Synthesis and Structure-Activity Relationship Study of Novel Nitrodiphenylurea Antibiotics

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Abstract

According to the World Health Organization, tuberculosis (TB) is the leading cause of death by infectious disease in the world. Tuberculosis is caused by the bacteria *Mycobacterium tuberculosis* and occurs globally. Additionally, in 2017, TB was reported in all 50 states. Due to the scope of TB, strict observation of patients is required to ensure adherence to the current drug regimen. However, most reported cases are in developing countries where proper care is difficult. With the emergence of multidrug-resistant TB exhibiting resistance to current treatments, novel antibiotics are needed urgently. Recently, our lab discovered a family of diphenyl ureas that exhibit antimicrobial activity against several bacterial strains, including *Mycobacterium*. Based on our lab's previous results, we have synthesized several diphenyl urea derivatives to examine their structure-activity relationship. Herein, we report the synthesis of the diphenyl ureas with varying nitro positions, chain lengths, and R-groups.

Background

- Globally, it is estimated that about 2 billion people are infected with tuberculosis (TB)
- In 2017, 10 million new people became ill with TB
  - 1.6 million of these people died
- Leading cause of death by infectious disease in the world

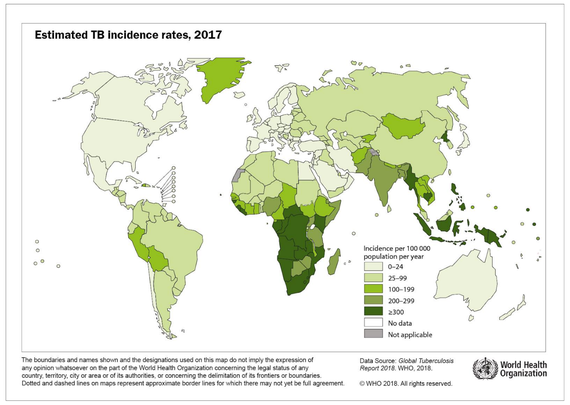


Figure 1. **Global Incidence Rates of Tuberculosis**

Treatment & Challenges

- Currently, the most effective TB treatment is a six-month course of four antibiotics
  - Isoniazid, rifampicin, pyrazinamide, and ethambutol
- Improper treatment can lead to MDR-TB
- Resistant to rifampin and isoniazid
- A six-month treatment course requires strict observation of patients to ensure they adhere to the drug regimen
- Proper care is difficult in developing countries because of the lack of medical support
- Side effects and toxicity are common

Delamanid

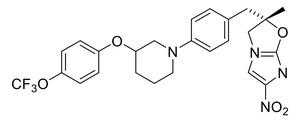
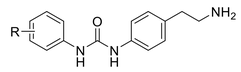


Figure 2. **Delamanid**

- Delamanid was recently approved to treat MDR-TB
- Similar to isoniazid, it inhibits the synthesis of mycolic acid in the bacteria's cell wall
- While we are unsure of the exact target of our antibiotics, the structural similarities between our lead nitro functionalized DPU and delamanid suggest that it may also target the bacteria's ability to make the cell wall

Previous Work

- Previously discovered a family of diphenyl ureas
- Kill zone assay results shown below
  - Most active compounds



Urea	R	Zone (mm)	
		S. aureus	*E. coli*
31	4-bu ester	11.8	9.0
29	--	8.0	8.5
24	3-Cl	8.7	10.5
22	4-nitro	8.0	9.0
21	3-nitro	7.8	33.0
12	4-t-bu	11.3	10.0
11	4-i-pr	6.7	11.2
07	3,4-dimethyl	10.7	9.5

Figure 3. **Antimicrobial Activity of Diphenyl Ureas**

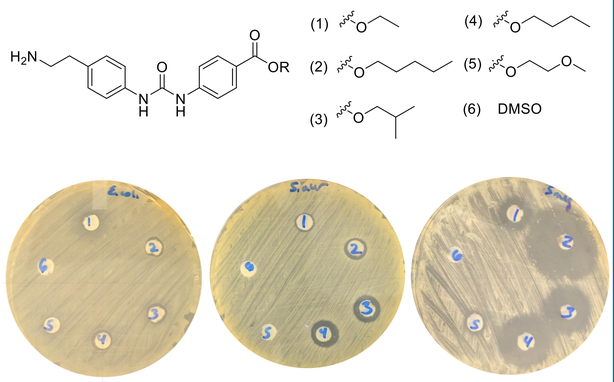


Figure 4: **Ester Derivatives**
Kill zone assays results from previous work done in our lab. Tests conducted on *E. coli*, *S. aureus*, and *Mycobacterium* show the potency of the 5 ester derivatives. Work completed by Phil Dietz and Dr. Morgan.

Hypothesis

Using our previous results, we believe we can synthesize novel diphenyl urea derivatives in order to build a structure-activity relationship and create more potent antibiotics against *Mycobacterium tuberculosis*

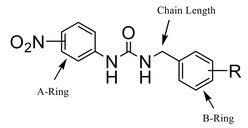


Figure 5. **Proposed Nitro-DPU Modifications**

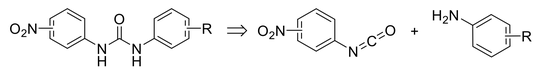


Figure 6. **Retro Synthesis of Diphenyl Urea Compounds**
General synthetic plan for making the nitro functionalized diphenyl urea compounds

Synthesis of DPU Derivatives

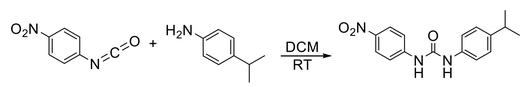


Figure 7. **Typical R-Group Nitro-DPU Synthesis**
Starting with commercially available 4-nitrophenyl isocyanate and 4-isopropylaniline, the diphenyl urea can be prepared in one step
Percent yield: 86%

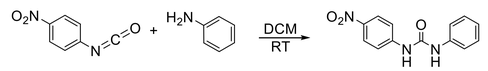


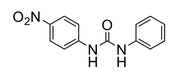
Figure 8. **Typical Chain Length Nitro-DPU Synthesis**
Starting with commercially available 4-nitrophenyl isocyanate and aniline, the diphenyl urea can be prepared in one step
Percent yield: 96%

References

World Health Organization. Global Tuberculosis Report. France: World Health Organization, 2018.

Sambhaji Y. Dhumal, Amarsinh R. Deshmukh, Manisha R. Bhosle, Vijay M Khedkar, Laxman U. Nawale, Ramrao A. Mane. "Synthesis and antitubercular activity of new 1,3,4-oxadiazoles bearing pyridyl and thiazolyl scaffolds." Bioorganic & Medicinal Chemistry Letters (2016): 3646-3651.

Spectra



Proton NMR Spectra **Carbon NMR Spectra**

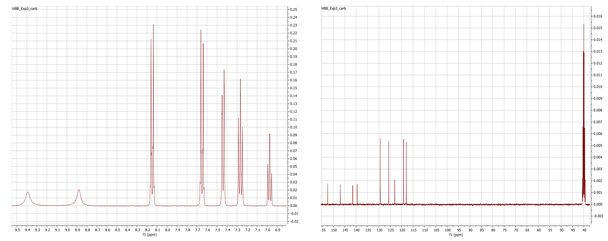
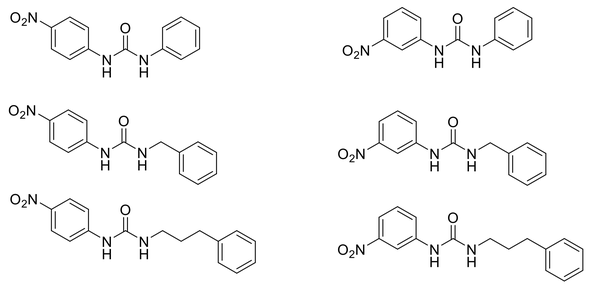


Figure 9. **NMR Spectra of Typical Chain Length Nitro-DPU Derivative**
Products verified by NMR analysis

Results

Chain Length Derivatives



R-Group Derivatives

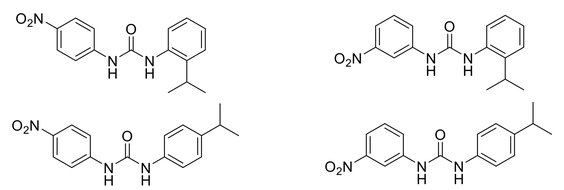


Figure 10. **Diphenyl Ureas Successfully Synthesized**
Each of the nitro functionalized diphenyl ureas made

Conclusion

A total of 10 novel nitro fictionalized diphenyl ureas were synthesized. Of these derivatives, 6 varied in chain length and 4 varied in R-groups.

Future Directions

Moving forward, we would like to finish the synthesis of our proposed nitro functionalized DPUs. Once the diphenyl ureas are successfully synthesized, they will be tested for their antimicrobial activity via kill zone assay test.

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