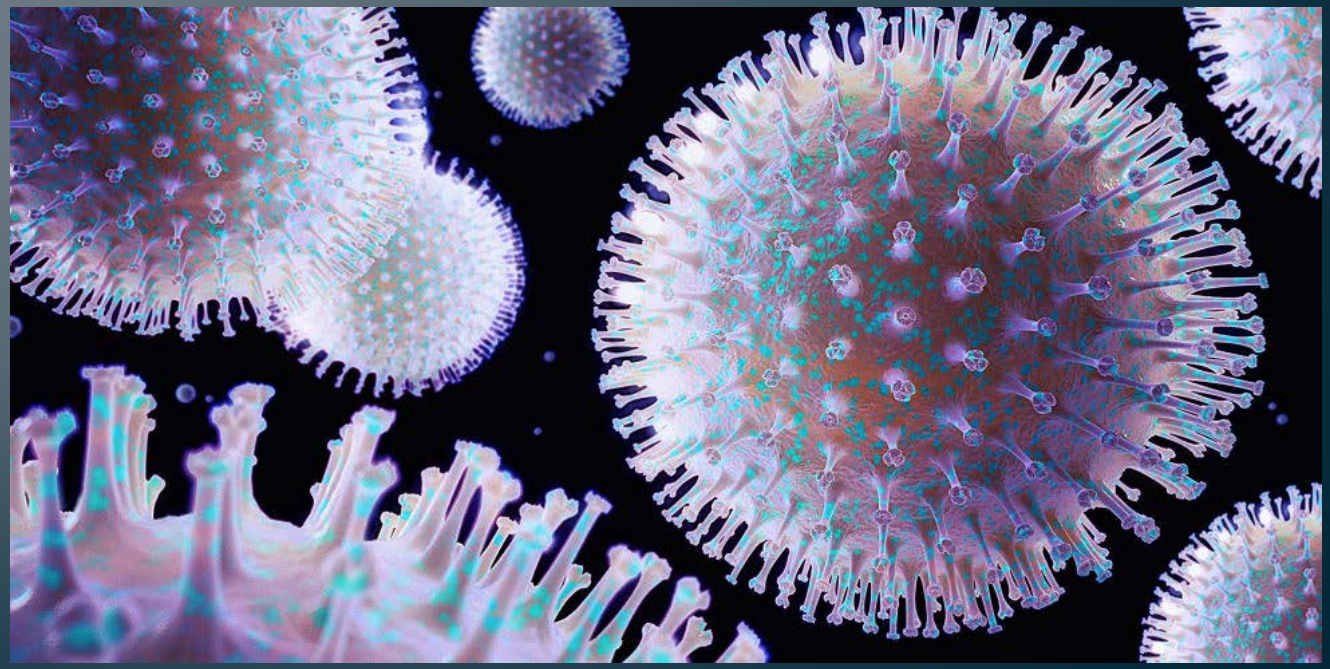
Synthesis, Antibacterial Properties and Molecular Modeling Studies of Quinolone-Triazole Hybrids

Hitesh Honkanadavar, Dr. Siva S. Panda

Current Problem

- Bacterial resistance is increasing due to high levels of antibiotic use
- New antibiotics are very difficult to create
- Recycling existing clinically used antibiotics is much more efficient



Available Drugs

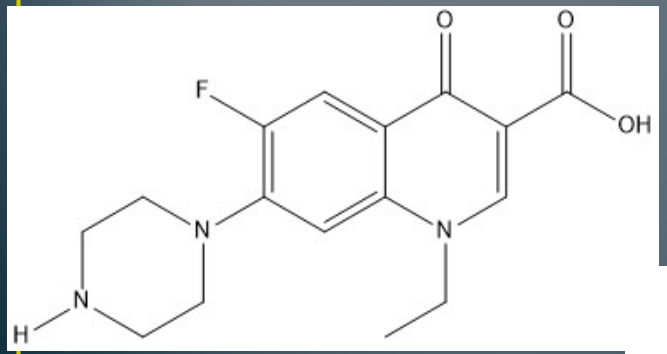
- Common antibiotics include cephalexin, ciprofloxacin, metronidazole, and azithromycin
- There are three types of antibiotics: Beta-Lactam, Macrolides, and Quinolones

Drawback/Solution

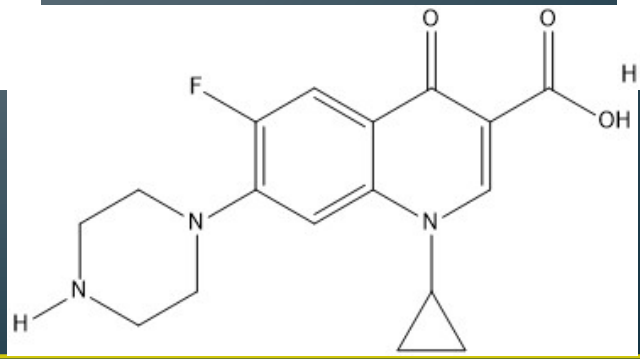
- Many antibacterial drugs are decreasing in efficacy because bacteria are becoming more resistant
- The most common solution is to increase the dosage of antibiotics given to the patient

What are we doing?

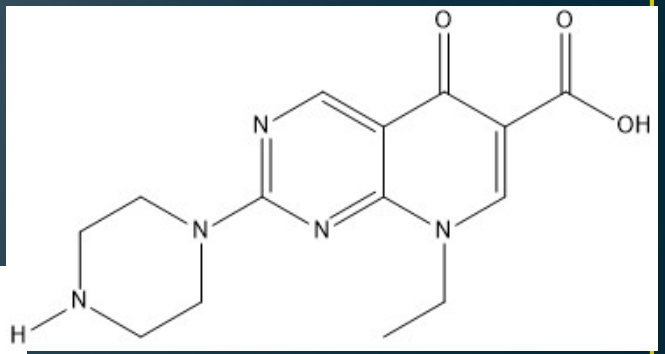
- Quinolone antibiotics: Ciprofloxacin, Norfloxacin, and Pipemedic acid
- 1,2,3-triazole containing compounds exhibit anti-inflammatory, anti-tumor, and anti-bacterial properties



Norfloxacin

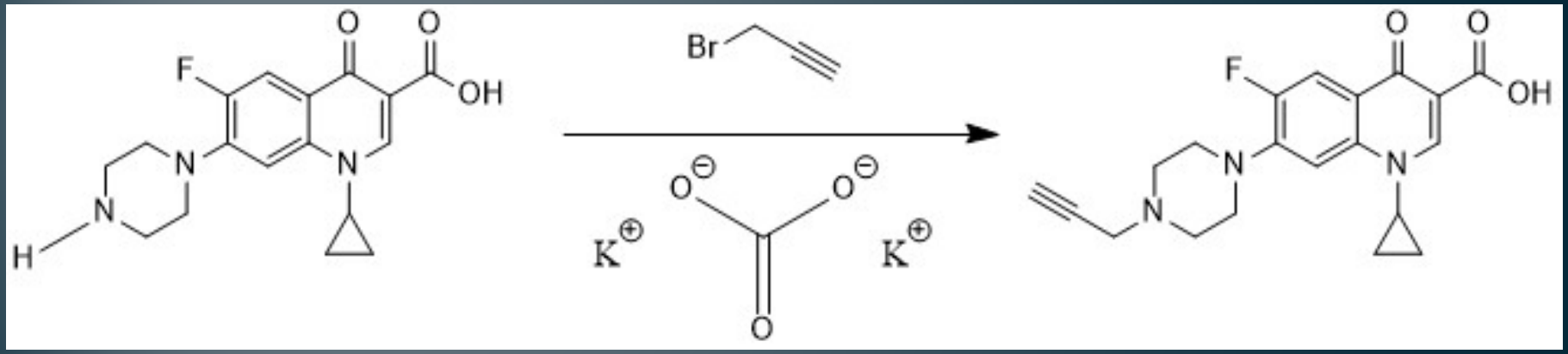


Ciprofloxacin



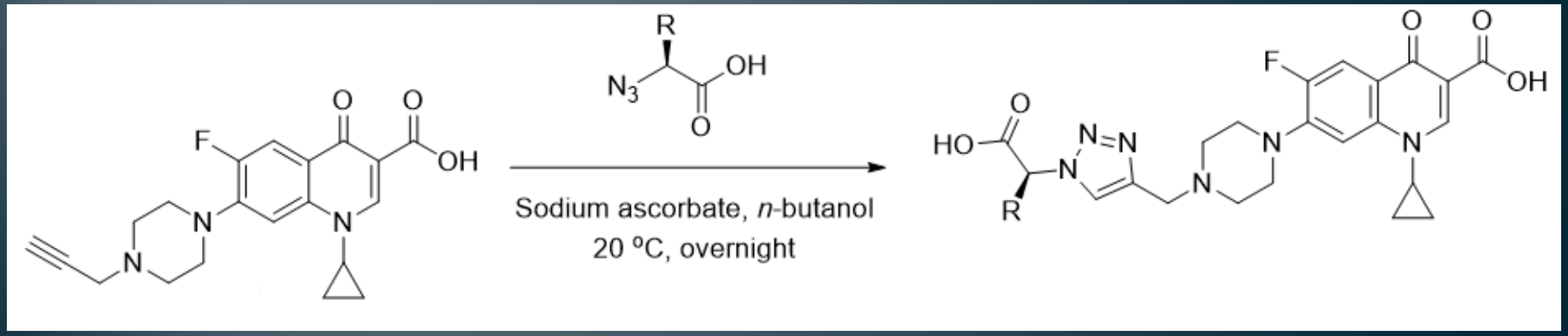
Pipemedic Acid

How did we do this?

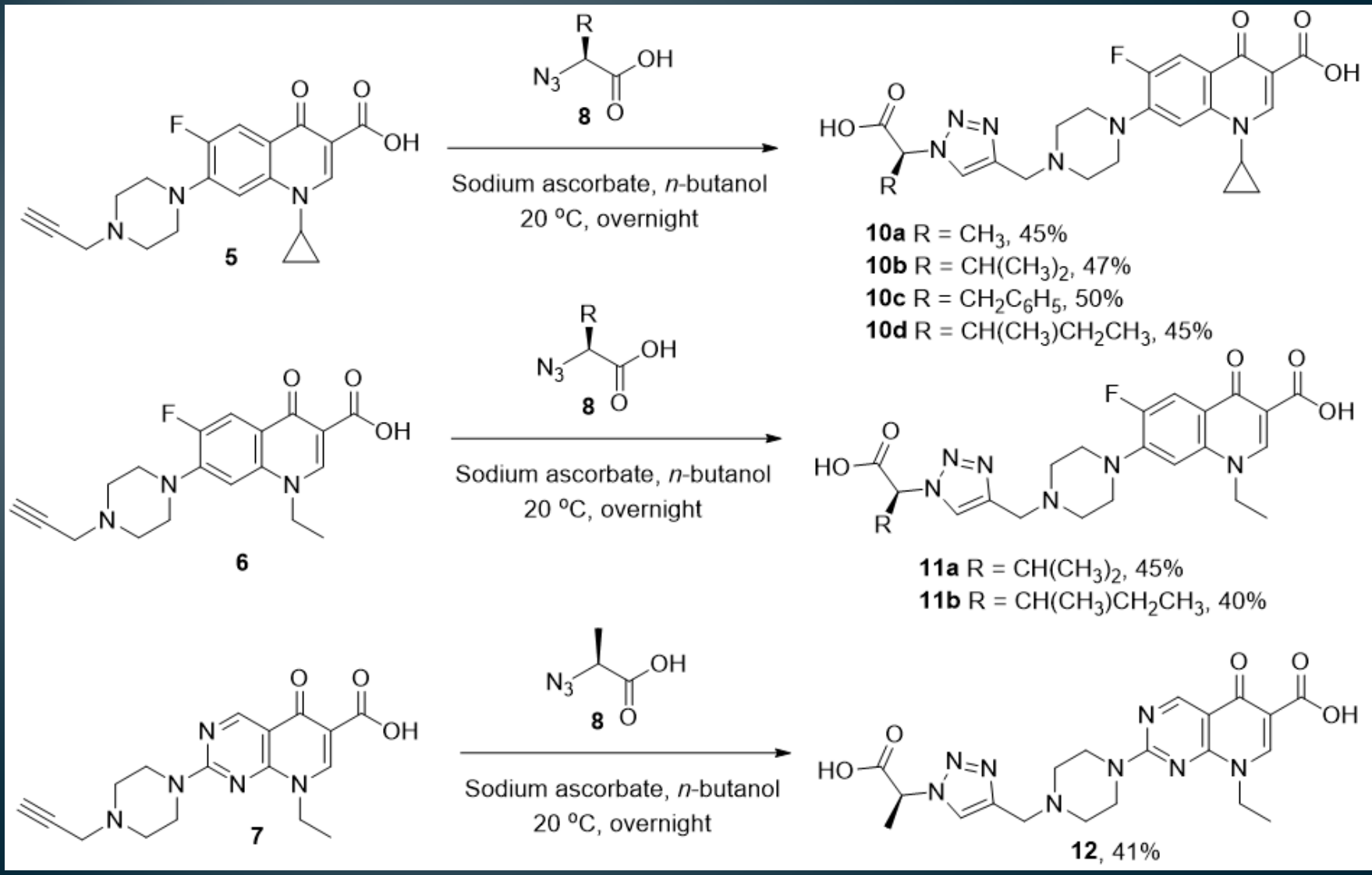


Click Chemistry

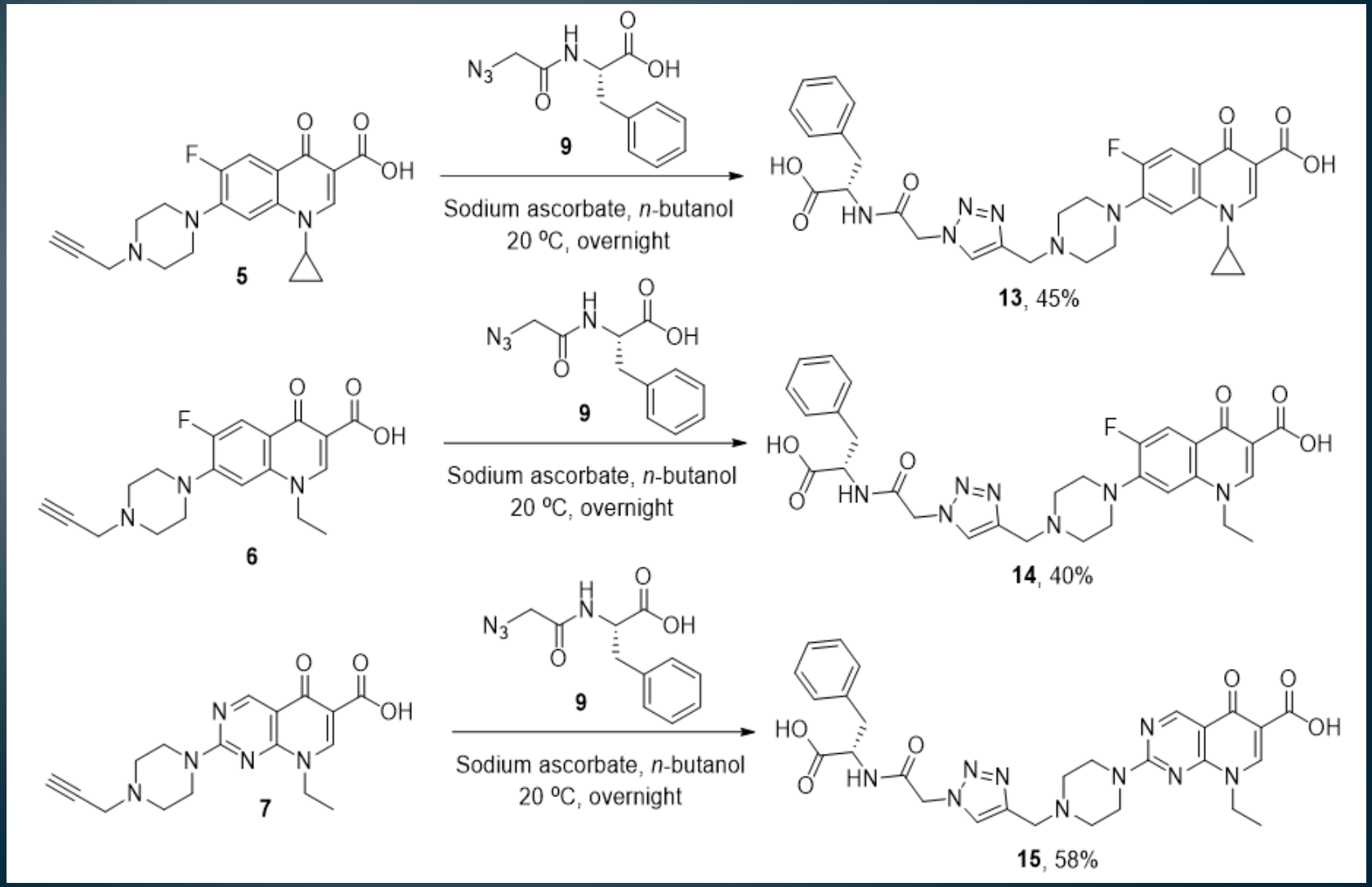
- High yielding reactions that are easy to conduct
- Designed to mimic natural processes



Products: Scheme 1

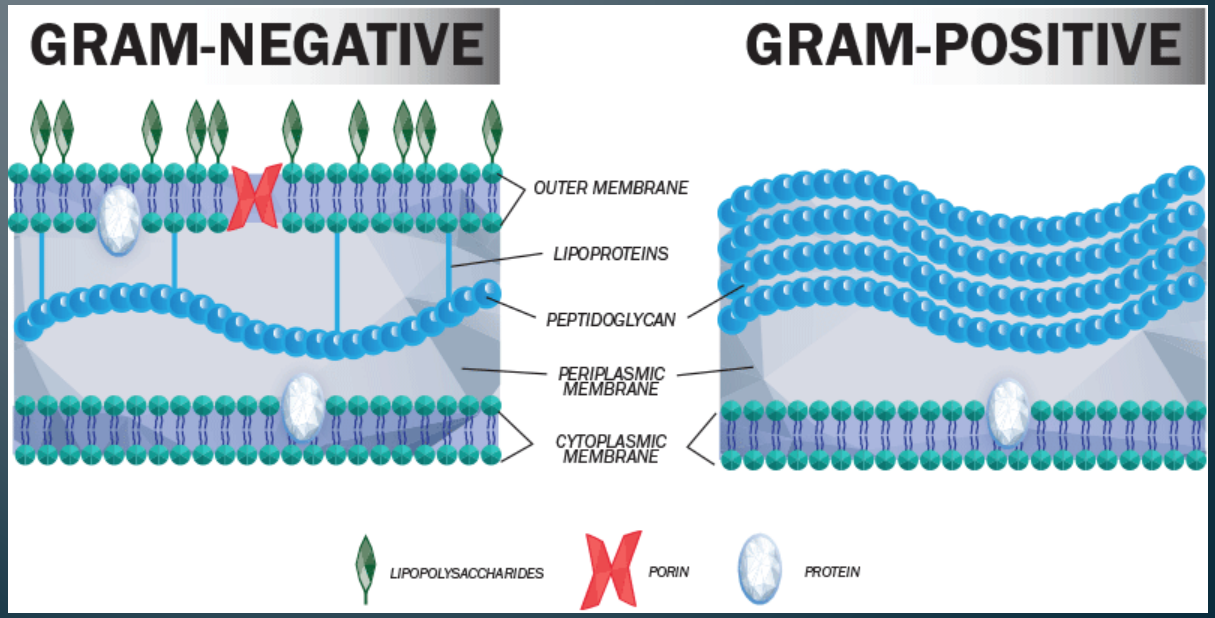


Products: Scheme 2



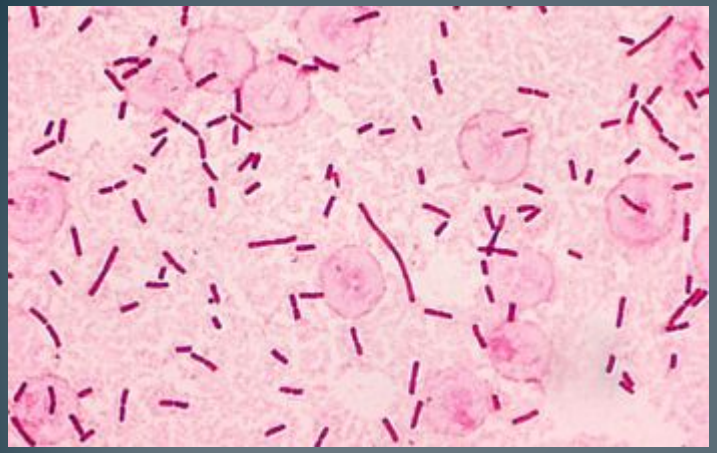
Testing of the products

- The products were tested against 2 gram negative bacteria strains (Salmonella Typhi and Pseudomonas aeruginosa) and 2 gram positive bacteria strains (Staphylococcus aureus and Streptococcus pyogenes)
- Gram Negative is more resistant than Gram Positive



Bacteria Strains

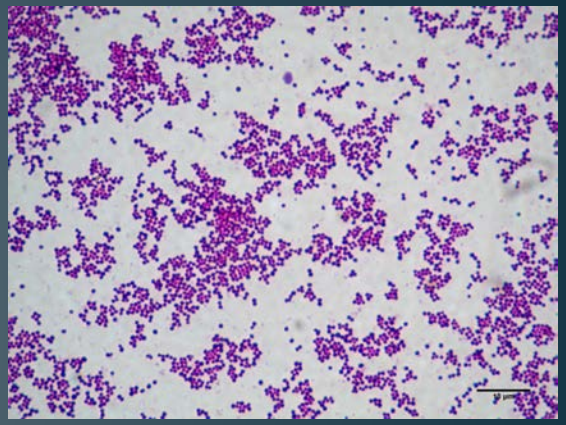
- Gram Negative



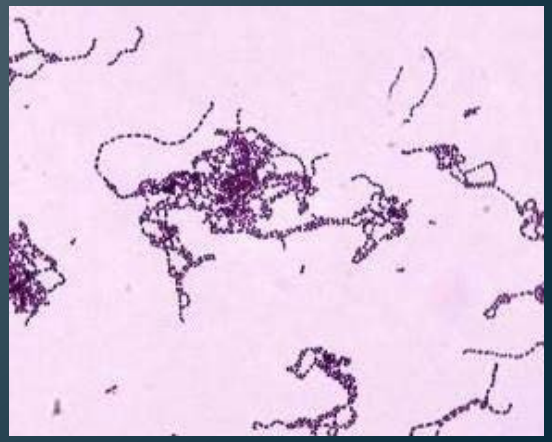
Salmonella Typhi

Pseudomonas aeruginosa

- Gram Positive



Staphylococcus aureus



Streptococcus pyogenes

Results

Entry	Compd.	Minimum inhibitory concentration (MIC), μg/mL (μM)			
		S. aureus ✚	*S. pyogenes* ✚	*S. typhi* ▭	*P. aeruginosa* ▭
1	**1**	1250 (3772.4)	1250 (3772.4)	2.4 (7.2)	4.8 (14.5)
2	**2**	1250 (3914.3)	625 (1957.2)	2.4 (7.5)	4.8 (15.0)
3	**3**	19.5 (64.3)	625 (2060.5)	NT	NT
4	**10a**	1250 (2580.0)	1250 (2580.0)	1250 (2580.0)	1250 (2580.0)
5	**10b**	1250 (2438.8)	1250 (2438.8)	1250 (2438.8)	1250 (2438.8)
6	**10c**	625 (1248.7)	625 (1248.7)	1250 (2497.4)	1250 (2497.4)
7	**10d**	1250 (2229.8)	1250 (2229.8)	1250 (2229.8)	1250 (2229.8)
8	**11a**	1250 (2373.9)	1250 (2373.9)	1250 (2373.9)	1250 (2373.9)
9	**11b**	1250 (2429.3)	625 (1214.6)	1250 (2429.3)	625 (1214.6)
10	**12**	625 (1369.2)	625 (1369.2)	1250 (2738.5)	625 (1369.2)
11	**13**	1250 (2023.8)	1250 (2023.8)	1250 (2023.8)	1250 (2023.8)
12	**14**	625 (1032.0)	625 (1032.0)	1250 (2064.0)	1250 (2064.0)
13	**15**	1250 (2120.0)	1250 (2120.0)	1250 (2120.0)	1250 (2120.0)

Ciprofloxacin

	Entry	Compd.	Minimum inhibitory concentration (MIC), μg/mL (μM)			
			S. aureus ✚	*S. pyogenes* ✚	*S. typhi* ▭	*P. aeruginosa* ▭
Ciprofloxacin	1	**1**	1250 (3772.4)	1250 (3772.4)	2.4 (7.2)	4.8 (14.5)
Scheme 1 Hybrid	4	**10a**	1250 (2580.0)	1250 (2580.0)	1250 (2580.0)	1250 (2580.0)
Scheme 1 Hybrid	5	**10b**	1250 (2438.8)	1250 (2438.8)	1250 (2438.8)	1250 (2438.8)
Scheme 1 Hybrid	6	**10c**	625 (1248.7)	625 (1248.7)	1250 (2497.4)	1250 (2497.4)
Scheme 1 Hybrid	7	**10d**	1250 (2229.8)	1250 (2229.8)	1250 (2229.8)	1250 (2229.8)
Scheme 2 Hybrid	11	**13**	1250 (2023.8)	1250 (2023.8)	1250 (2023.8)	1250 (2023.8)

Norfloxacin

	Entry	Compd.	Minimum inhibitory concentration (MIC), μg/mL (μM)			
			S. aureus ✚	*S. pyogenes* ✚	*S. typhi* ▭	*P. aeruginosa* ▭
Norfloxacin	2	**2**	1250 (3914.3)	625 (1957.2)	2.4 (7.5)	4.8 (15.0)
Scheme 1 Hybrid	8	**11a**	1250 (2373.9)	1250 (2373.9)	1250 (2373.9)	1250 (2373.9)
Scheme 1 Hybrid	9	**11b**	1250 (2429.3)	625 (1214.6)	1250 (2429.3)	625 (1214.6)
Scheme 2 Hybrid	12	**14**	625 (1032.0)	625 (1032.0)	1250 (2064.0)	1250 (2064.0)

Pipemedic Acid

	Entry	Compd.	Minimum inhibitory concentration (MIC), μg/mL (μM)			
			S. aureus ✚	*S. pyogenes* ✚	*S. typhi* ▭	*P. aeruginosa* ▭
Pipemedic Acid	3	**3**	19.5 (64.3)	625 (2060.5)	NT	NT
Scheme 1 Hybrid	10	**12**	625 (1369.2)	625 (1369.2)	1250 (2738.5)	625 (1369.2)
Scheme 2 Hybrid	13	**15**	1250 (2120.0)	1250 (2120.0)	1250 (2120.0)	1250 (2120.0)

Results

- Addition of the triazole ring mildly enhanced the antibacterial properties of the antibiotics against the gram positive strains of bacteria
- There was no improvement of antibacterial properties against the gram negative strains of bacteria

Future Studies

- More quinolones can be experimented with triazole rings
- Triazole rings can also be introduced into Beta-Lactam and Macrolide Antibiotics
- Other pharmacophoric compounds can be substituted with triazole rings on antibiotics

Acknowledgements

- Dr. Siva S. Panda
- Sean Thomas
- Honor Society of Phi Kappa Phi

Questions?