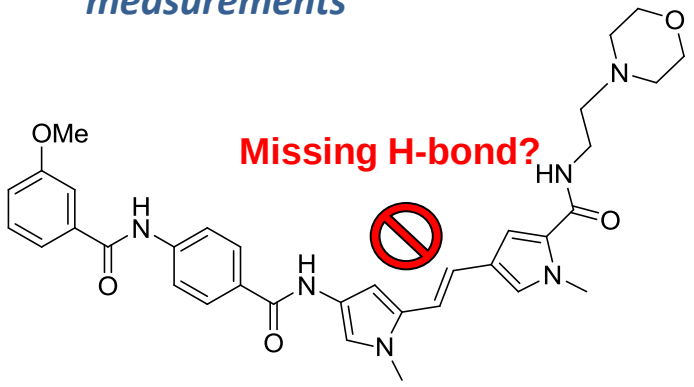
Bind to target DNA as shown by T_m measurements





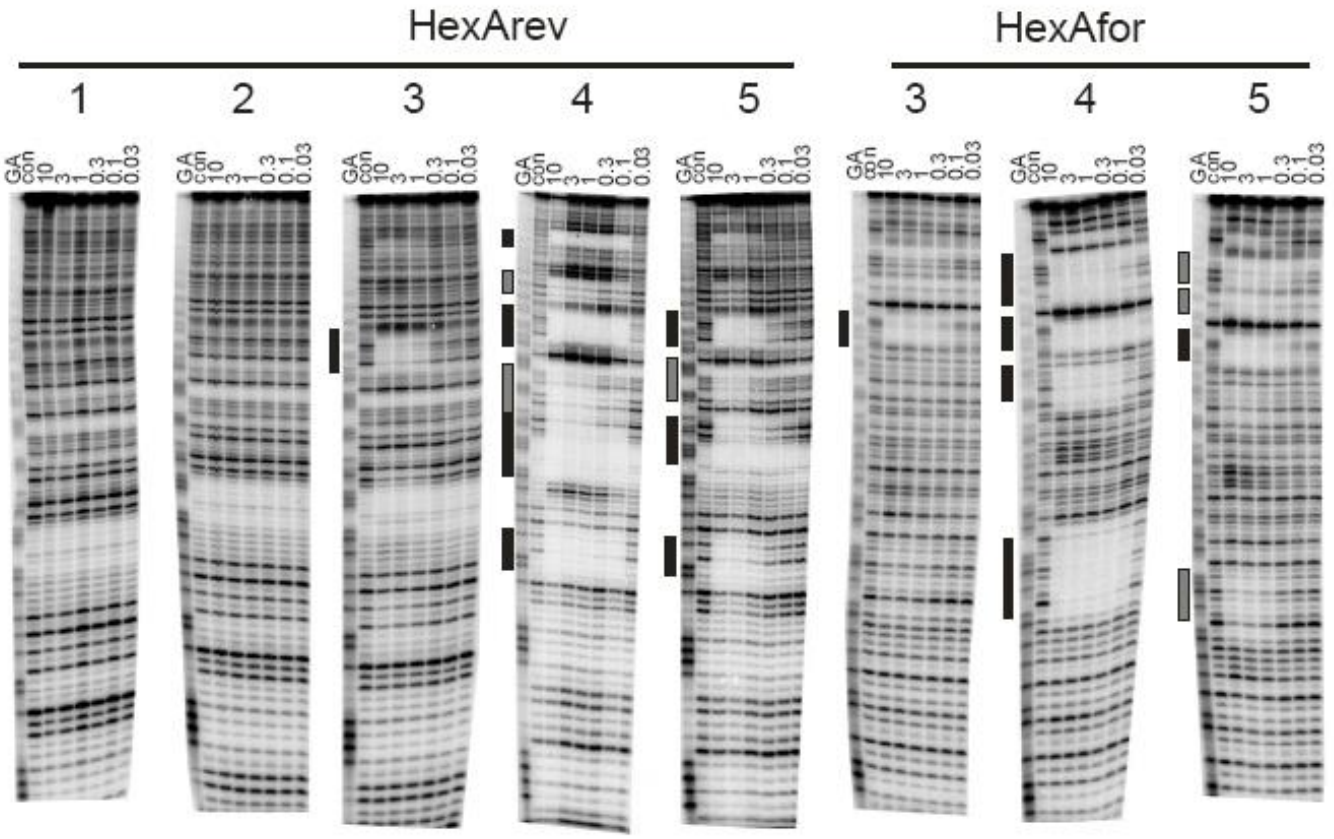
Inactive antibacterial compounds.

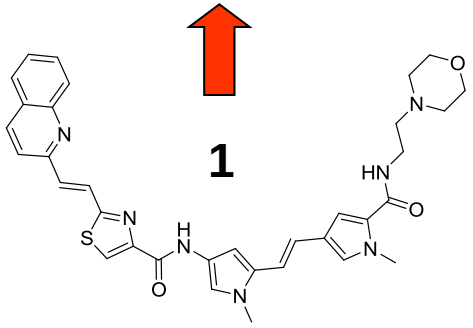
Do not bind to target DNA as shown by T_m measurements

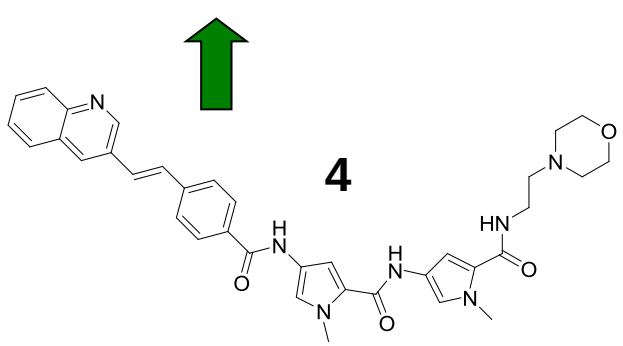


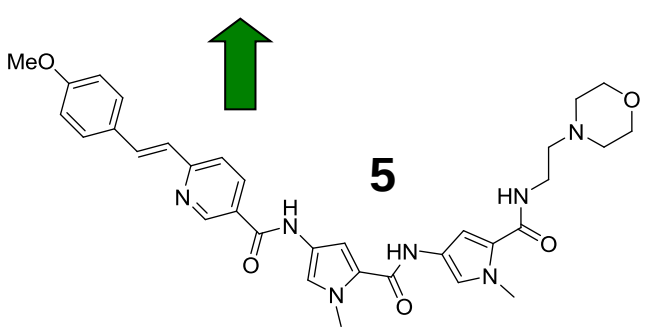
Target oligonucleotide = GCGATATATGCG/CGCTATATACGC

Footprinting evidence



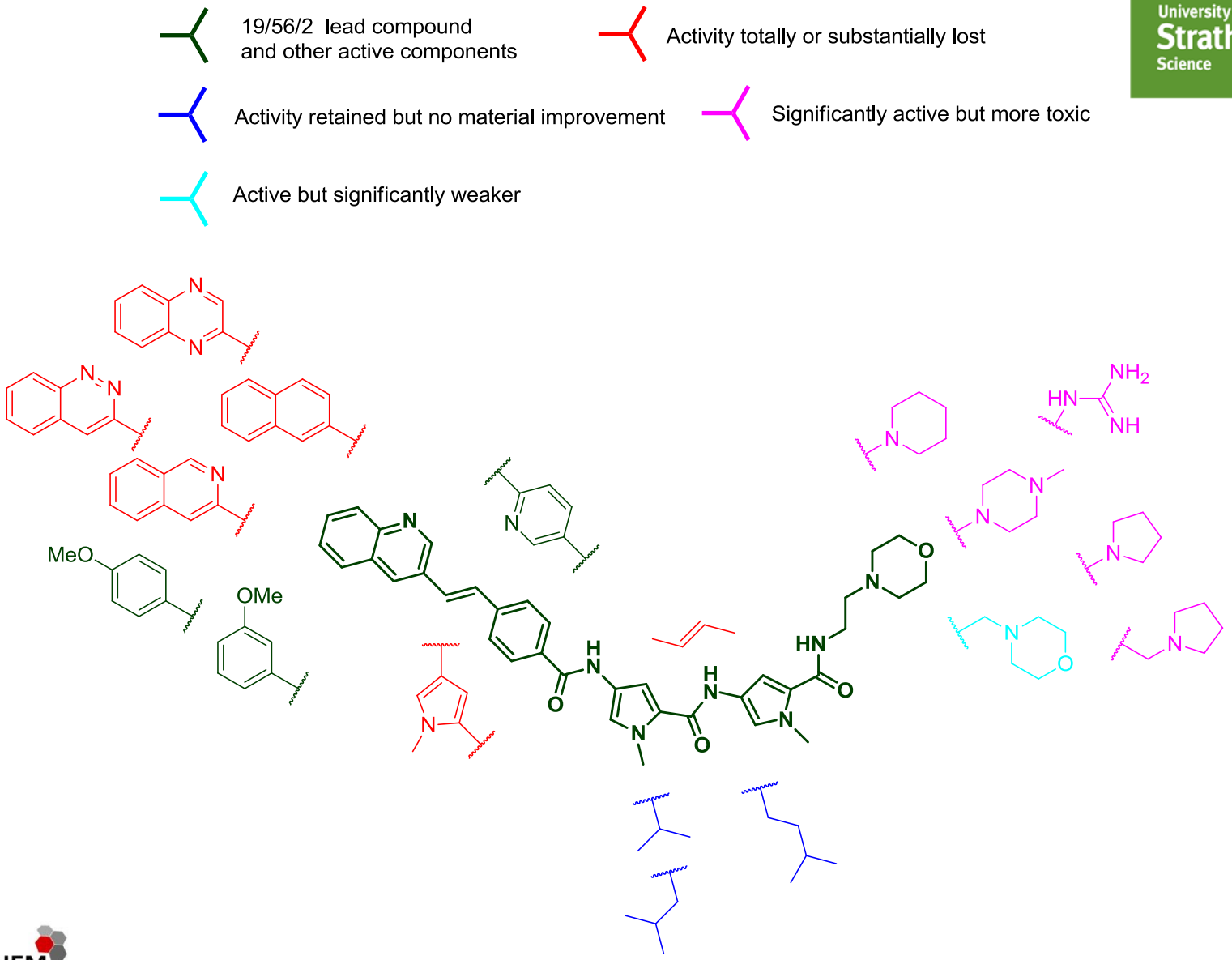






Prof Keith Fox, Southampton

SAR summary for antibacterial activity



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Species and resistant strains

Organism	MGB-BP-3				
	n=	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MBC_{50} (mg/L)	MBC_{90} (mg/L)
Group B Streptococci	15	0.25	1	0.25	1
Group C Streptococci	15	0.25	1	0.5	1
Group G Streptococci	15	0.5	0.5	0.5	0.5
Methicillin-resistant *Staphylococcus aureus*	15	1	2	1	2
Methicillin-resistant *Staphylococcus epidermidis*	15	0.25	0.5	0.5	2
Methicillin-susceptible *Staphylococcus aureus*	15	0.5	1	1	2
Methicillin-susceptible *Staphylococcus epidermidis*	15	0.25	0.5	0.25	2
Streptococcus constellatus	15	0.25	0.5	0.5	1
Streptococcus mitis	15	0.5	2	0.5	2
Streptococcus pyogenes	15	0.25	0.5	0.25	2
Vancomycin-resistant *Enterococcus faecalis*	15	2	2	>32	>32
Vancomycin-resistant *Enterococcus faecium*	15	1	2	>32	>32
Vancomycin-susceptible *Enterococcus faecalis*	15	1	2	>32	>32
Vancomycin-susceptible *Enterococcus faecium*	15	1	2	>32	>32

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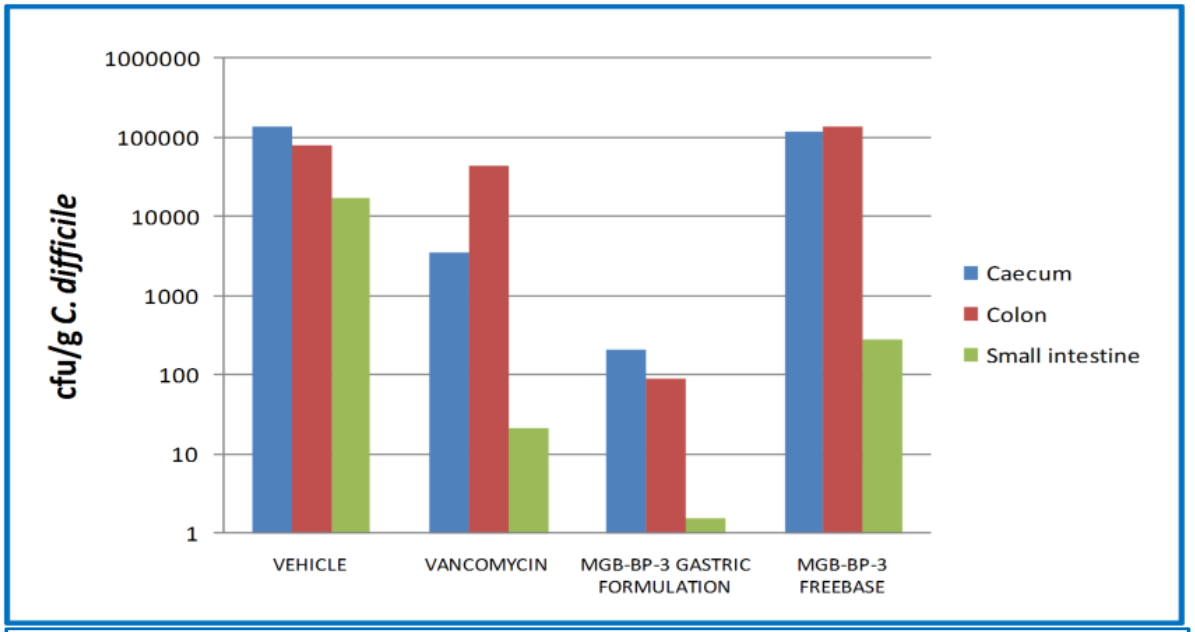
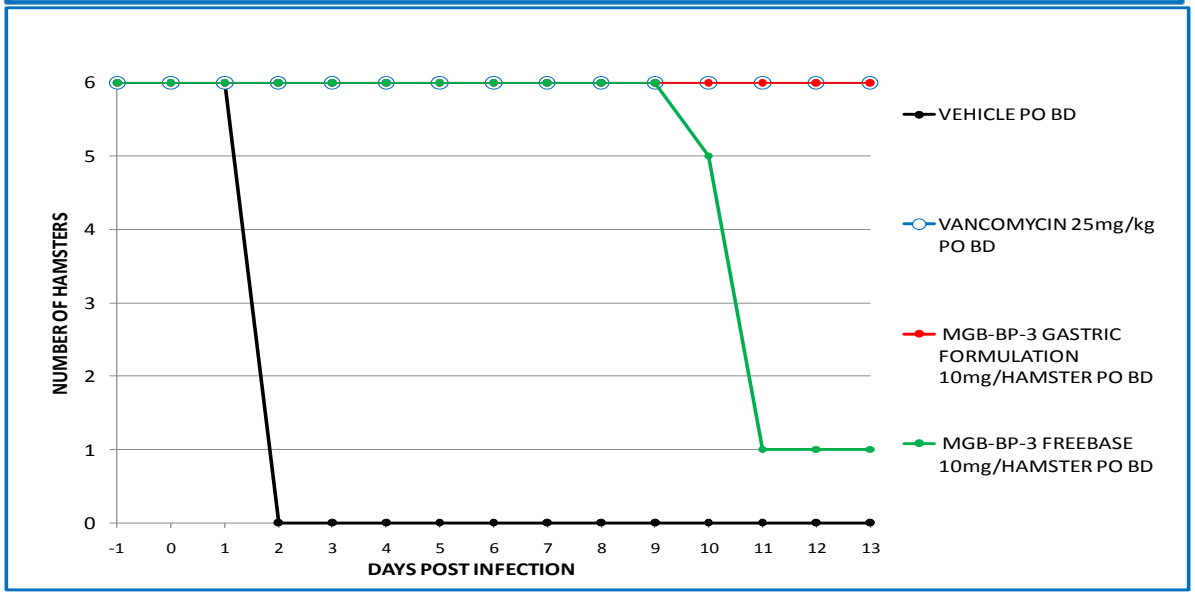
Innovative Development Company

Formulated drug against *C. difficile*





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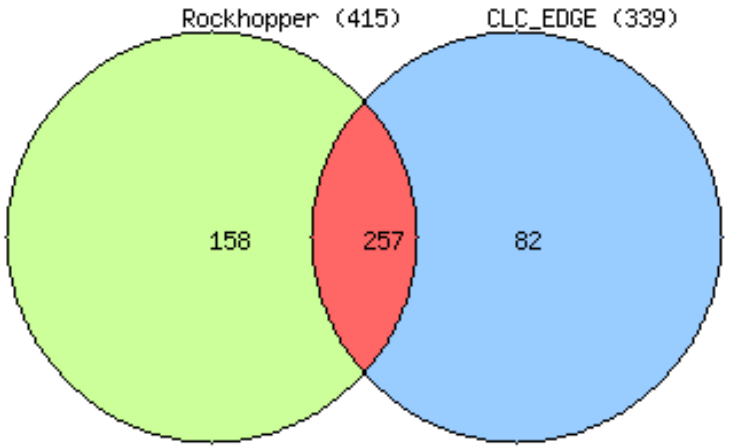
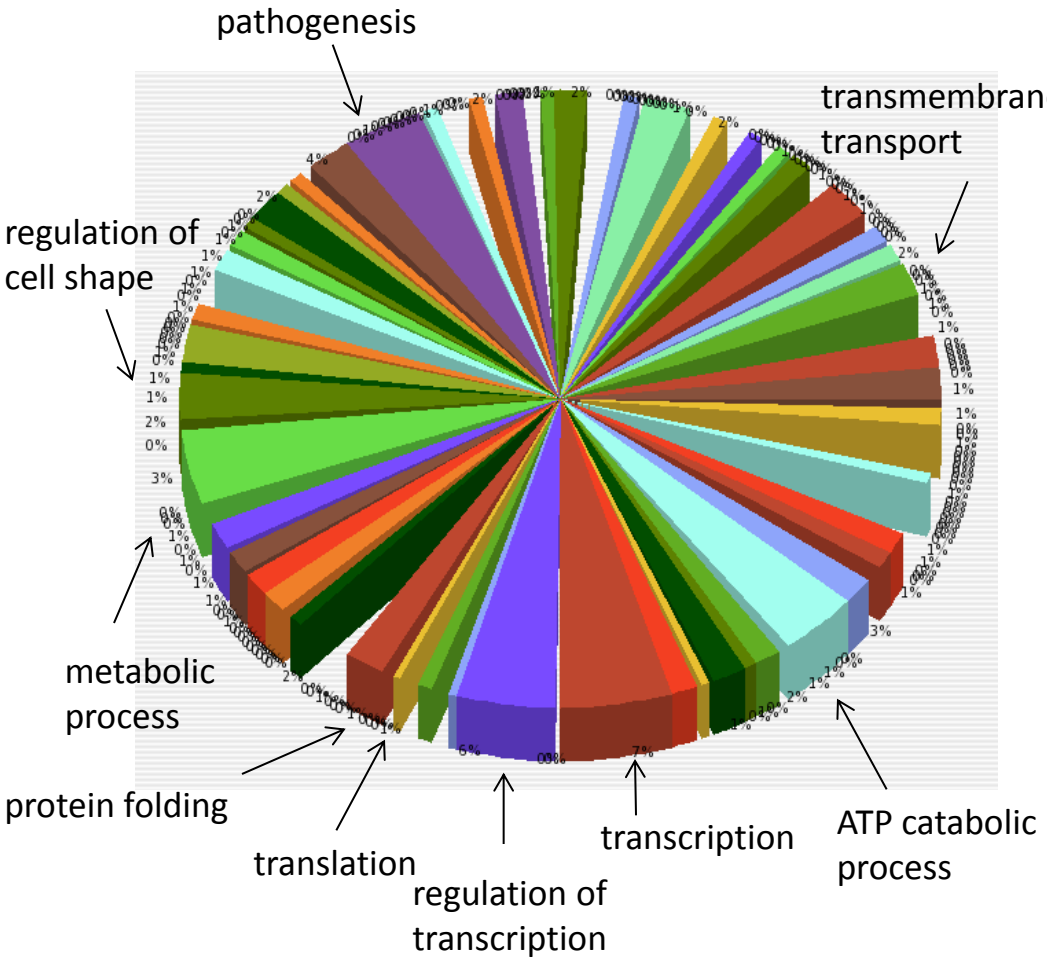
Genes significantly downregulated

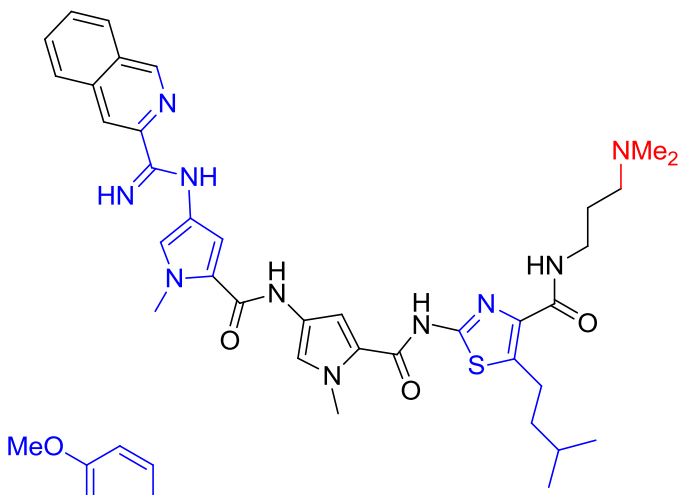
- 257 downregulated genes common to both data analysis methods





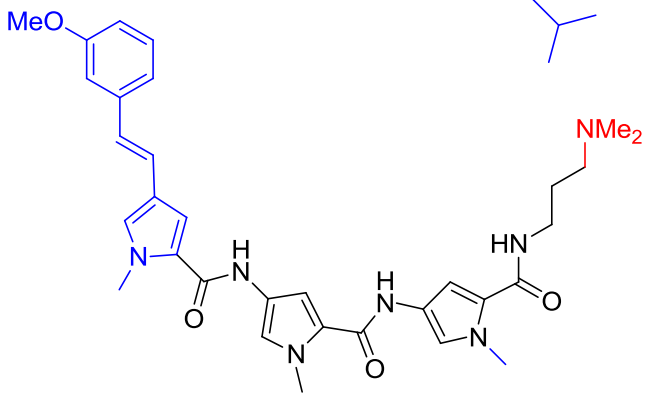
Dr Nick Tucker, Dr Leena Niemenen, Prof Iain Hunter

Antifungal activity



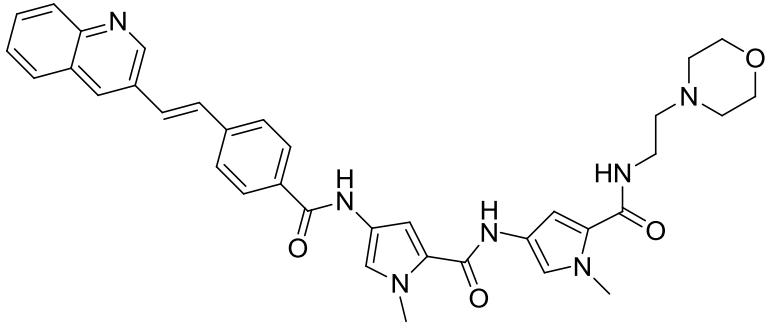
MIC = 6.25 μM vs. *Candida, Aspergillus*

MIC > 50 μM for bacteria



MIC = 1.6 μM vs. *Candida*

MIC ~ 20 μM for bacteria



Lead antibacterial compound

MIC > 50 μM for fungi

Other activities with specific compounds

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- Anti-trypanosomal activity: *T. brucei* (human) and *T. congolense* (animal): *in vivo* proof of concept model for animal disease.

- Anti-leishmanial activity: *L. major, L. donovani, L. mexicani* with *in vivo* proof of concept model.

- Anti-plasmodial activity: *P. falciparum*: compounds active against chloroquine resistant strains.

- Antiviral activity: active compounds against hepatitis C virus, remarkable because it is a single strand RNA virus.

- Anticancer activity: against lung cancer and prostate cancer cells with a proof of concept *in vivo* model for lung cancer.

- Compounds tested were selected by screening a subset of our library and are not optimised for the stated indication.