

# DEVELOPING DIARYLMIDAZOLES AS ANTIBIOTICS USING AN OPEN SOURCE APPROACH

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## ABSTRACT

Antimicrobial resistance (AMR) poses an increasing threat to global public health.<sup>1</sup> However, development of new antibiotics has slowed, and despite a clear and increasingly urgent medical need, large pharmaceutical companies have been pulling out of antibiotic drug development; and small-to-medium-sized entities that have successfully brought new antibiotics to market have subsequently gone bankrupt.<sup>2</sup> It is clear, therefore, that the current incentives are not enough to solve this problem. The failure of traditional market forces to foster innovation in antibiotic drug development presents an opportunity for an open source approach encompassing maximal data and resource sharing to efficiently deliver a public good.<sup>2</sup> To that end, the Open Source Antibiotics (OSA) consortium<sup>3</sup> has been created. We here describe the open source drug discovery approach, using OSA's hit-to-lead development of a series of diarylimidazoles to treat methicillin-resistant *S. aureus* (MRSA) infection as an example. Starting with a small array of compounds which were found to have activity against MRSA when screened by the Community for Open Antimicrobial Drug Discovery (CO-ADD), the OSA consortium have elucidated detailed structure-activity relationships of this chemotype, as well as determined sites of metabolism and performed preliminary investigations into the mechanism of action.

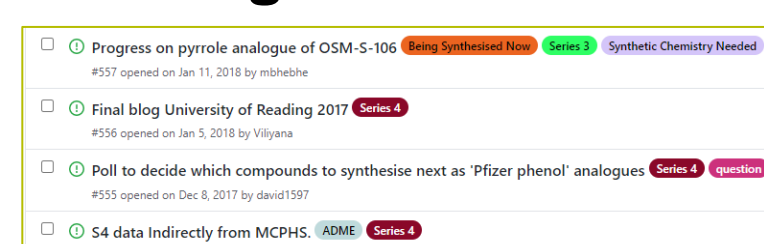
## OPEN SOURCE DRUG DISCOVERY

### The Six Laws<sup>4</sup>

1. All data and ideas are freely shared.
2. Anyone may participate at any level.
3. There will be no patents.
4. Suggestions are the best form of criticism.
5. Public discussion is more valuable than private email.
6. An open project is bigger than, and is not owned by, any given lab.



### Open Project Meetings

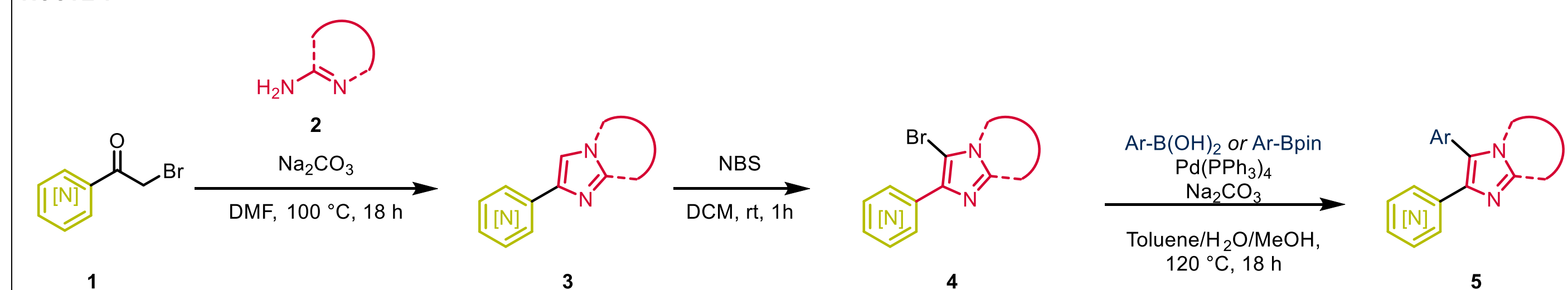


### Electronic Lab Notebooks

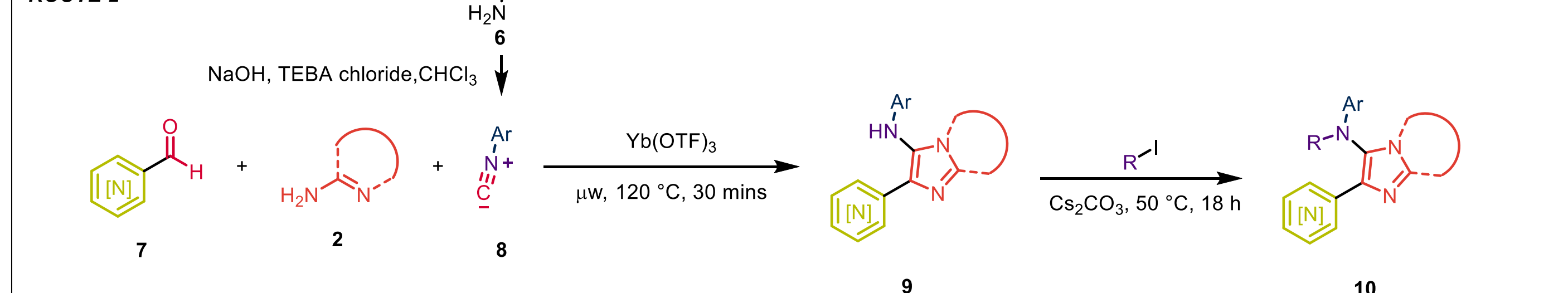
### GitHub Issue Tracker

## SYNTHESIS

### ROUTE 1



### ROUTE 2

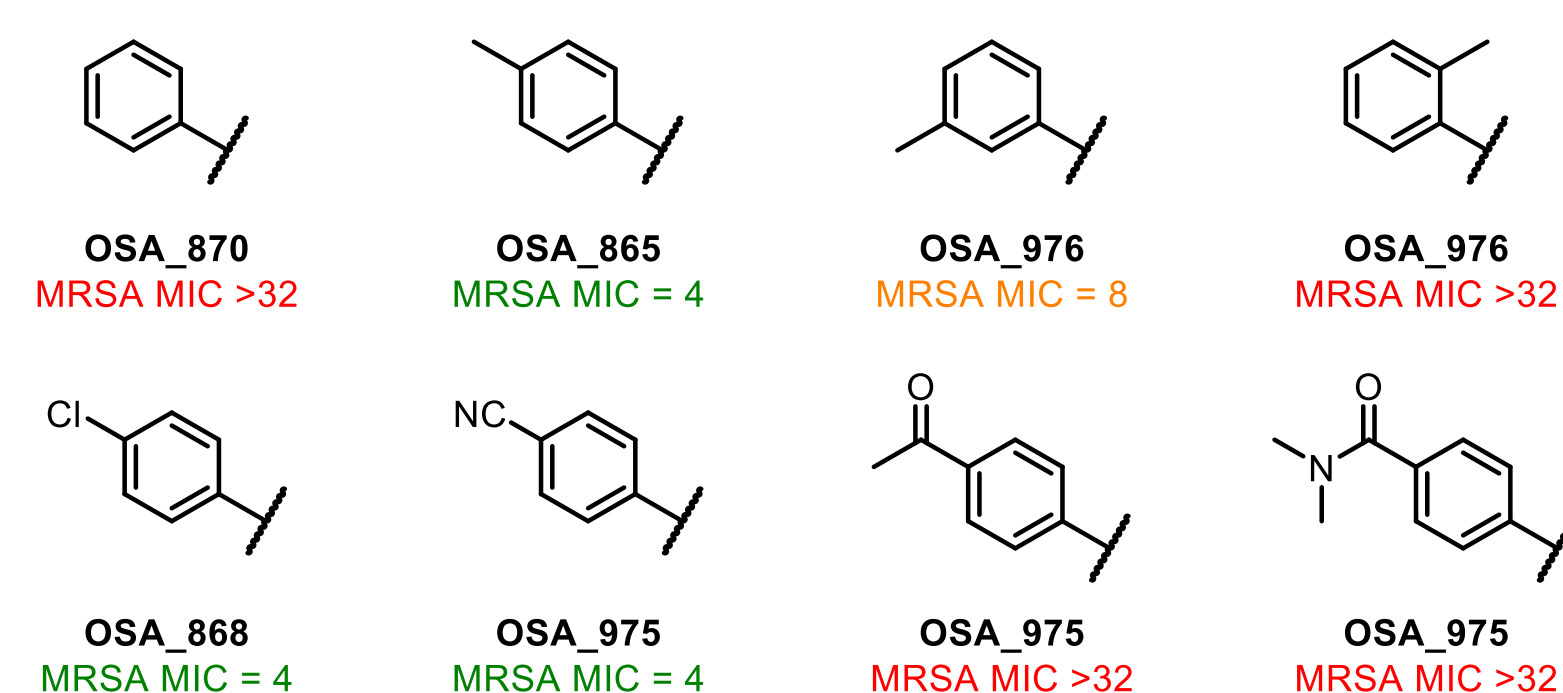


## REFERENCES

- <sup>1</sup>Hernando-Amado, S. *et al.* Defining and combating antibiotic resistance from One Health and Global Health perspectives. *Nature Microbiol.* 2019, 4: 1432-1442. <https://doi.org/10.1038/s41565-019-0503-9>
- <sup>2</sup>Klug, D. *et al.* There is no market for new antibiotics: this allows an open approach to research and development [version 1; peer review: 1 approved]. *Wellcome Open Res.* 2021, 6: 146. <https://doi.org/10.12688/wellcomeopenres.16847.1>
- <sup>3</sup>Open Source Antibiotics, available at <https://github.com/opensourceantibiotics>
- <sup>4</sup>Todd, MH. Six laws of open source drug discovery. *ChemMedChem* 2019, 14: 1804-1809. <https://doi.org/10.1002/cmdc.201900565>

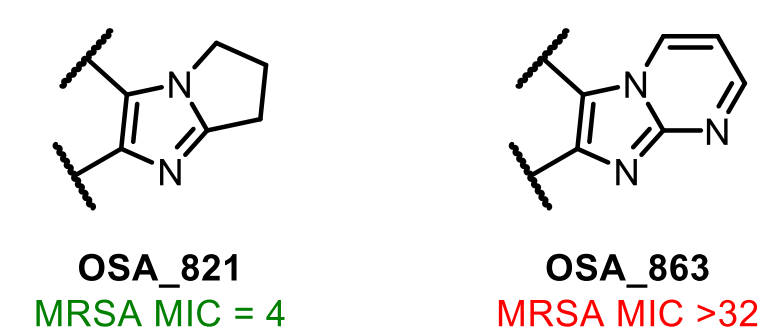
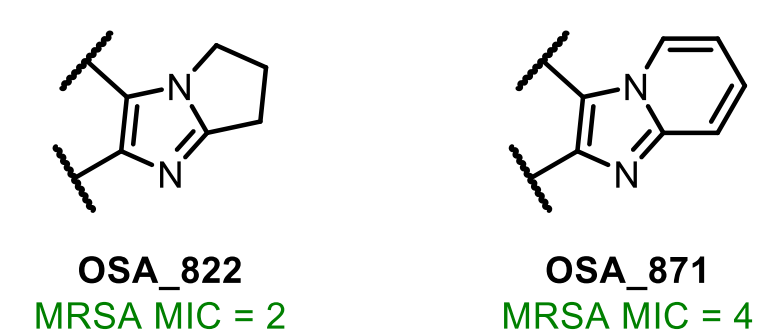
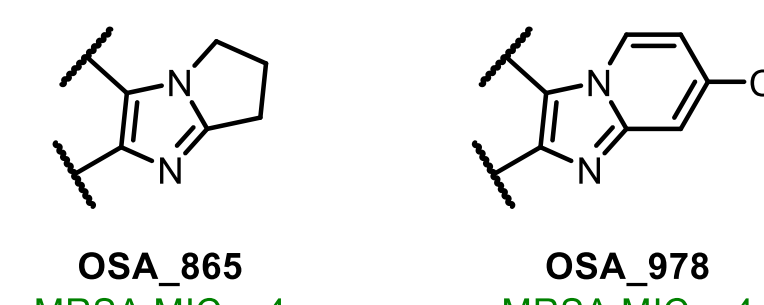
## STRUCTURE-ACTIVITY RELATIONSHIPS

### Para substituents improve activity...

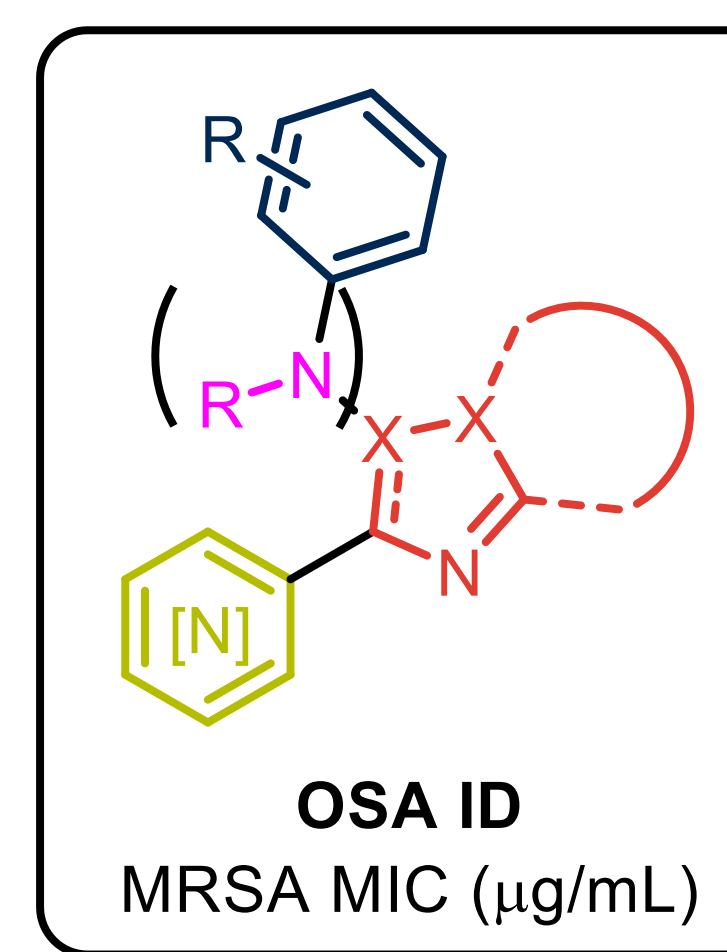
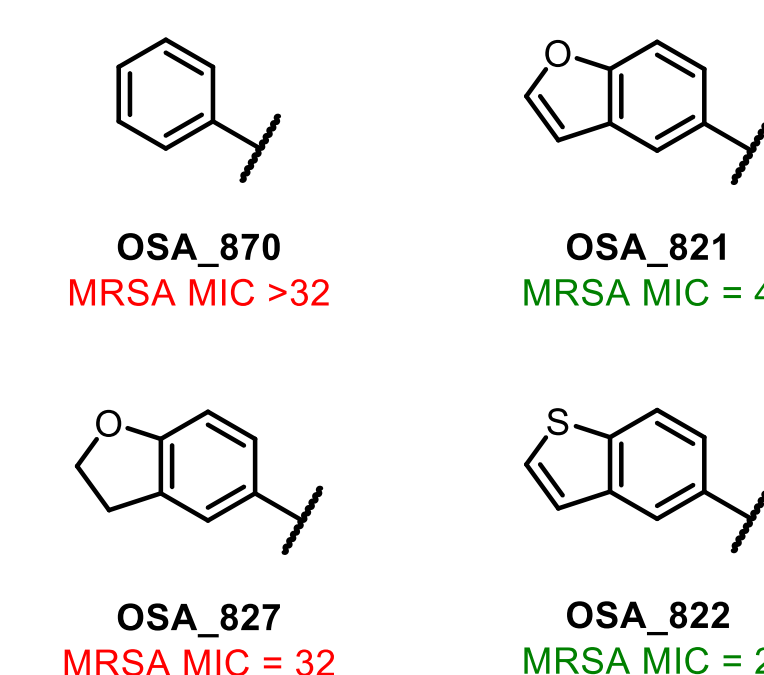


...though not uniformly.

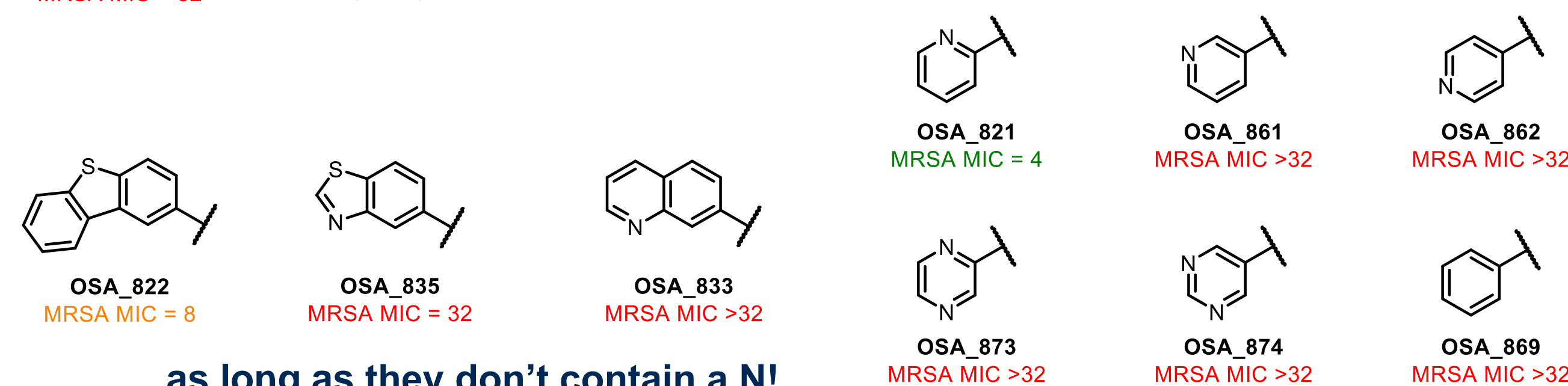
Aromatic cores are usually equipotent with aliphatic.



### Fused heterocycles are tolerated...

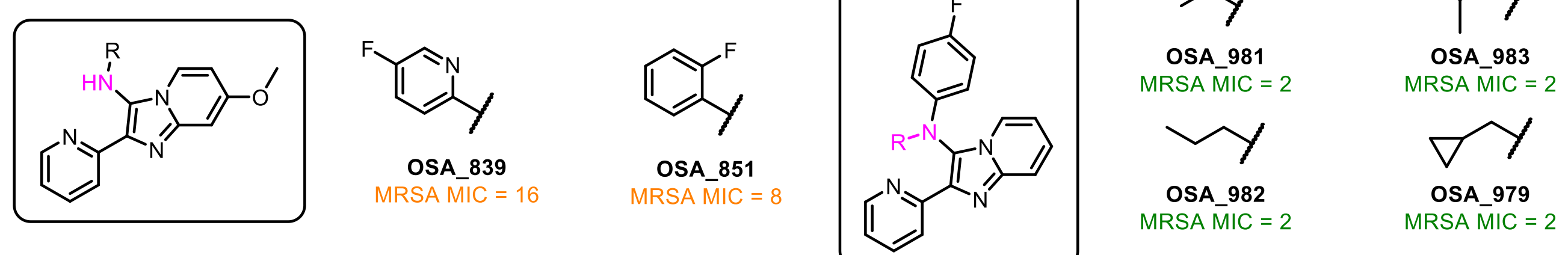


The 2-pyridyl is required for activity.



...as long as they don't contain a N!

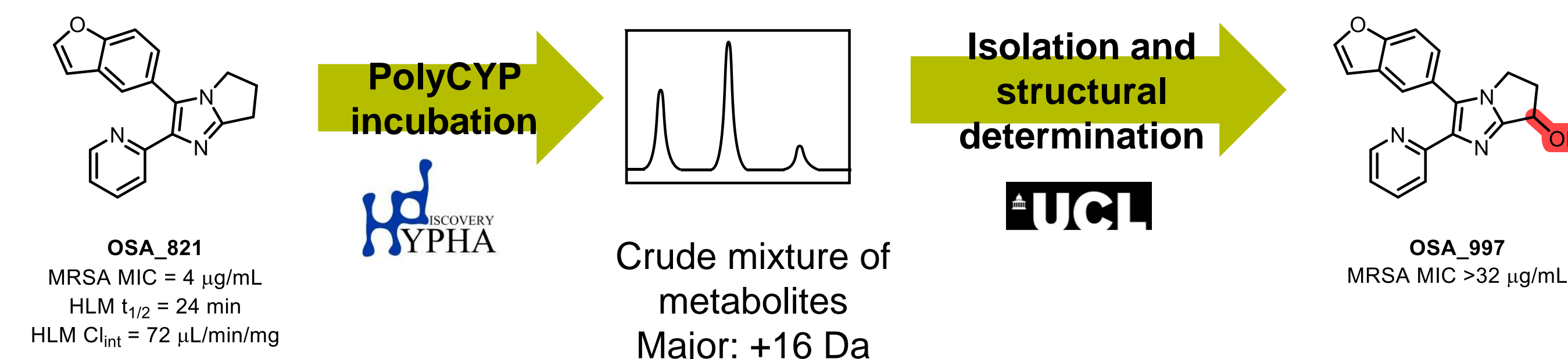
### Nitrogen linkage is tolerated...



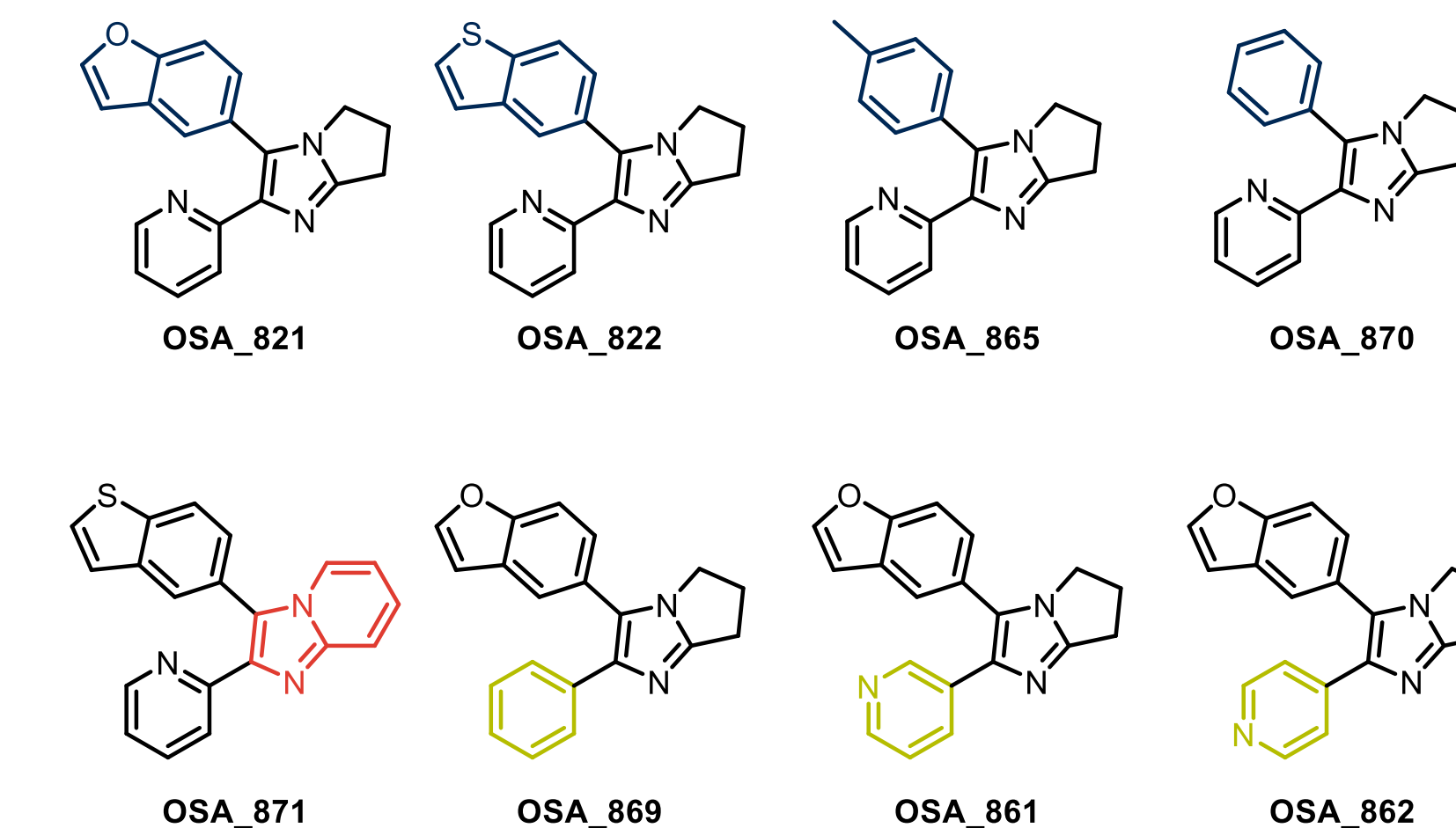
...and alkyl substitution of the N seems to increase potency.

## METABOLISM AND TOXICITY

### Metabolite ID



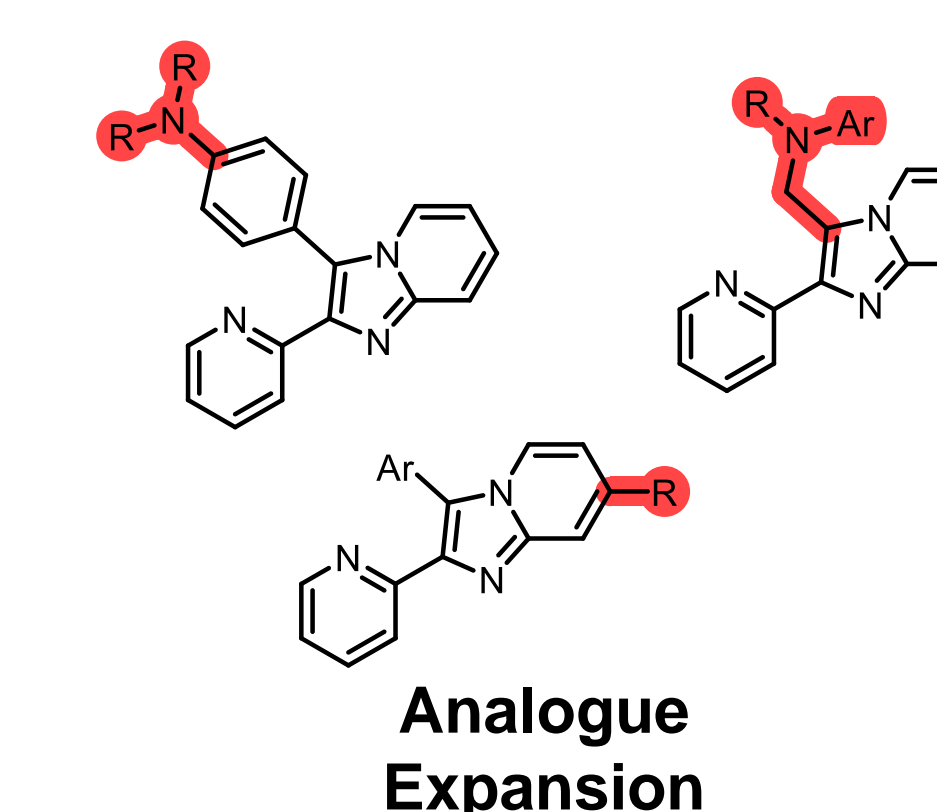
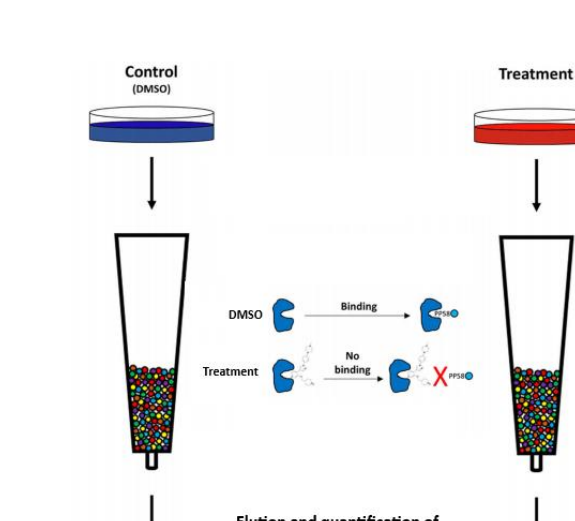
### Toxicity



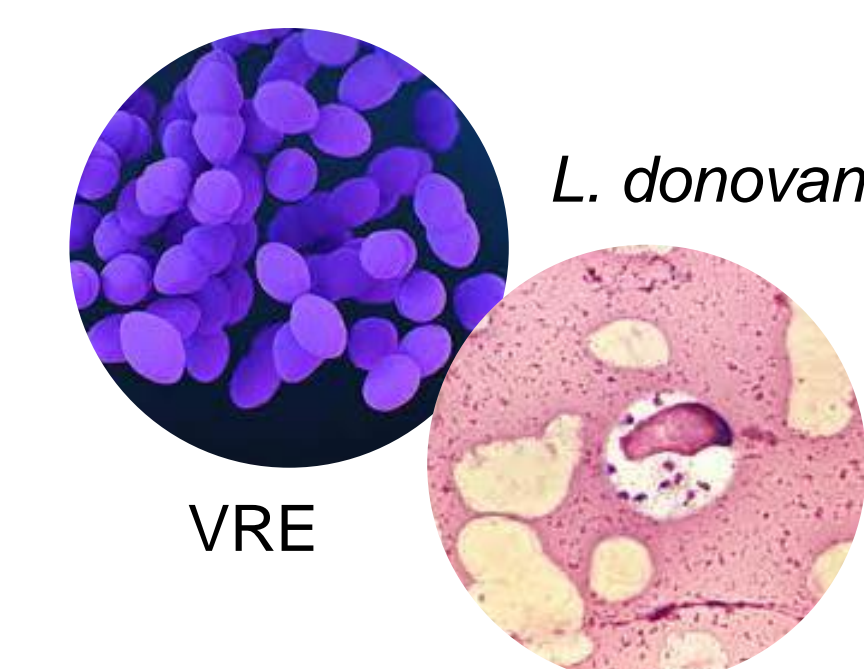
OSA ID	MRSA MIC (ug/mL)	HEK293 CC <sub>50</sub> (ug/mL)
821	2	1.6
822	2	2.9
861	>32	>32
862	>32	>32
865	4	2.1
869	>32	13.7
870	32	3.5
871	4	5.5

## ONGOING WORK

### MIB Experiments: Mechanism of Action/Toxicity



### Cross-Screening



## CONNECT WITH US!



- We're on Twitter @OSantibiotics
- Read a summary of the project on the [wiki](#)
- Find details to join our weekly meetings on the [Issues page](#)



## ACKNOWLEDGEMENTS

