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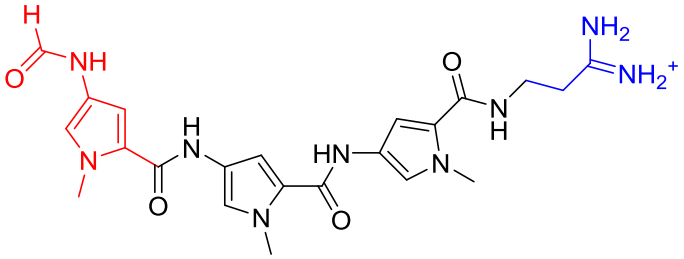
Strathclyde Minor Groove Binders (S-MGBs)
- a family of anti-infective agents.

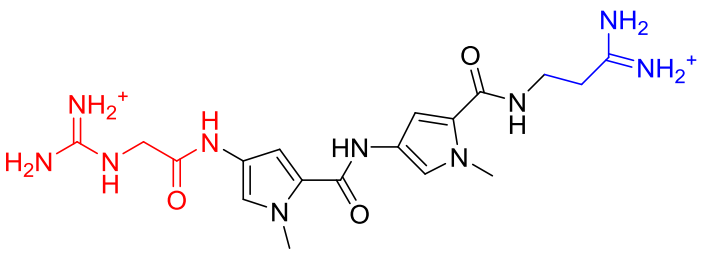
Colin Suckling
Research Professor

WestCHEM

Origin of S-MGBs

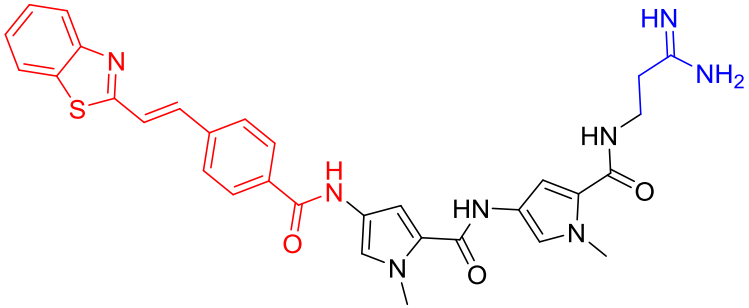


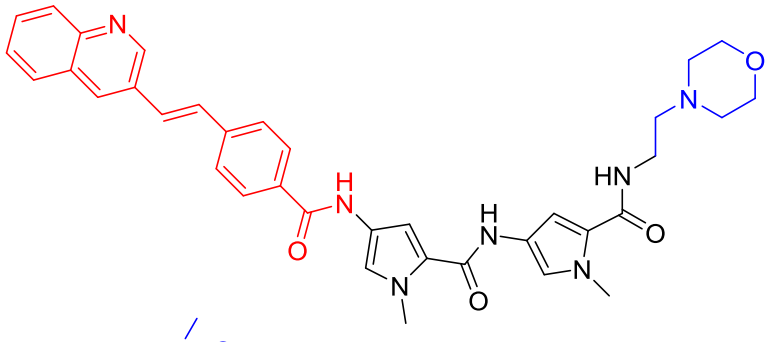
distamycin

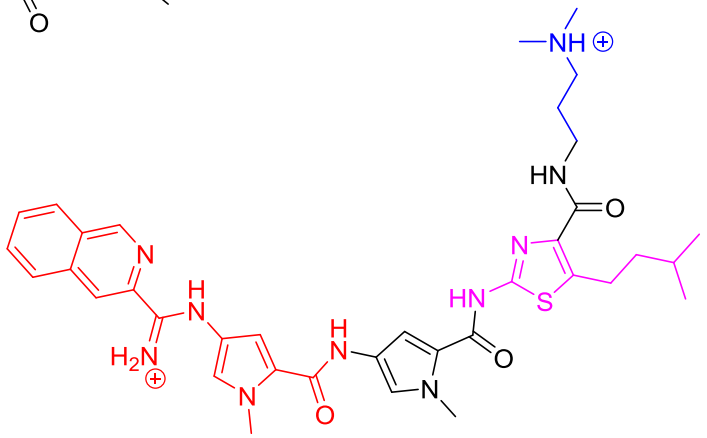


netropsin

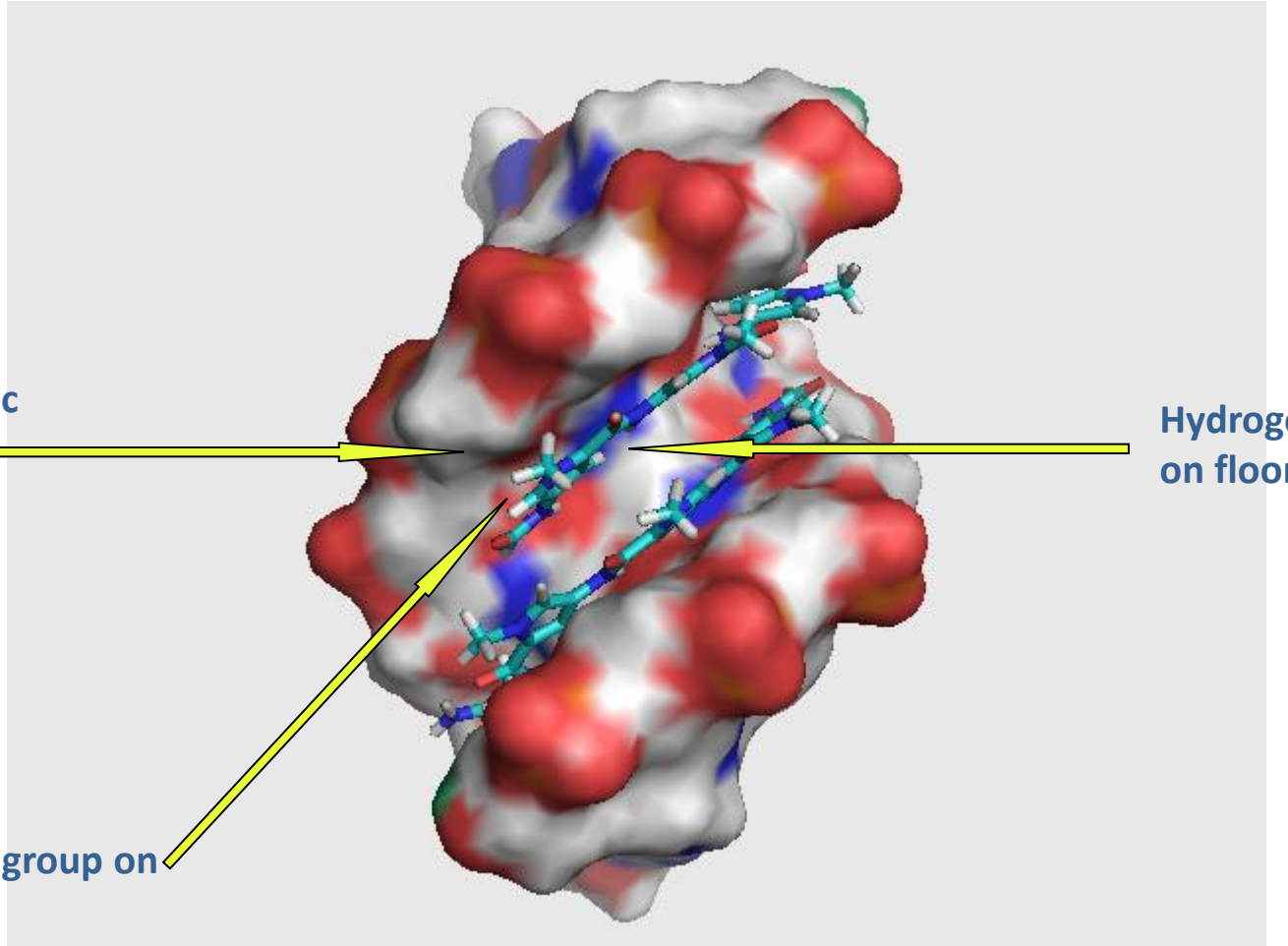
Add larger head groups, vary tail groups, introduce other features of diversity







Primary design concept for S-MGBs

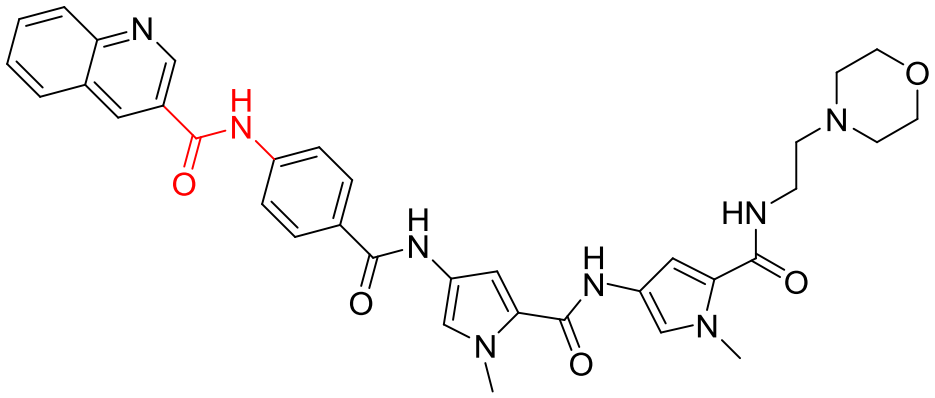


An amide isostere – the key structural change

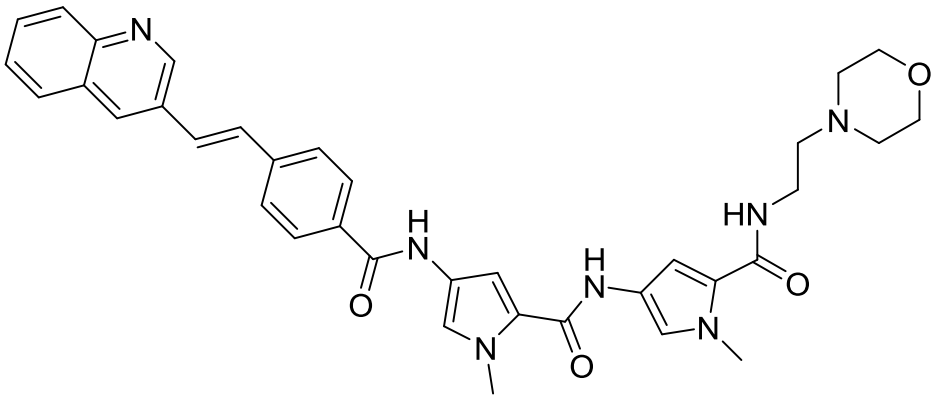
Amide: planar, H-bond donor and acceptor, hydrolysable.

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

One hydrogen bond lost.

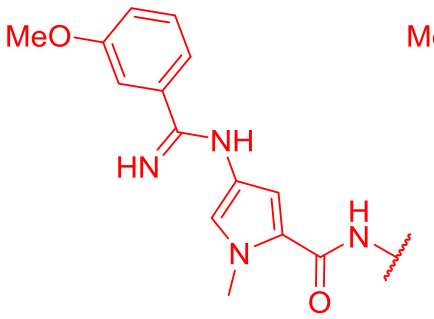


T_m measurements show that loss of a hydrogen bond does not weaken binding to DNA oligos in this group of compounds.

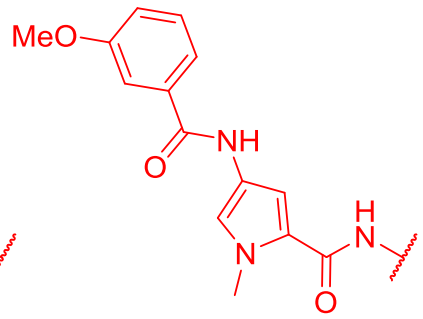


Abedawn Khalaf, Roger Waigh, Iain Hunter, Carol Clements

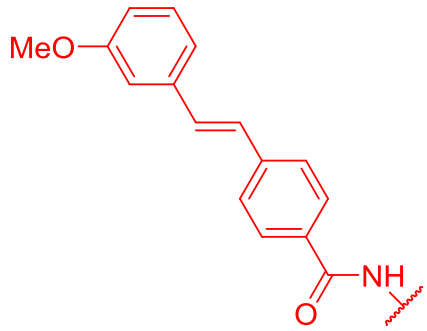
Structural features of S-MGBs



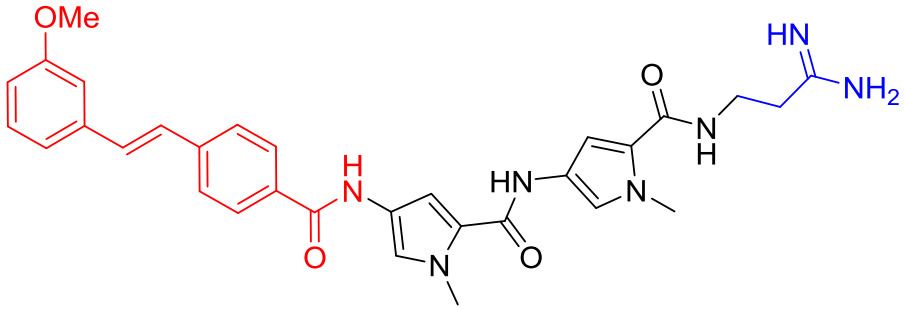
Amidine linked head group

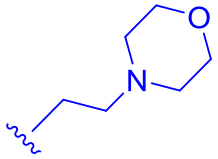


Amide linked head group

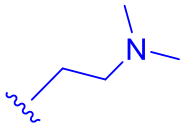


Alkene linked head group

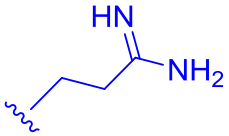




Morpholino tail group



Dimethylamino tail group



Amidine tail group

MGB-BP3 as an AMR valuable drug

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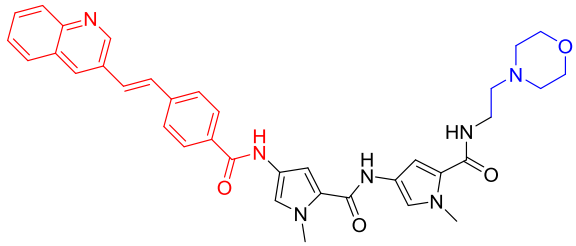
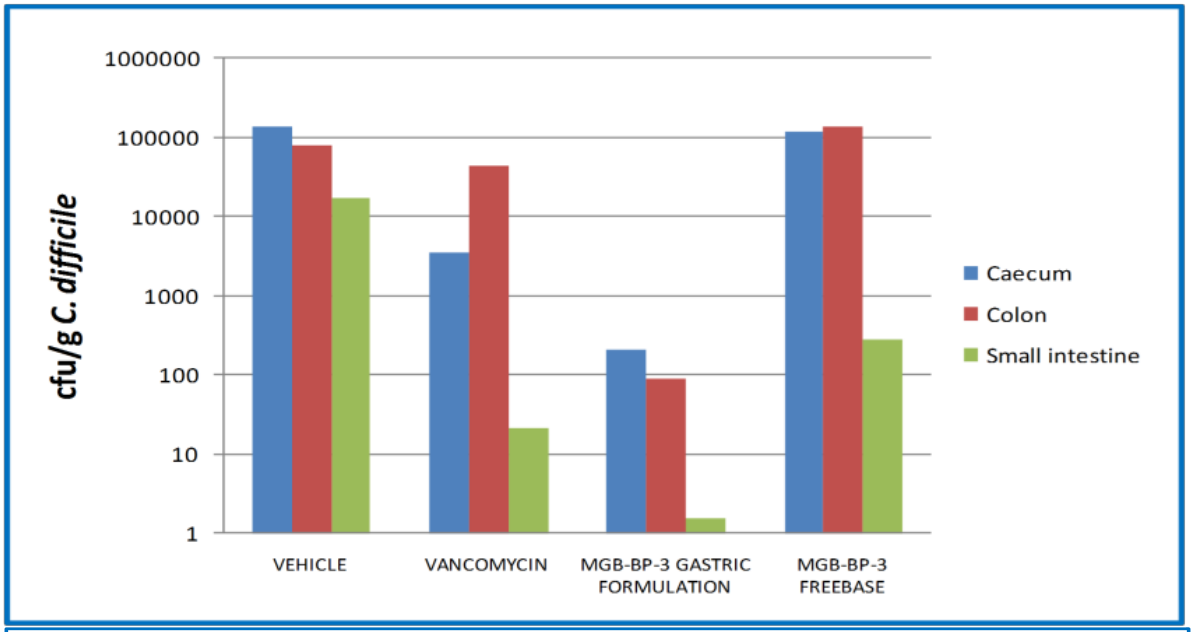
Organism	MGB-BP-3				
	n=	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MBC_{50} (mg/L)	MBC_{90} (mg/L)
Group B Streptococci	15	0.25	1	0.25	1
Group C Streptococci	15	0.25	1	0.5	1
Group G Streptococci	15	0.5	0.5	0.5	0.5
Methicillin-resistant *Staphylococcus aureus*	15	1	2	1	2
Methicillin-resistant *Staphylococcus epidermidis*	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

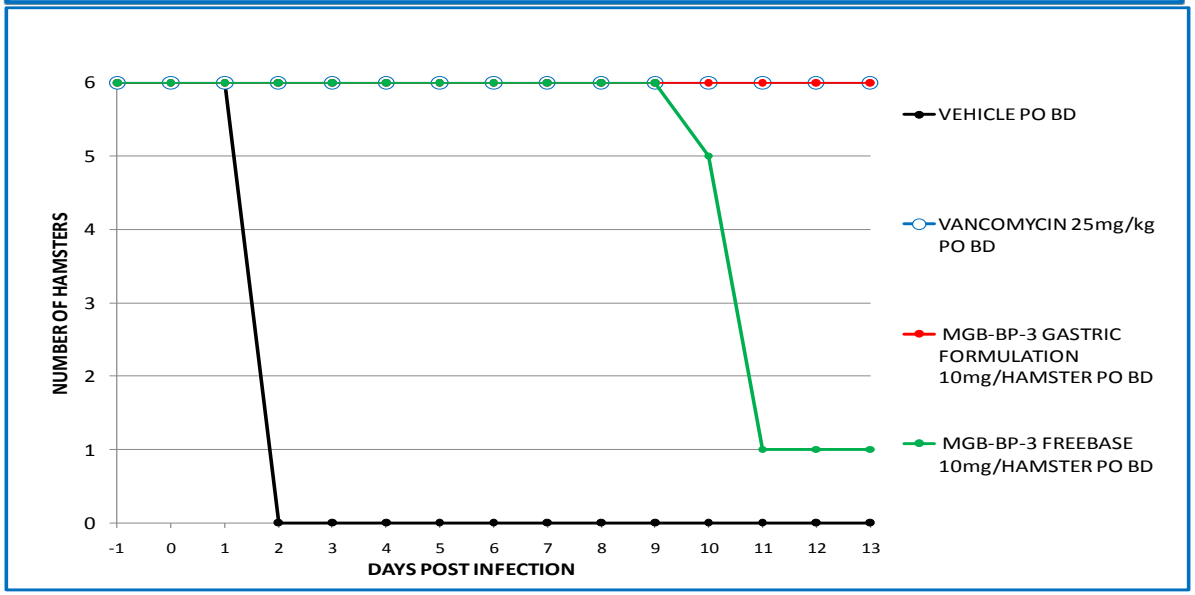


MGB-BP-3

MGB Biopharma
Innovative Development Company

Formulated drug against *C. difficile*





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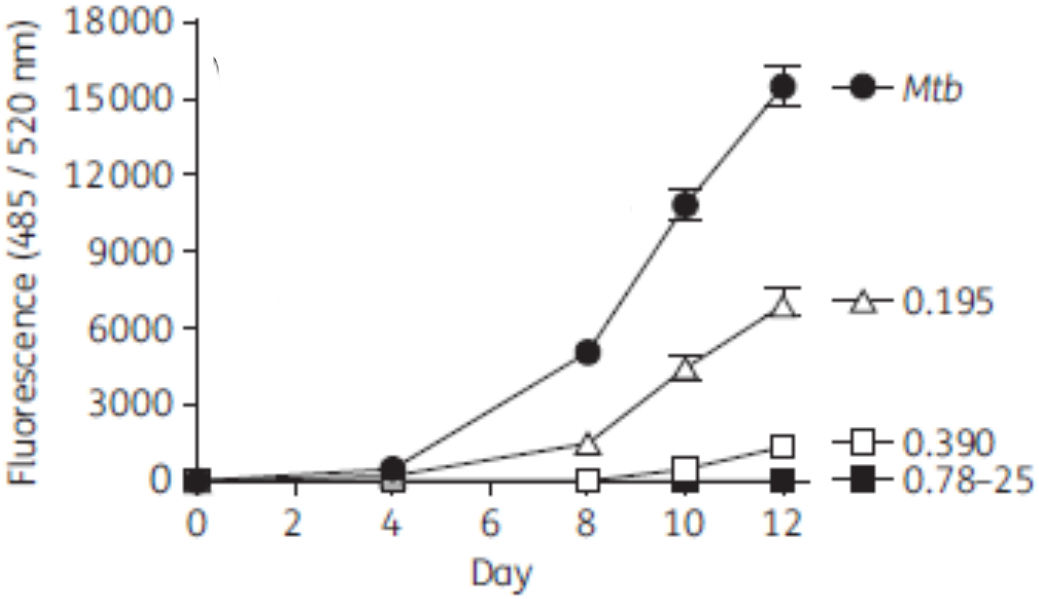
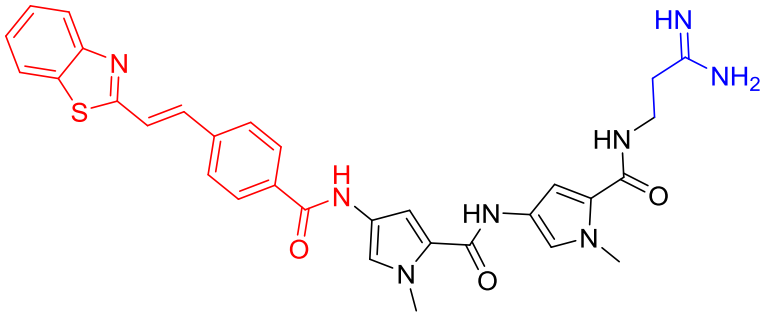
MGB Biopharma
Innovative Development Company

MGB362 is active against *M. tuberculosis*



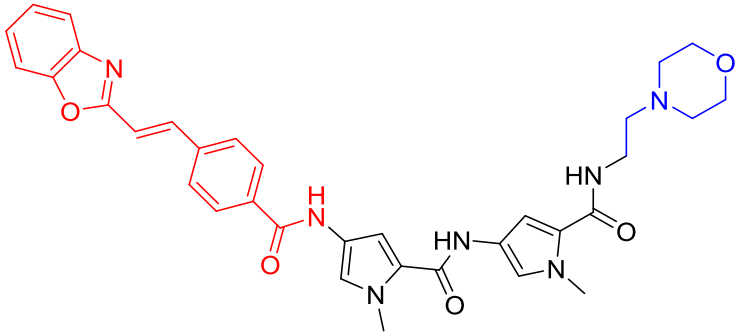


MIC_{99} HR37-Gfp	0.391 μM
IC_{50} clinical strain HN878 in macrophages	4.09 μM

Evaluation of Minor Groove Binders (MGBs) as novel anti-mycobacterial agents, and the effect of using non-ionic surfactant vesicles as a delivery system to improve their efficacy
Lerato *et al. Journal of Antimicrobial Chemotherapy,* **2017** doi:10.1093/jac/dkx326

Reto Guler

MGB169 is active against chloroquine resistant *Plasmodium falciparum*



EC_{50} chloroquine sensitive 3D7	39 nM
chloroquine resistant Dd2	38 nM

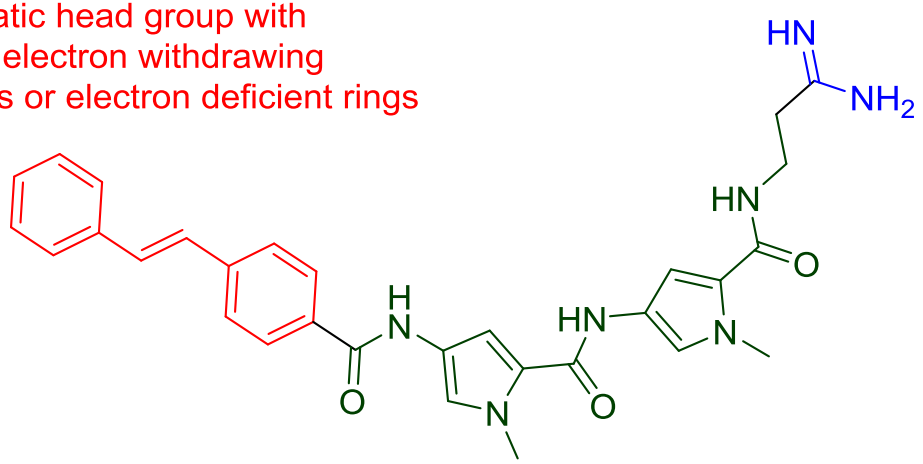
Selective anti-malarial minor groove binders *Bioorg. Med. Chem. Lett.* **2016**, 26, 3326-3329 http://dx.doi.org/10.1016/j.bmcl.2016.05.039

Vicky M. Avery

Summary of SAR for antitrypanosomal activity.

Basic tail group in which high activity is associated with high pK_a.
Amidine > *t*-amine > morpholine

Aromatic head group with some electron withdrawing groups or electron deficient rings



Constant region in this series.

Lack of cross resistance to diminazene

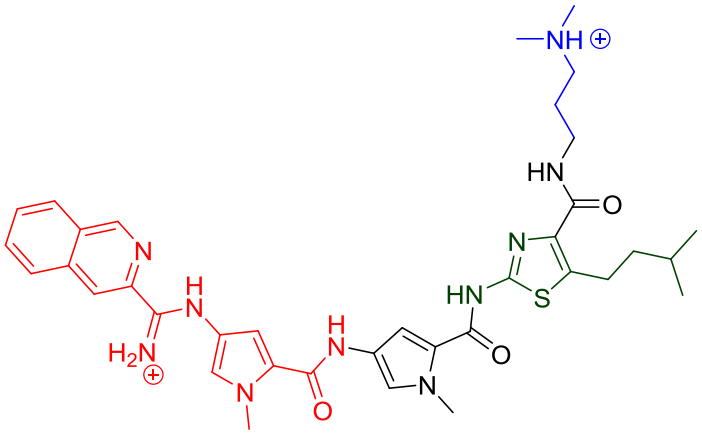
S-MGB	*T. congolense* WT EC_{50} (μM)	*T. congolense* DimR EC_{50} (μM)	RF	*T. congolense* EMS MUT DimR EC_{50} (μM)	RF
248	0.27 ± 0.02	0.18 ± 0.01	0.7	0.22 ± 0.03	0.8
234	0.51 ± 0.06	0.64 ± 0.03	1.3	0.70 ± 0.005	1.4
235	1.40 ± 0.24	0.66 ± 0.08	0.5	1.19 ± 0.12	0.9
246	2.13 ± 0.17	1.82 ± 0.06	0.9	2.03 ± 0.07	1.0
247	2.36 ± 0.10	1.66 ± 0.10	0.7	1.78 ± 0.10	0.8
2	4.50 ± 0.22	4.41 ± 0.25	1.0	4.52 ± 0.18	1.0
1	7.99 ± 0.85	5.26 ± 0.15	0.7	6.68 ± 1.06	0.8
Diminazene	0.20 ± 0.01	2.06 ± 0.10	10.4	2.36 ± 0.10	12.0

In vitro trypanocidal activity of selected S-MGBs against two diminazene-resistant *T. congolense* lines (DimR and EMS MUT DimR) as compared to wild type (WT).

Ratios (RF) close to unity indicate that the two strains compared are of essentially equal sensitivity to the S-MGB. The data suggest that the S-MGBs do not act by the same mechanism as diminazene.

Michael Barrett, Federica Giordani

Selectivity in antifungal MGBs
Candida albicans and *Cryptococcus neoformans*



MGB325
MIC_{70} *Cryptococcus neoformans* 0.25 μg/mL
Candida albicans **inactive**

The outer chain mannans of *C. albicans* contain negatively charged phosphodiester links, absent from *C. neoformans*.
The phosphodiester anion could sequester these dicationic MGBs explaining the lack of activity.

An evaluation of Minor Groove Binders as anti-fungal and anti-mycobacterial therapeutics
European Journal of Medicinal Chemistry, **2017**, 136, 561-572. doi.org/10.1016/j.ejmech.2017.05.039

Fraser J. Scott

The antibacterial drug, MGB-BP-3, and AMR

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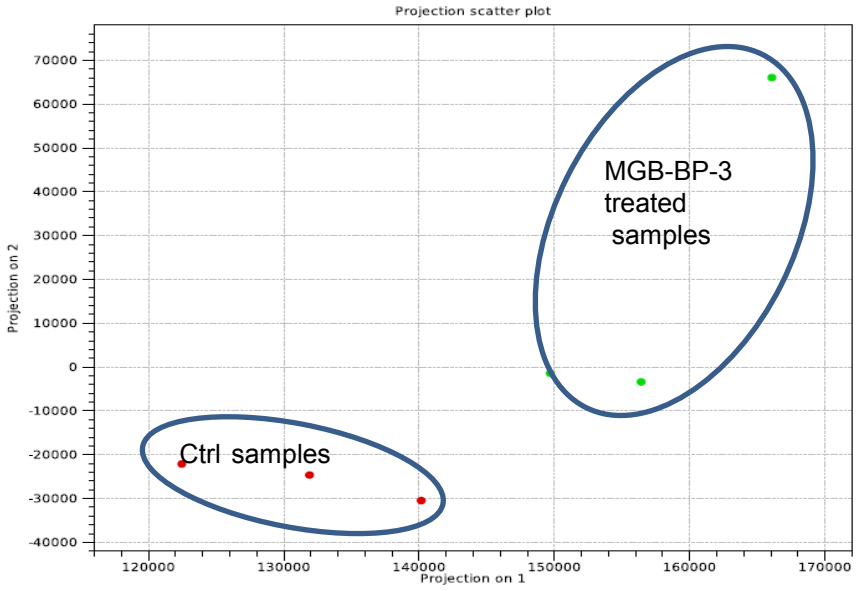
- Is the multiple target multiple effect design plan of S-MGBs real?
- What effects does binding to DNA by MGB-BP-3 have?
- Are these effects consistent with a reasonable interpretation of the biology of BP3?
- Is MGB-BP-3 resilient to the development of resistance?

Iain Hunter, Nick Tucker, Leena Nieminen, Kimon Lemonidis

University of Strathclyde Glasgow

RNA-seq shows MGB-BP-3 alters transcription



RNA-Seq analysis identified 698 transcripts showing significant changes in expression profile. Treated and non-treated samples grouped by principal component analysis.

Key enzymes of glycolysis were enhanced whereas the pentose phosphate pathway was reduced; flux through the TCA cycle was likely reduced significantly as citrate synthase and isocitrate dehydrogenase were reduced.
Importantly, several *essential genes* are downregulated.

These changes are associated with energy depletion.
In addition, biosynthesis of nucleotides and certain amino acids were altered.

Metabolomics study of *T. brucei brucei* also shows significant changes in the production of nucleotides and amino acids on treatment with MGB234.

Target binding sites suggested by RNA-seq match those found by footprinting

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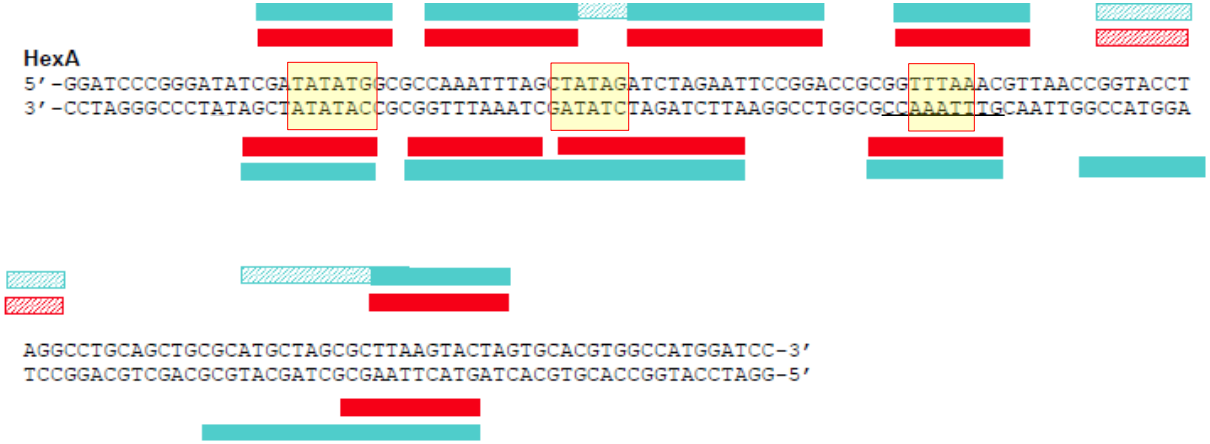
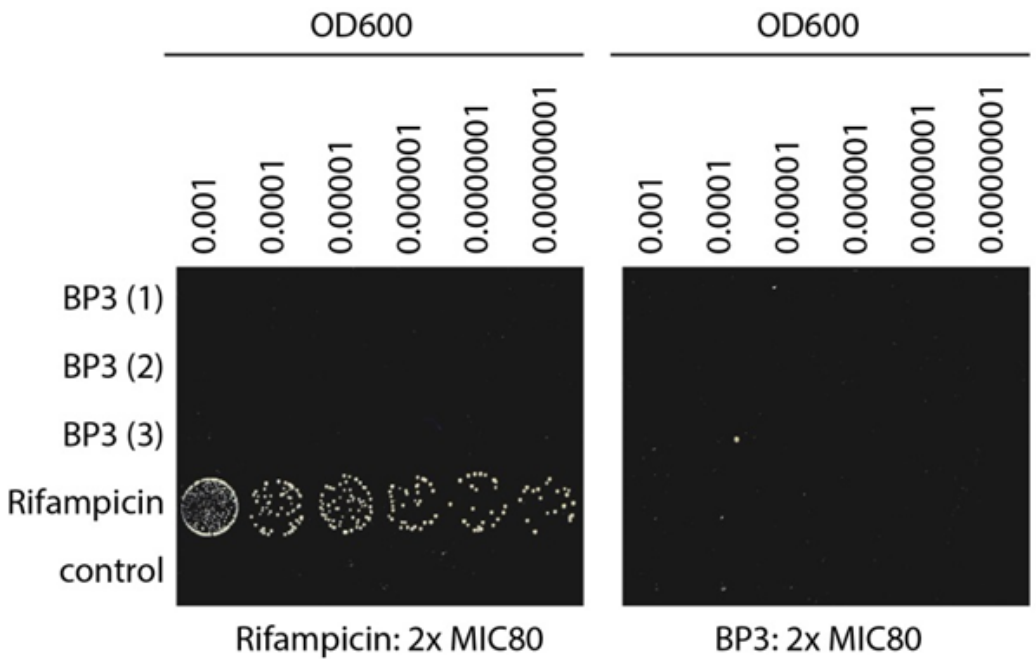
MGB-BP-3 binding sites *S. aureus* genes' promoter sequences (red)

csp1	ttttaatttattttcaaaaaacacTGTACAttatgccaatatgagcgTATAGTtggtct
csp2	ttatcacagaaaataaaataatgcTTTACTtctatatttaaaagtgTATAATgaaagtt
rex	cattttacagtataaaacgccgtcTTGAAActaagatatttatttttTAAAATtcaata
pstp	aaacaacatttttatagaaacctaTTGCACtttaacgtcaataagtaTATTTTtatatt
dnaA	ttttagcaacatattcacaggtatTTGACAtatagagaactgaaaaagTATAATtgtgt
aag	gtacacatctatatggagactcatTTGAAAgtcaacgcttcgttaacTATACTaaaaat

MGB-BP-3 binding sites (red) on the test oligonucleotide, Hex-A (Keith Fox, Southampton)



Evolution of resistance to MGB-BP-3?



Assessment of *S. aureus* resistance to MGB-BP-3
Serial passaging of either BP-3 (3 independent populations at up to 0.5 MIC80) or rifampicin (one population at up to 0.4 MIC80) for 80 generations. 5 µl of cultures at corresponding OD600 were spotted on agar plates containing either rifampicin or BP3 at 2x MIC80 concentrations.

Similarly resistance of *T. congolense* has not been observed using MGB234 or MGB360

Characteristics of the S-MGB family

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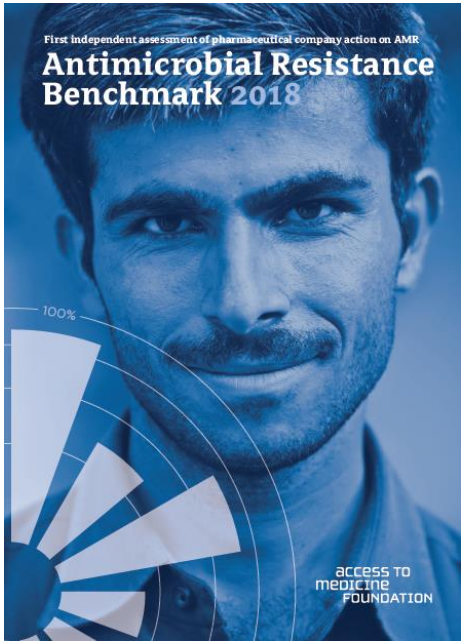
- Activity of therapeutically significant levels *in vitro* against Gram-positive bacteria, parasites, and fungi.
- Different compounds most effective against different infectious agents.
- Serious therapeutic challenges such as TB and new fungal infections can in principle be met by appropriate S-MGBs.
- Evidence available from studies of *S. aureus* and *Trypanosoma* is consistent with S-MGBs' having an effect on several biological pathways, in accord with their design.
- Resistance has not been found so far when sought in studies with *S. aureus* and *Trypanosoma*.

S-MGBs, when fully developed, have the potential to make a substantial contribution to anti-infective therapy with a greatly reduced risk of the rapid emergence of resistance.
S-MGBs are drugs for the AMR era and are of their time.



And finally … according to the Access to Medicine Foundation, January 2018

University of Strathclyde Science

To qualify as novel, a candidate must fulfil one or more of the criteria defined by WHO[6]:

- it represents a new chemical class;
- aims at a new target;
- has a new mode of action;
- and/or has an absence of cross-resistance
- from existing antimicrobials.

Figure 28. What makes an antibiotic novel?

There are nine novel drug candidates in companies' clinical pipelines, five fulfilling all four criteria defined by the WHO.[6] A majority (six) of these are developed by biopharmaceutical companies.

Company	Antibiotic	Clinical phase	Pathogen	New drug class	New target	New MoA*	Absence of CR**
MGB Biopharma	MGB-BP-3	Phase I	*C. difficile*	●	●	●	●
Polyphor	Murepavadin (POL7080 iv)	Phase II	*P. aeruginosa*	●	●	●	●
Roche	Anti-*S. aureus* TAC (RG7861)***	Phase I	*S. aureus*	●	●	●	●
Summit	Ridinilazole	Phase II	*C. difficile*	●	●	●	●
GSK	GSK3036656	Phase I	*M. tuberculosis*	●	●	●	●

Acknowledgments

‘The differing biological fates of DNA minor groove-binding (MGB) antibiotics in Gram-negative and Gram-Positive bacteria’ 2014-2017 BBSRC BB/N007999/1.

‘A new drug discovery pipeline for animal African trypanosomiasis’. 2016-2019, BBSRC, BB/N007638/1.

‘Accelerating Clinical Introduction of Novel Antibacterial Drugs’ Chief Scientist’s Office, 2016-2017, TCS 16.24