Design of “pseudo-natural product” inhibitors of DNA gyrase

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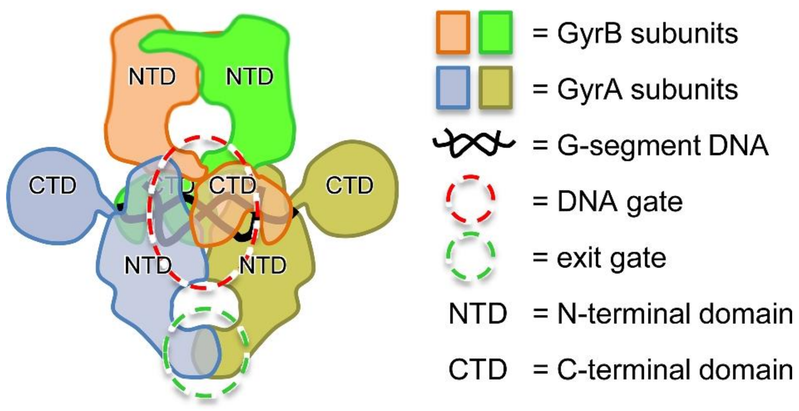
1. Introduction

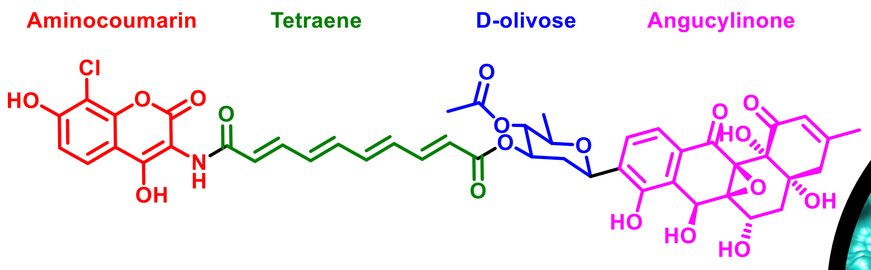
- Antimicrobial resistance poses a huge threat to society, with the predicted number of deaths owing to resistance estimated to rise from 700,000 in 2014 to 10,000,000 by 2050.[1] New compounds must therefore be found to combat resistance.
- DNA gyrase is an essential topoisomerase enzyme found in bacteria which catalyses negative supercoiling of closed-circular double-stranded DNA.
- Previous work has found that certain members of the simocyclinone class of natural products, found in *Streptomyces* strains present in soil, inhibit the binding of DNA gyrase to DNA.[2] However, the structures of these natural products make these compounds difficult to synthesise.

2. DNA gyrase

- DNA gyrase is a type IIA topoisomerase enzyme.

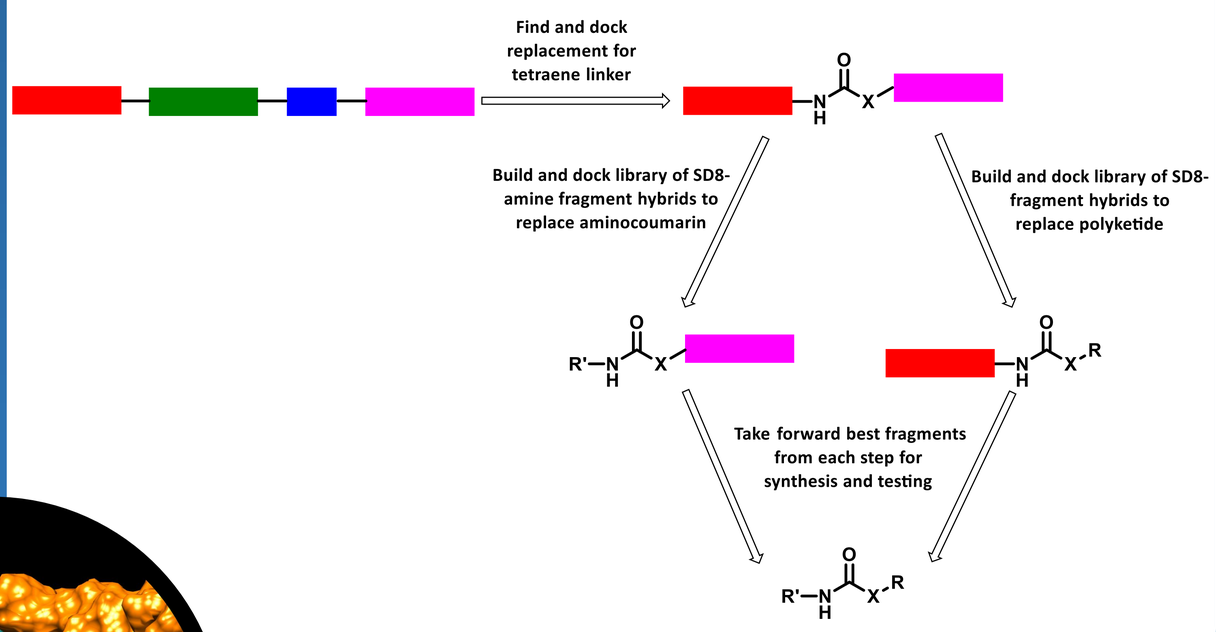


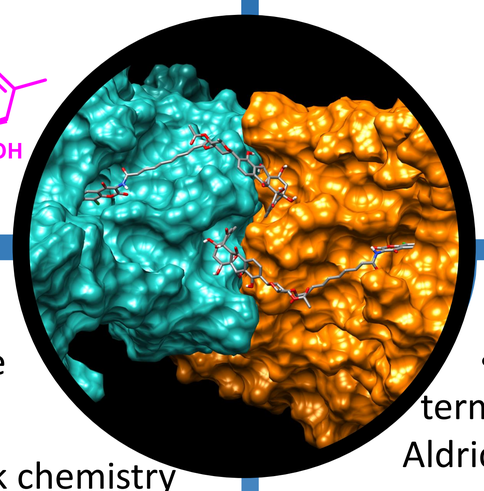
- It is the only topoisomerase capable of catalysing the introduction of negative supercoils into bacterial DNA
- Inhibited by the simocyclinones (e.g. SD8) which bind to GyrA



3. Problems and aims

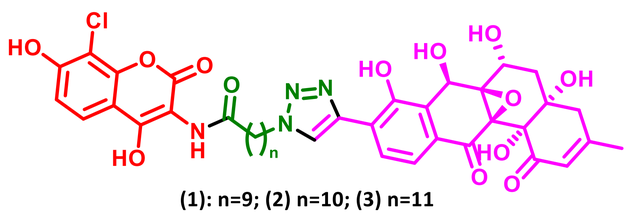
- SD8 is unable to penetrate cell membranes and is difficult to synthesise
- Aim is to design “pseudo-natural products” based on SD8 *in silico* and to test these compounds against DNA gyrase and cells





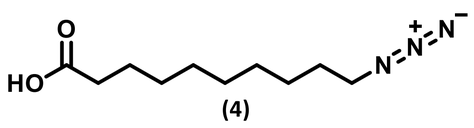
4. Linker design

- Examined use of terminal azidoalkyl acids to replace tetraene and D-olivose regions.
- Azides can react with alkynes to form triazoles via Click chemistry
- Generated a series of alkyl-triazolo linked compounds *in silico* which were then docked into GyrA



(1): n=9; (2) n=10; (3) n=11

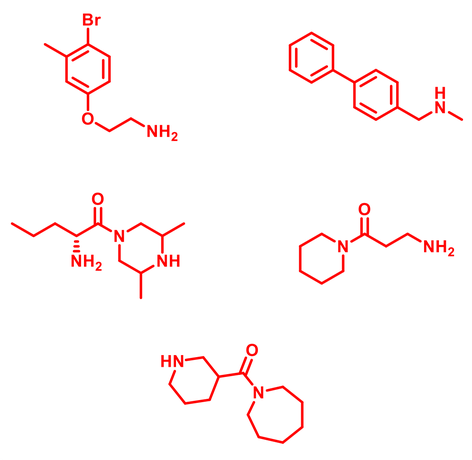
- Compound **(2)** had highest docking score so 10-azidodecanoic acid to be used for future *in silico* design steps.

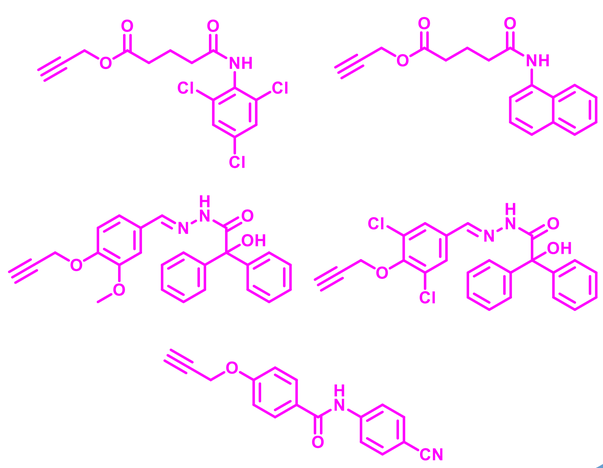


(4)

5. *In silico* hybrid testing

- Libraries of amines (to replace aminocoumarin) and terminal alkynes (to replace angucyclinone) prepared from Aldrich Market Select
- Libraries used to generate hybrids which were docked into GyrA, top 5 scorers taken forward for synthesis





Conclusions and Future Work

- DNA gyrase is an essential bacterial enzyme, and so is a good target for novel antimicrobials
- A series of fragments to replace various components of SD8 have been identified *in silico* to show potential for binding to DNA gyrase
- Synthesis of SD8-fragment hybrids is currently underway, starting with SD8-alkyne hybrids
- Hybrids will then be used in a supercoiling assay to determine activity, following which the best angucuclinone-replacing alkyne will be taken forward to study the aminocoumarin-replacing amines

References and acknowledgements

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3 M. J. Buttner, M. Schäfer, D. M. Lawson and A. Maxwell, *FEMS Microbiol. Rev.*, 2018, **42**, 100-112

Central image adapted from PDB ID 4CKL

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