Scaffold Proposal Form

The Chemistry Center for Combating Antibiotic Resistant Bacteria (CC4CARB) is a NIH NIAID lead initiative. CC4CARB is an innovative chemistry center focused on the synthesis and delivery of rationally designed focused libraries to the scientific community for use in Gram-negative antibacterial drug discovery programs. The ultimate objective of CC4CARB is to create a large collection of chemical matter specifically targeting Gram-negative antimicrobial drug discovery. Your input is a valuable component in the CC4CARB program, and your time and consideration are appreciated.

Section 1. Contact Information

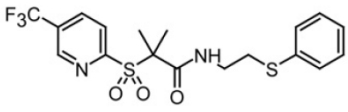
(The contact information must be fully completed.)

First Name	Name	Organization	for NIAID via RTI International
Last Name		Address	3040 Cornwallis Road
Email	monad@rti.org		
Phone No	xxx-xxx-xxxx	City	RTP State NC
		Zip/Postal Code	27709 Country USA

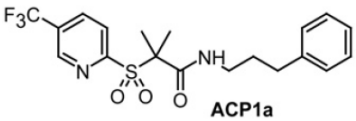
Section 2. Scaffold Proposal

(This section must be fully completed and be concisely written to support why the scaffold should be considered for inclusion into the CC4CARB library.)

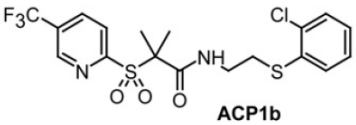
1. **Scaffold Description:** *Provide a short description of the scaffold being proposed. A sketch or ChemDraw of your proposed scaffold molecular structure is preferred. Please indicate the source of the scaffold and/or idea (literature, lab finding, screening hit, etc.), including literature references if the idea came from the literature.*



ACP1



ACP1a



ACP1b

The scaffold was identified in the literature as a potential candidate for CC4CARB

2. **Rationale for Inclusion:** *Relay a rationale (1000 words or less) with references of why your proposed scaffold is potentially effective against antibiotic resistant bacteria, Gram-negative bacteria preferred. Innovation and novelty will be prioritized if accepted.*

Substituted sulfonylpyridines have been shown to activate Caseinolytic protease subunit P (ClpP), which is a serine protease[1, 2]. ClpP plays an important role in protein homeostasis in bacteria and contributes to various developmental processes, as well as virulence[3, 4]. Activation of ClpP directly engages the bacterial protein degradation machinery and causes induction of

non-regulated protein destruction leading to cell death. Therefore, ClpP is considered as a potential drug target against Gram-positive and Gram-negative bacteria.

1. Binepal, G.; Mabanglo, M. F.; Goodreid, J. D.; Leung, E.; Barghash, M. M.; Wong, K. S.; Lin, F.; Cossette, M.; Bansagi, J.; Song, B.; Balasco Serrao, V. H.; Pai, E. F.; Batey, R. A.; Gray-Owen, S. D.; Houry, W. A., Development of Antibiotics That Dysregulate the Neisserial ClpP Protease. ACS Infect Dis 2020, 6, 3224-3236.
2. Seleem, M. A.; Rodrigues de Almeida, N.; Chhonker, Y. S.; Murry, D. J.; Guterres, Z. D. R.; Blocker, A. M.; Kuwabara, S.; Fisher, D. J.; Leal, E. S.; Martinefski, M. R.; Bollini, M.; Monge, M. E.; Ouellette, S. P.; Conda-Sheridan, M., Synthesis and Antichlamydial Activity of Molecules Based on Dysregulators of Cylindrical Proteases. J Med Chem 2020, 63, 4370-4387.
3. Gur, E.; Biran, D.; Ron, E. Z., Regulated proteolysis in Gram-negative bacteria--how and when? Nat Rev Microbiol 2011, 9, 839-48.
4. Konovalova, A.; Sogaard-Andersen, L.; Kroos, L., Regulated proteolysis in bacterial development. FEMS Microbiol Rev 2014, 38, 493-522.

3. **Known analogs (optional):** *If known, please include a description of the existing medicinal chemistry structural literature around or involving the scaffold, including key references. This could include applications outside of antimicrobial research.*

   See above references

4. **Antimicrobial Testing:** *Provide a short description of proposed or potential antimicrobial experiments, including key microbes if known. Testing can include related assays such as Gram-negative penetration or use as adjuvants with other antimicrobials (efflux pump inhibition, membrane penetration disruption, etc).*

   No current plans. Will test when NIAID testing begins.

5. **Library Design (optional):** *Provide a short description of any library design concepts based on the scaffold. A sketch or ChemDraw of a library schematic, with points of diversity (R1, R2, R3) is welcome. Library design is not required. CC4CARB chemists will actively consult with each submitter to design an Individual Library Production Plan (ILPP) for the scaffold if accepted.*

   Sulfonylpyridines have been shown to be active against Gram-negative microbes, but their potency and antimicrobial profile could be enhanced by improving the Gram-negative permeability of these structures, without losing their ClpP activity. The addition of siderophores is suggested due to the phenyl rings present in the base structures.

Section 3. Additional Documents

Please include:

- CV or NIH biosketch.
- PDFs of key references if available

Section 4. Project Support Survey

(*This section is optional. However, please support our objective and provide the contact information for colleagues that may be interested in participating in CC4CARB.)*

1. Relay colleagues that may be interested in participating in the CC4CARB.

Colleague No 1	Colleague No 2
First Name:	First Name:
Last Name:	Last Name:
Email address:	Email address:
Phone No.:	Phone No.:
Institution:	Institution:

2. How did you learn about the CC4CARB project?

Disclaimers

- Submitted scaffold proposals will be confidential; however, compounds synthesized as a result of an accepted proposal will be made public as part of the CC4CARB collection.
- A CC4CARB representative may be in contact, if additional information is needed for the proposal.
- There is no compensation for the preparation of scaffold proposals submitted to CC4CARB; however, funds are available for the preparation of scaffold library plans (ILPPs)
- No basis for claims against the U.S. Government shall arise because of a response to this project or from the Government's use of such information. The information submitted through the CC4CARB portal will be accessed and reviewed by a Scientific Advisory Board, NIH NIAID, and RTI staff.
- Information submitted through this portal will be stored on a secure RTI server, and to the extent required under the Freedom of Information Act (FOIA), the submitted information may be subject to public disclosure.