Synthesis and antimicrobial evaluation of 1,2,3-triazole containing phenanthridines

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Quaternary Ammonium Compounds Are Widely Used as Antimicrobial Agents

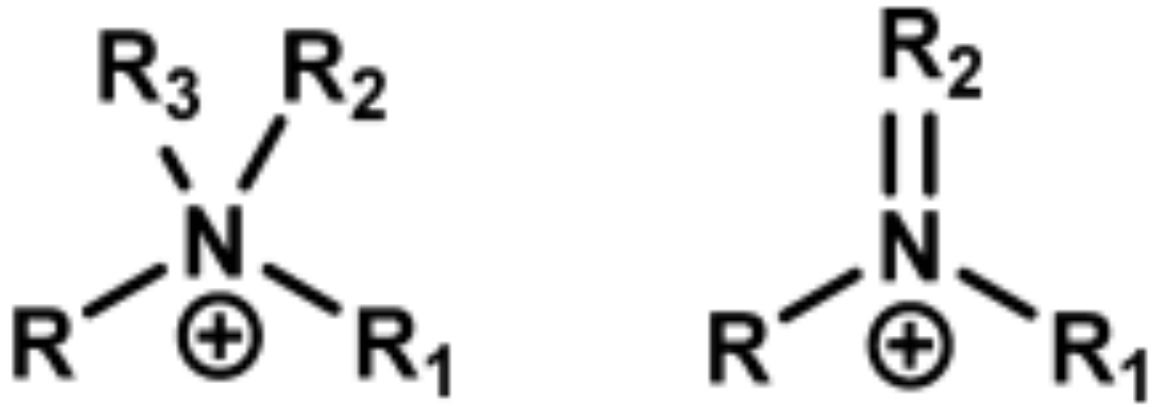
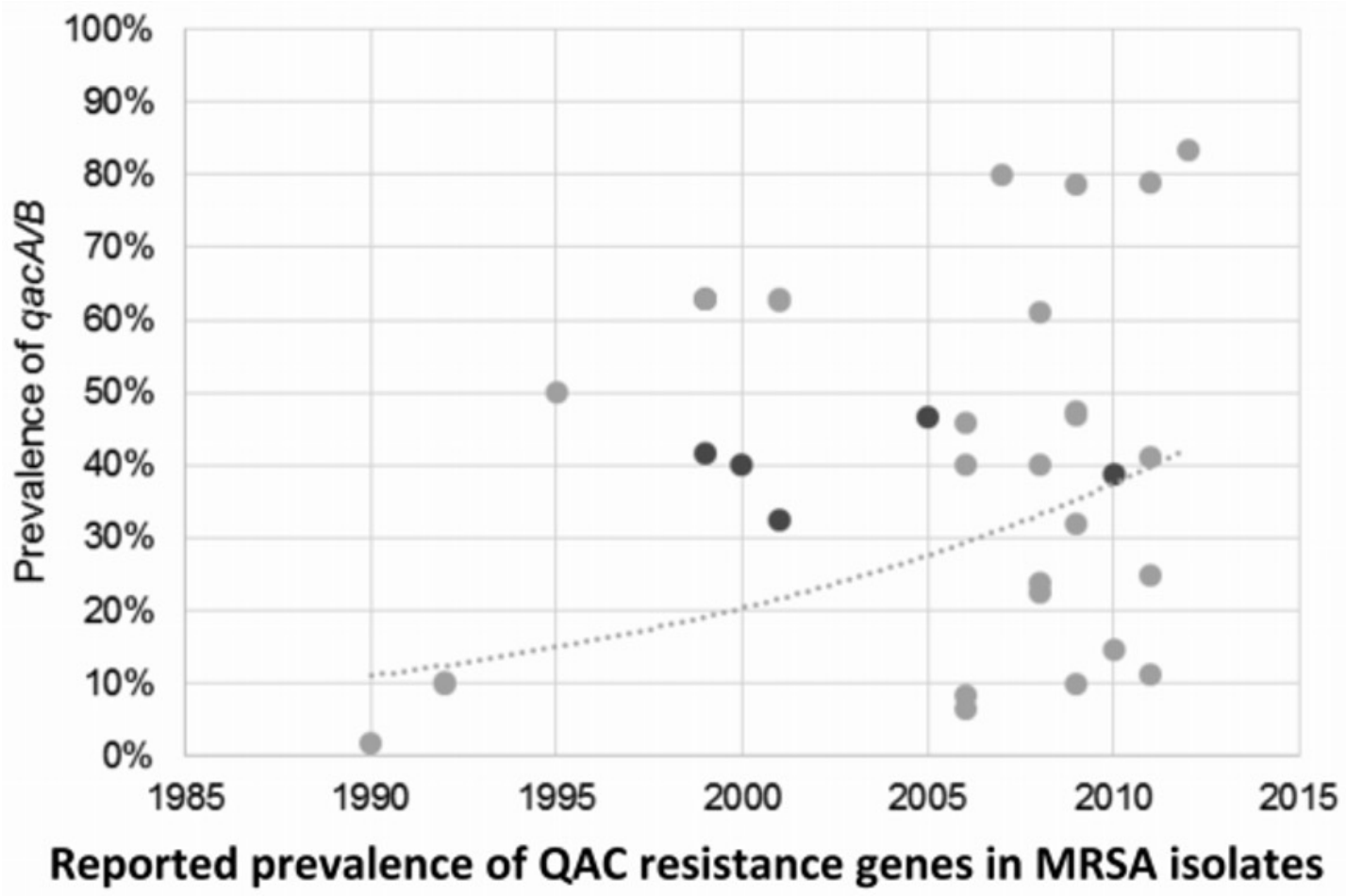


Figure 1. General structure of QACs.

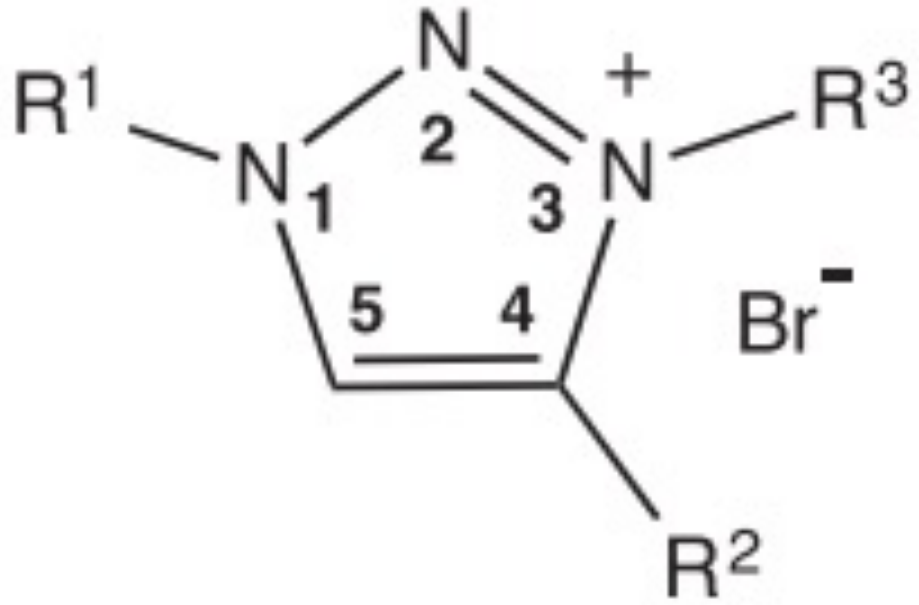
Jennings *et al.* 2019

Need for Development of Novel Antimicrobial Compounds

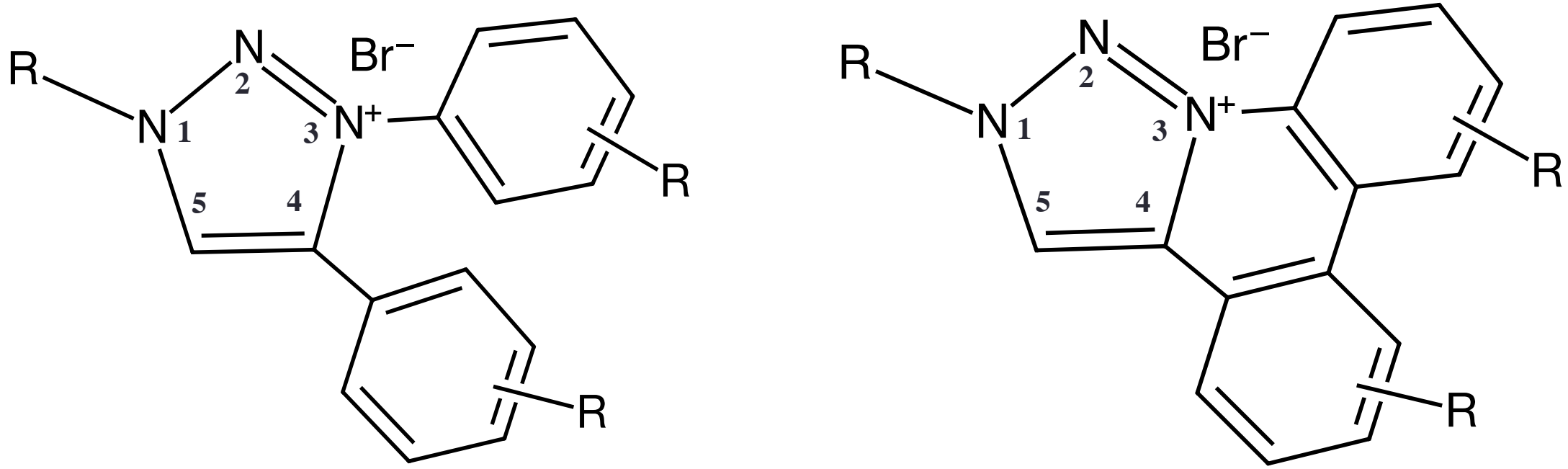


Jennings *et al.* 2019

Previous Work in the Fletcher Lab

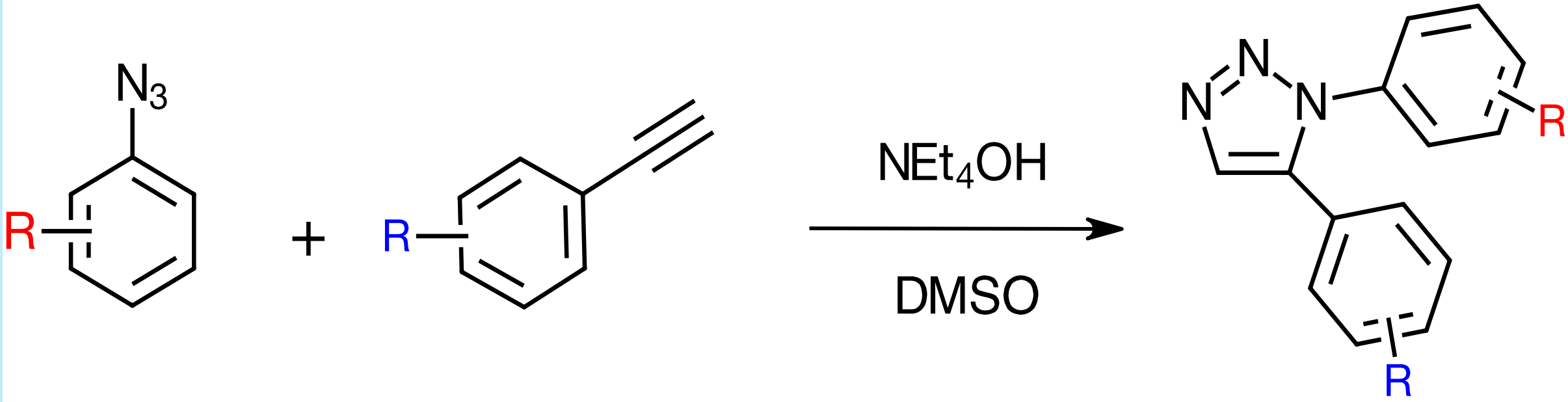


Fletcher *et al.* 2018



Objective: to synthesize fused and nonfused 1,2,3-triazolium salt analogs and investigate their antimicrobial properties.

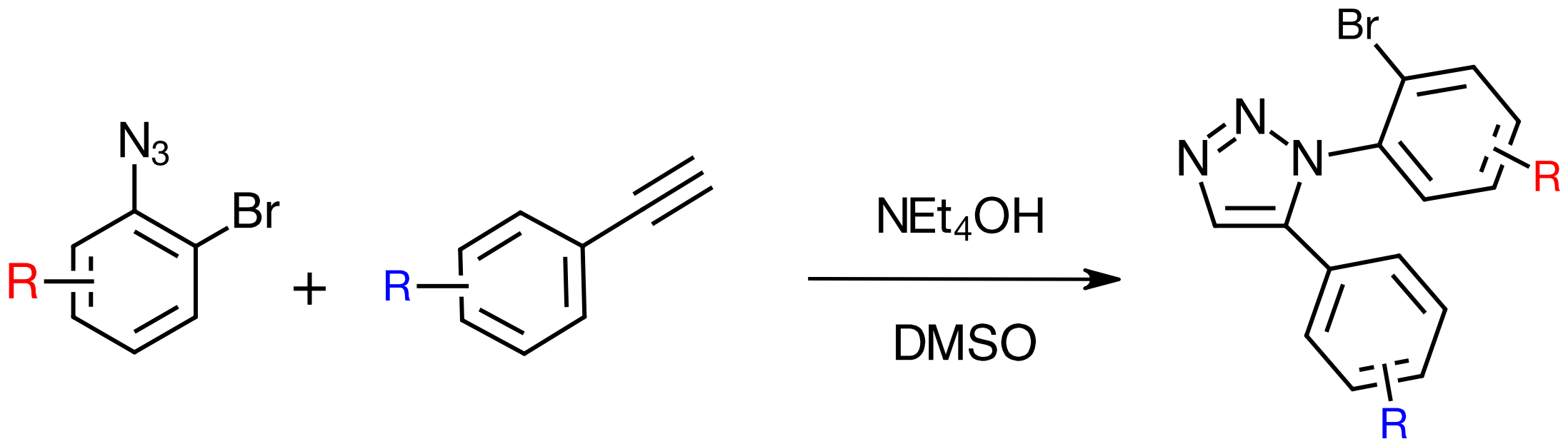
Click Cycloaddition Reaction: Nonfused



R: t-Butyl, Cl, Cl_2, or H.

R: t-Butyl, Cl, Cl_2, or H.

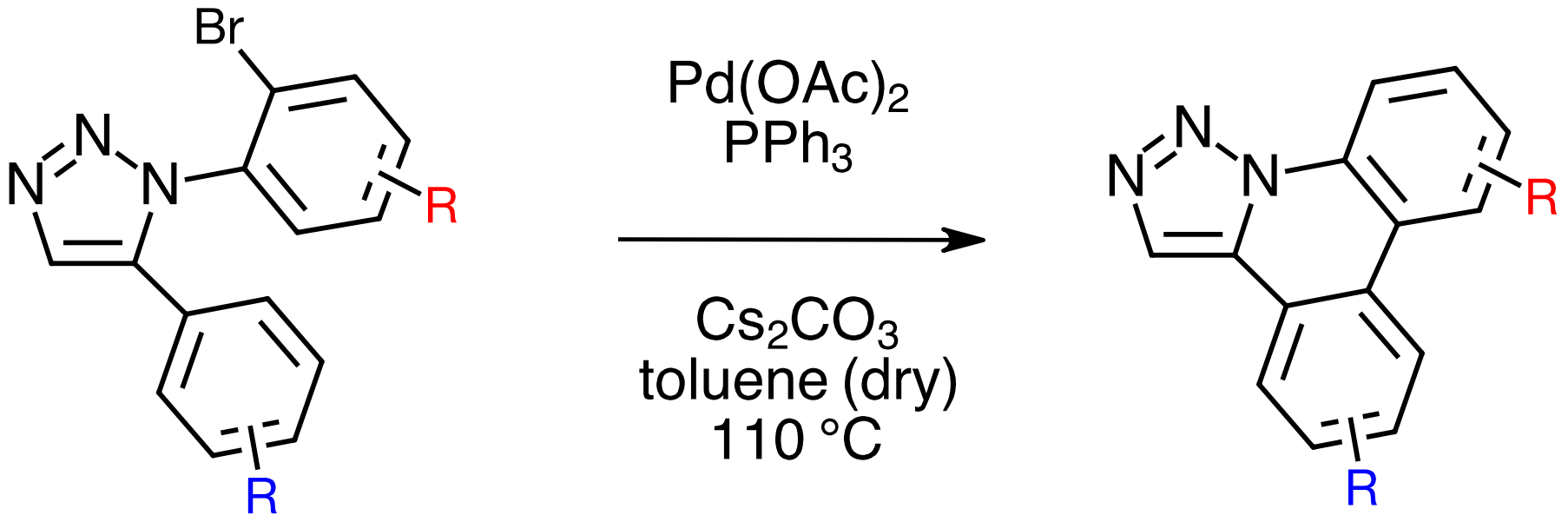
Click Cycloaddition Reaction: Fused



R: t-Butyl, Cl, Cl_2, or H.

R: t-Butyl, Cl, Cl_2, or H.

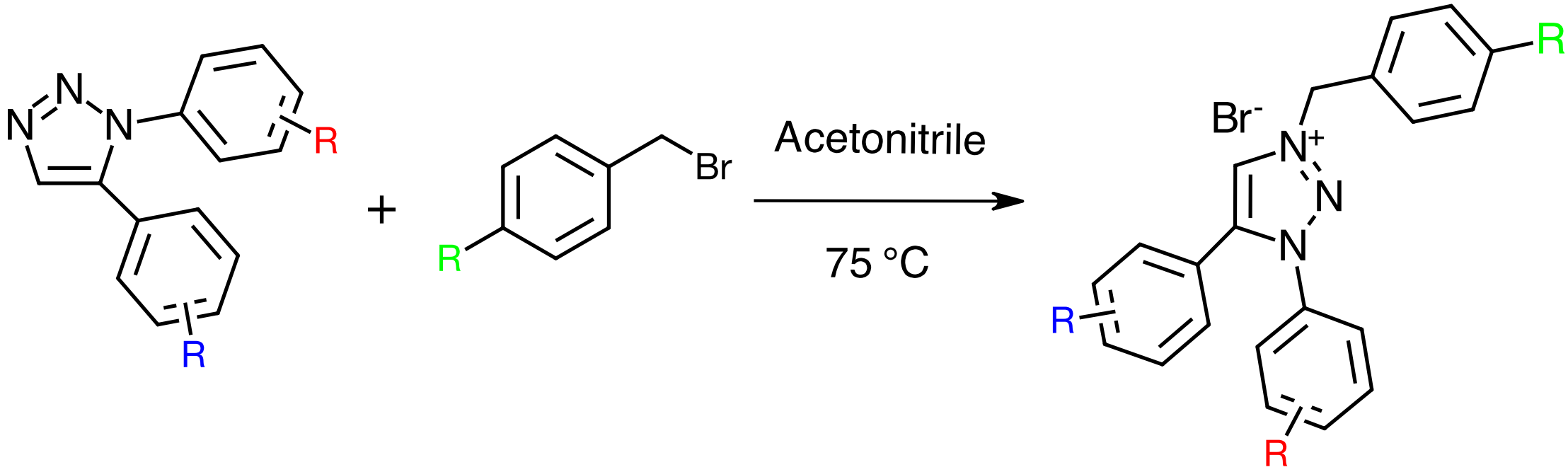
Fusion Reactions



R: t-Butyl, Cl, Cl_2, or H.

R: t-Butyl, Cl, Cl_2, or H.

Salt Reaction: Unfused

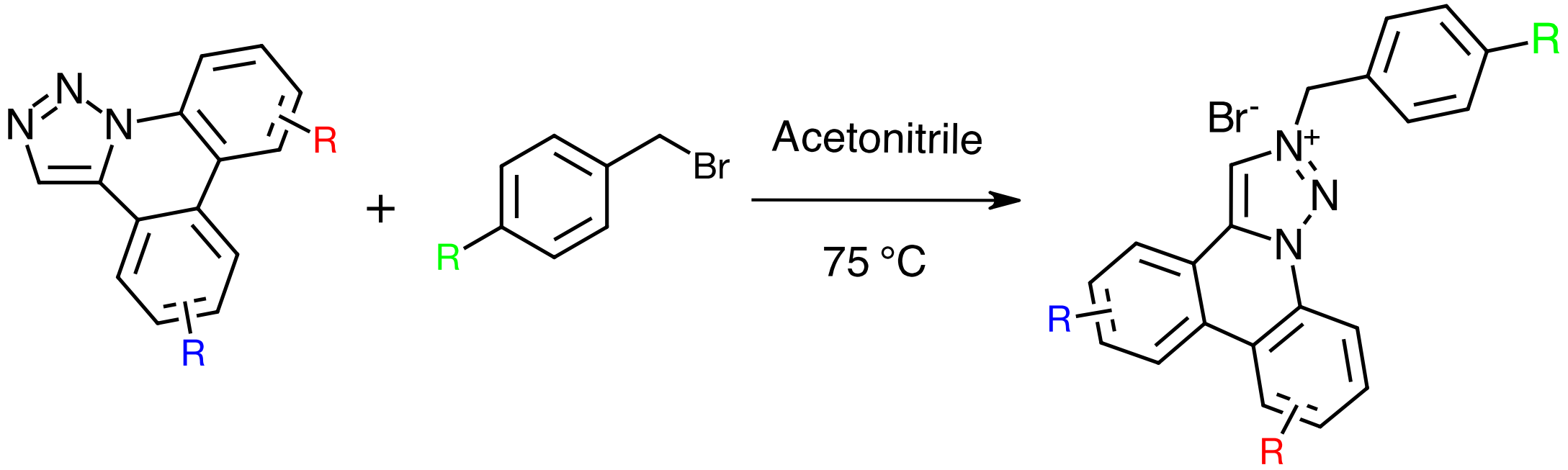


R: t-Butyl, Cl, Cl_2, or H.

R: t-Butyl, Cl, Cl_2, or H.

R: t-Butyl or H.

Salt Reaction: Fused

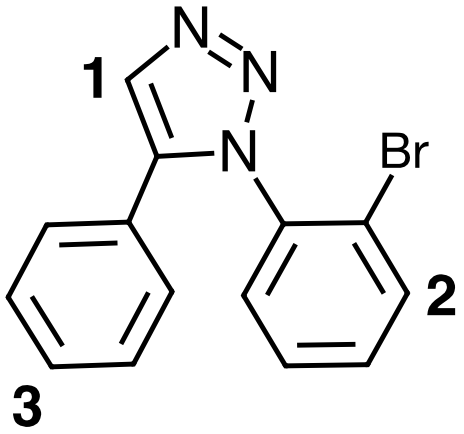


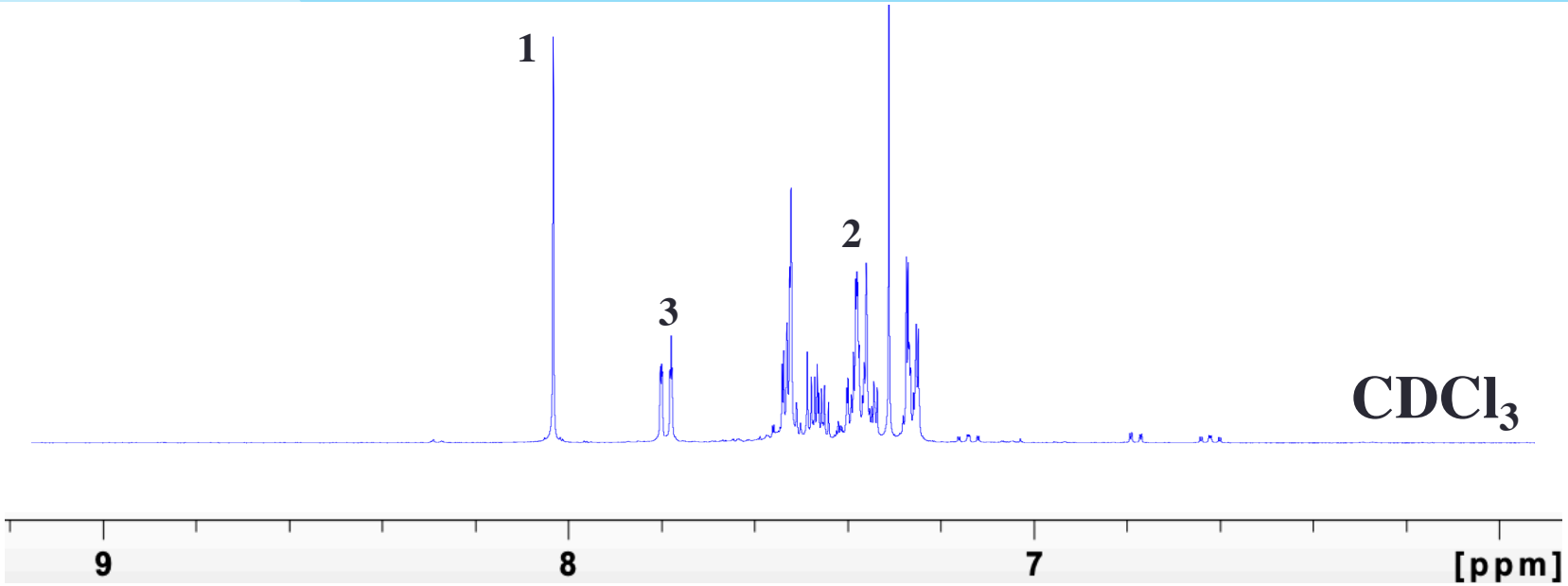
R: t-Butyl, Cl, Cl_2, or H.

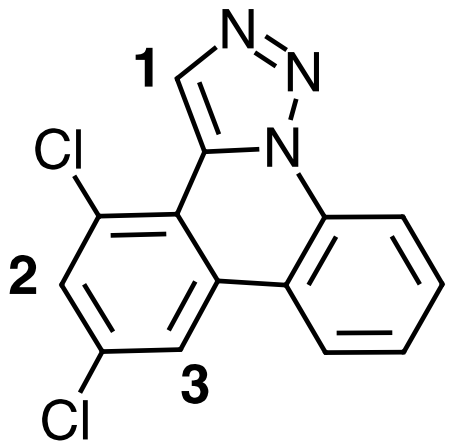
R: t-Butyl, Cl, Cl_2, or H.

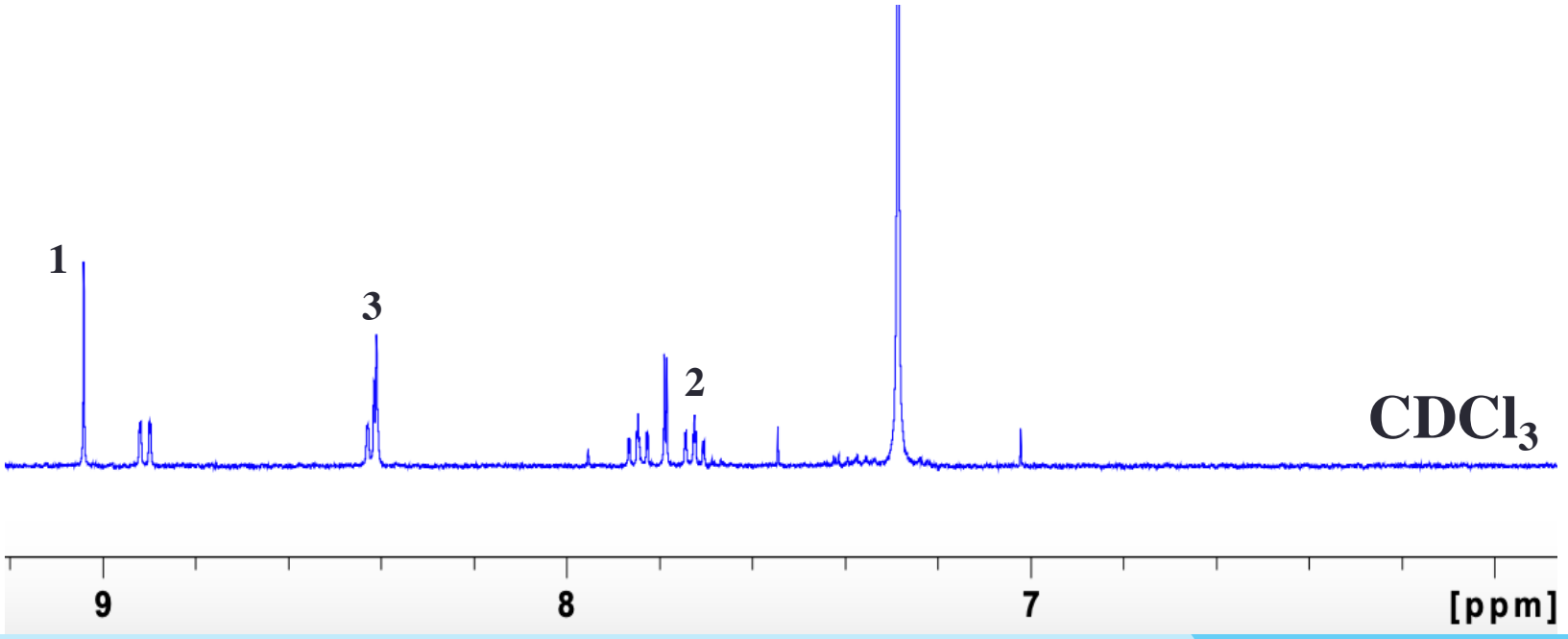
R: t-Butyl or H.

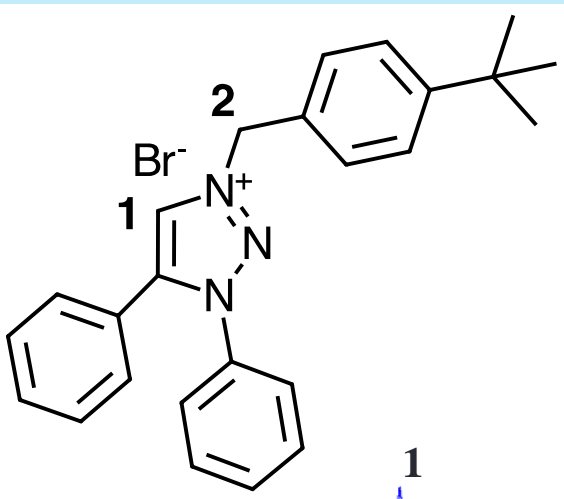
^{1}H NMR Product Analysis Examples

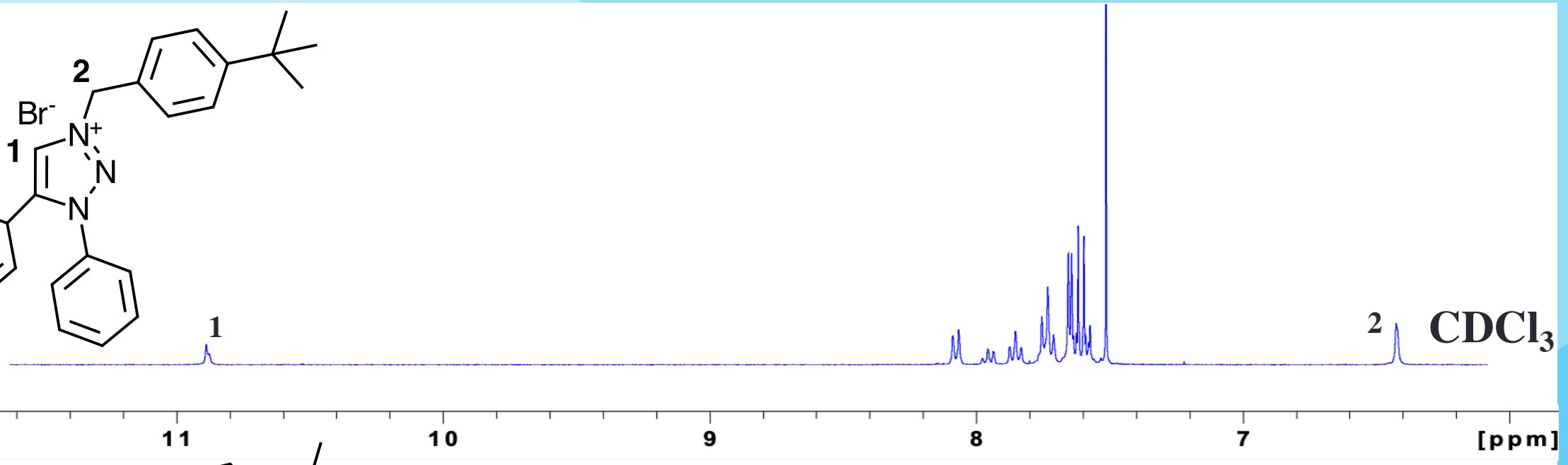

N
N
1
N
Br
2
3

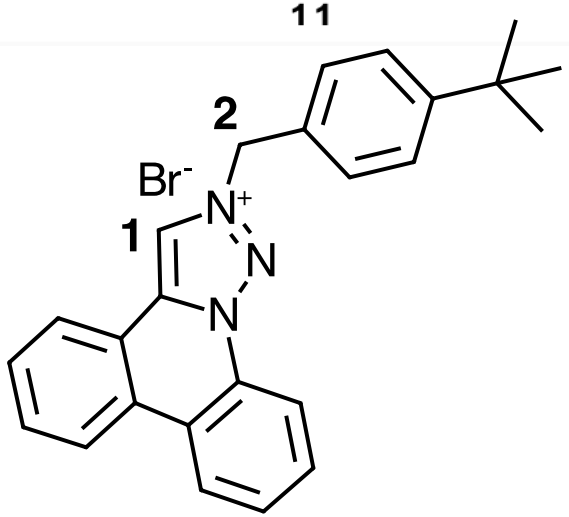

1
3
2
CDCl3
9
8
7
[ppm]

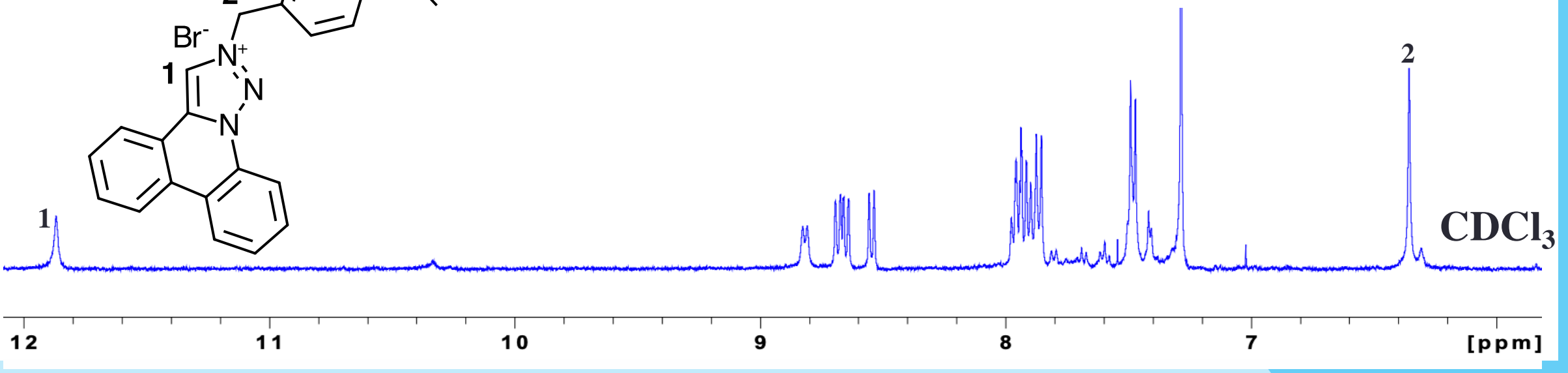

N
N
1
Cl
N
2
3
Cl


1
3
2
CDCl3
9
8
7
[ppm]


2
Br-
N+
1
N
N

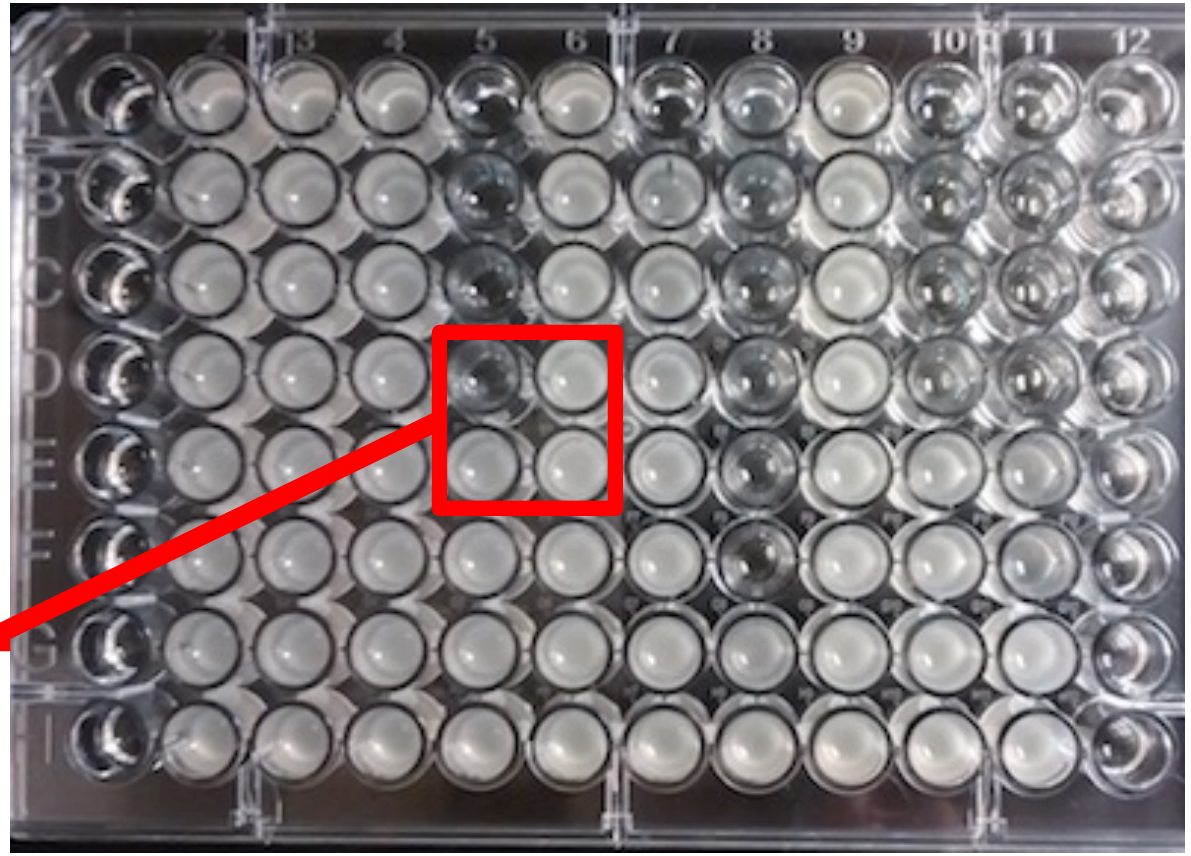

1
2
CDCl3
12
11
10
9
8
7
[ppm]


2
Br-
N+
1
N
N


1
2
CDCl3
12
11
10
9
8
7
[ppm]

Minimum Inhibitory Concentration (MIC) Assay

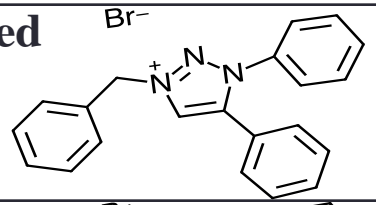
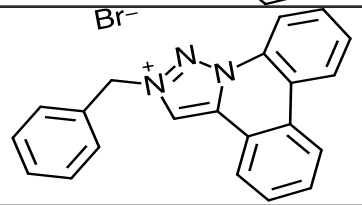
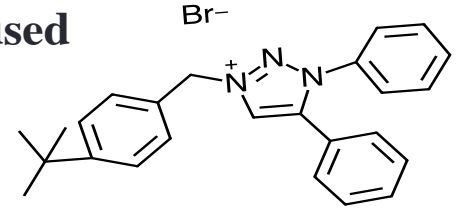
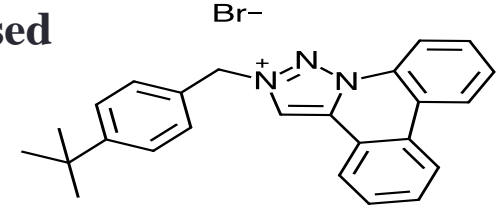
Turbidity (cloudiness) shows microbe growth, while transparency means there is inhibition of growth.

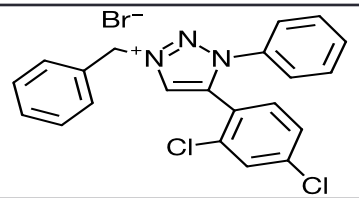
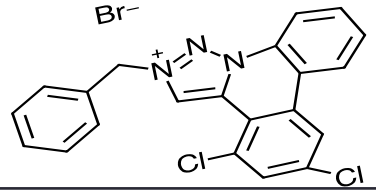
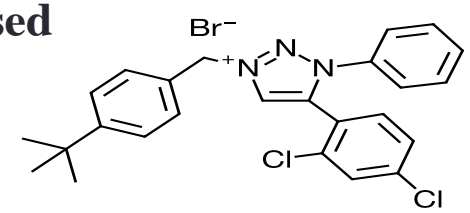
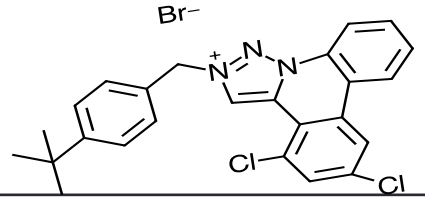


Conc. (µM)
250
125
62
31
16
8
4
2

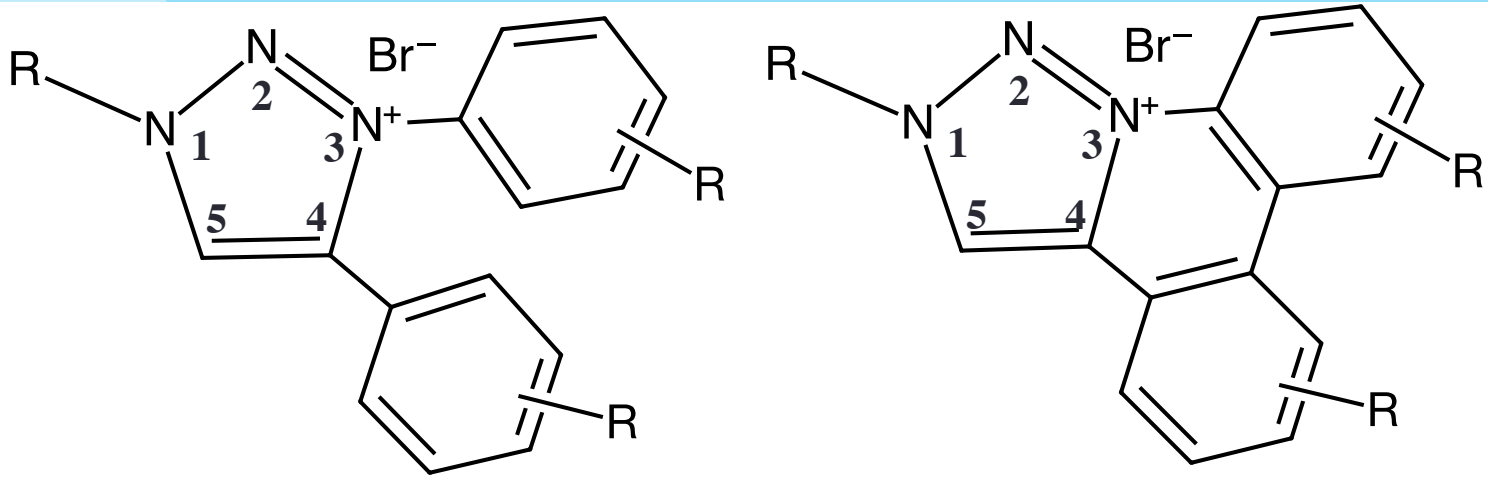
12 X 8 96 Well Plate Assay.

Fused-Ring Phenanthridine Analogs Generally Showed Increased MIC Potency

Compound	Yield	Minimum Inhibitory Concentration (μM)					
		Gram (+)		Gram (-)		Yeast	
		B. sub	S. epid	E. aero	E. coli	C. alb	S. cerv
Unfused 	73%	>250	250	>250	>250	>250	>250
Fused 	55%	62	6.2	>250	>250	>250	250
Unfused 	88%	25	6.2	>250	>250	>250	250
Fused 	45%	6.2	0.8	125	62	250	62

Compound	Yield	Minimum Inhibitory Concentration (μM)					
		Gram (+)		Gram (-)		Yeast	
		B. sub	S. epid	E. aero	E. coli	C. alb	S. cerv
Unfused 	89%	250	62	>250	250	>250	>250
Fused 	21%	12.5	3.1	>250	250	>250	250
Unfused 	86%	6.2	6.2	>250	250	125	62
Fused 	18%	3.1	0.4	250	16	250	62
Benzalkonium chloride		0.4	0.2	125	62	31	4

Conclusions



- Fused-ring chloro-substituted analogs were significantly more potent than their non-fused counterparts.
- Analogs possessing 4-tert-butylbenzyl substituents at the N3 position had the strongest antimicrobial potency.

Future Directions

- MICs of chloro substituted analogs
- Using the knowledge of the chloro analogs in other studies

Acknowledgements

- Dr. James Fletcher
- Eilidh Chowanec, Laura Cogua, Johnny Zigmond
- INBRE Program
- NIH for grant 2P20GM103427-14A1

Questions?