

INDIVIDUAL LIBRARY PRODUCTION PLAN-4

Scaffold: Sulfonylpyridines
Proposed by: NIAID
Date: 5/24/21



Submitted By:

Name

Email Address

Introduction

This Library Production Plan is focused on synthesis of substituted sulfonylpyridines, which may have antibacterial activities against Gram negative species. 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.

Considerable SAR has already been developed around the sulfonylpyridines resulting in leads ACP1, ACP1a and ACP1b with improved potency for ClpP activation. We plan to synthesize compounds based on these leads to improve penetration into the outer membrane of Gram negative bacteria by using three strategies: 1) Design based on eNTRY rules^{5, 6}; 2) Zwitterionic species to improve penetration through Porin channels⁷; and 3) Siderophore strategy. The overall library design is displayed in Figure 1.

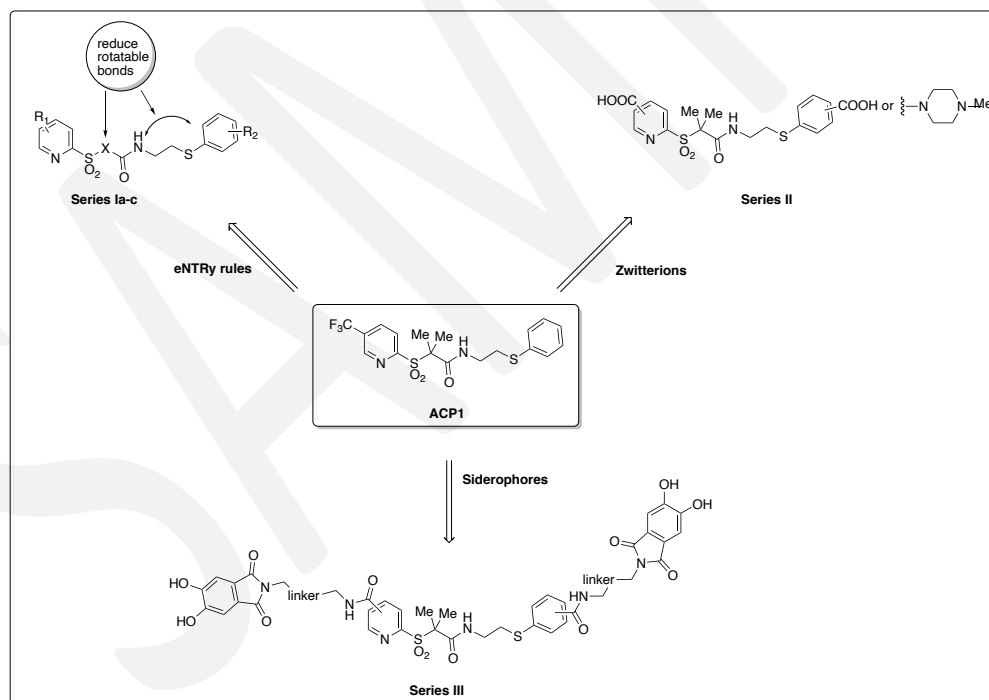


Figure 1. Proposed sulfonylpyridine library compounds

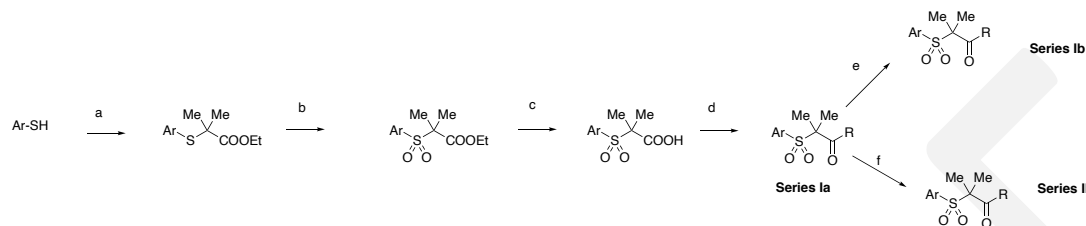
We propose to synthesize ~120 compounds with 50 mg each to allow characterization and >25 mg to be added to the CC4CARB library. All final products will be characterized by ¹H NMR, ¹³C NMR and MS, where applicable, and analyzed by HPLC to ensure >95% purity.

SAB Comments

None.

Proposed Synthesis Protocol

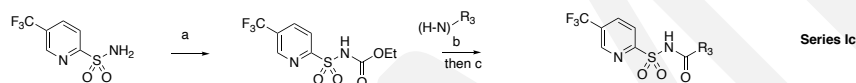
Compounds in Series Ia, Series Ib and Series II will be synthesized using a modified protocol described by Binopal et al. (Scheme 1)¹ followed by hydrogenation of the aryl nitrile (Series Ia) or hydrolysis of the aryl nitrile (Series II).



Scheme 1: Synthesis of Series Ia, Series Ib and Series II compounds

Reagents and conditions: (a) $\text{BrC}(\text{CH}_3)_2\text{COOEt}$, KOH, EtOH, reflux; (b) *m*CPBA, NaHCO_3 , DCM, 0°C -rt; (c) $\text{LiOH}\cdot\text{H}_2\text{O}$, THF/ H_2O , rt; (d) (i) PyBOP, DIPEA, DMF, rt OR $(\text{COCl})_2$, DCM, cat. DMF, 0°C -rt; (ii) H-R, NEt_3 , DCM, reflux; (e) Raney Ni, H_2 , MeOH, rt; (f) HCl, H_2O , 75°C

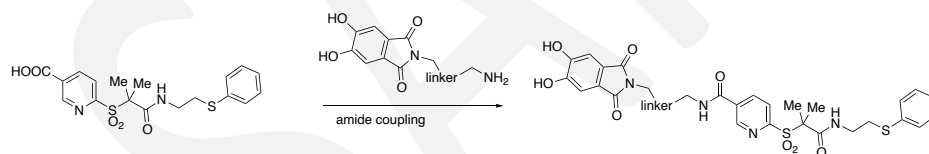
Compounds in Series Ic will be synthesized by refluxing the arylsulfonylcarbamate or thienopyridine carboxylic acid ester with substituted piperazine derivatives⁸.



Scheme 2: Synthesis of Series Ic compounds

Reagents and conditions: (a) EtOCOCI , HOAc, acetone, reflux; (b) toluene, reflux; (c) Raney Ni, H_2 , MeOH, rt

Compounds in Series III will be synthesized by amide coupling of the corresponding carboxylic acid (from Series II) with linker amine precursors (Scheme 3).



Scheme 3: Synthesis of Series III compounds

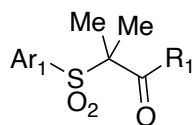
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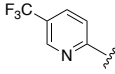
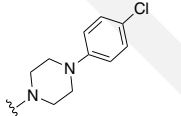
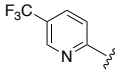
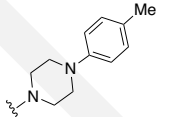
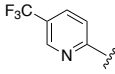
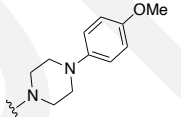
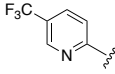
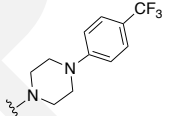
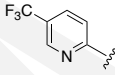
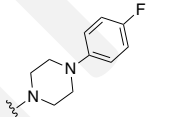
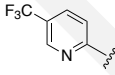
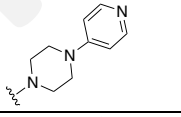
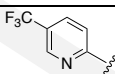
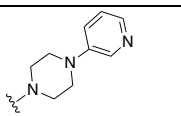
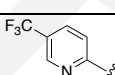
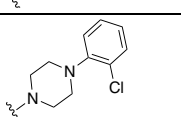
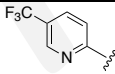
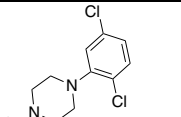
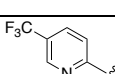
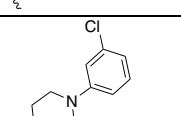
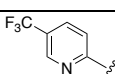
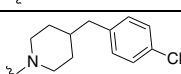
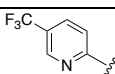
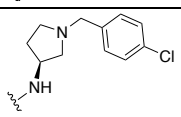
We expect the synthesis of 120 compounds to be completed 12 months after approval.

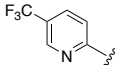
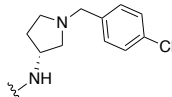
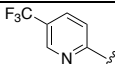
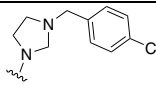
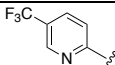
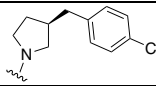
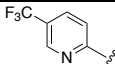
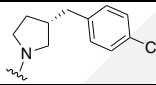
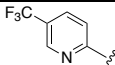
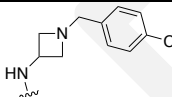
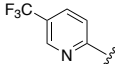
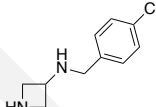
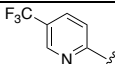
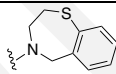
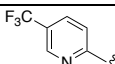
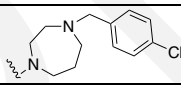
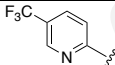
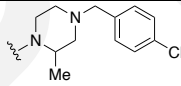
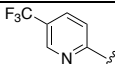
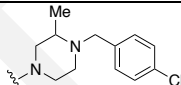
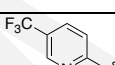
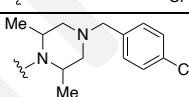
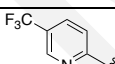
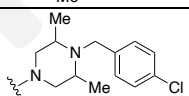
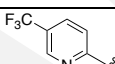
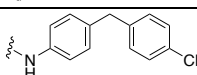
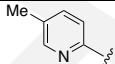
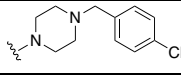
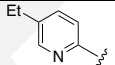
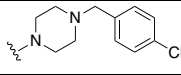
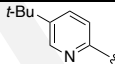
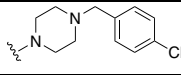
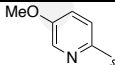
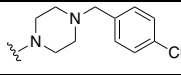
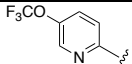
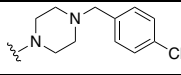
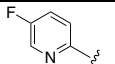
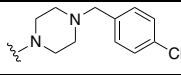
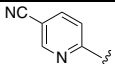
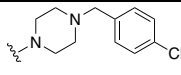
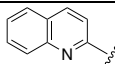
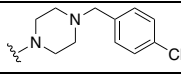
References

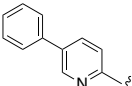
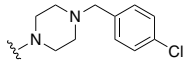
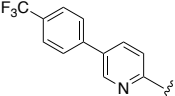
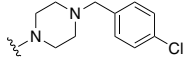
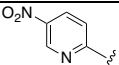
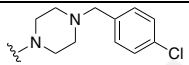
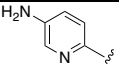
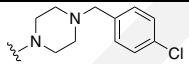
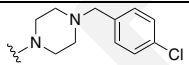
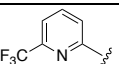
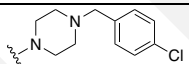
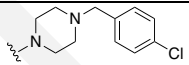
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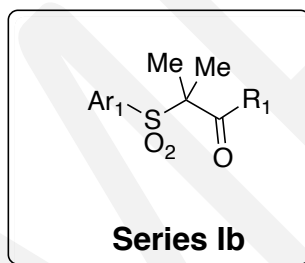
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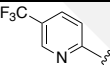
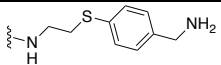
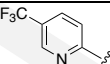
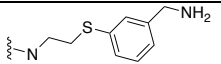
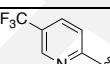
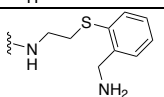
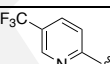
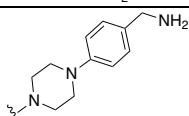
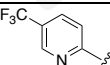
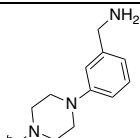
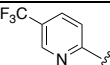
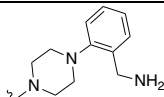
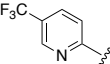
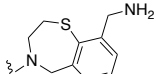
Table 1. Proposed sulfonylpyridine analogs list

Series Ia

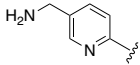
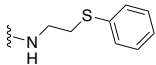
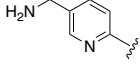
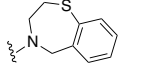
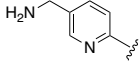
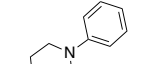
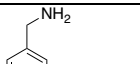
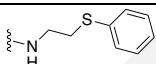
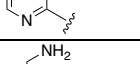
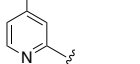
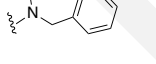
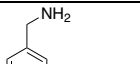
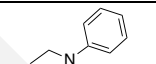
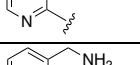
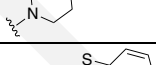
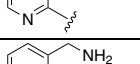
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CC4-4-P4		
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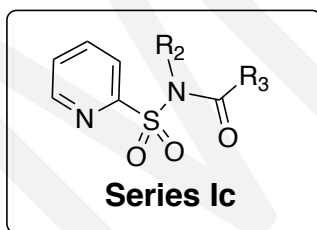
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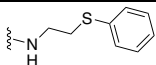
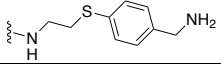
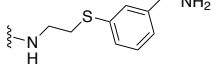
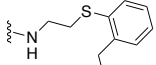
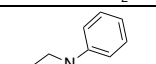
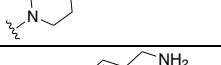
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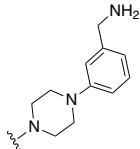
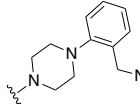
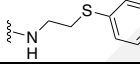
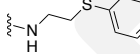
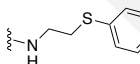
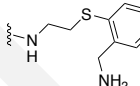
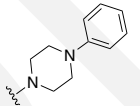
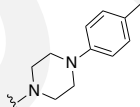
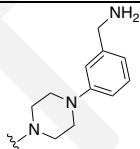
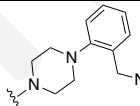


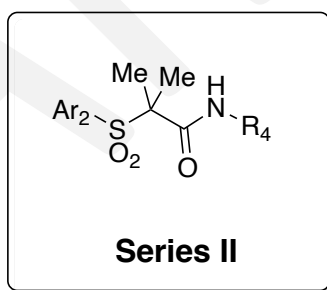
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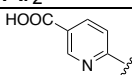
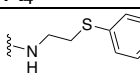
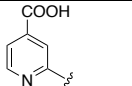
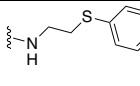
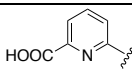
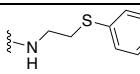
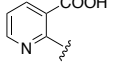
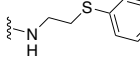
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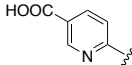
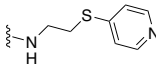
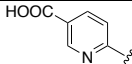
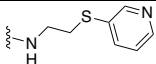
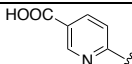
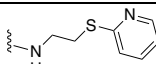
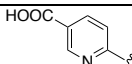
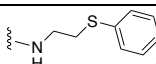
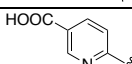
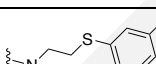
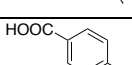
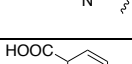
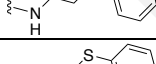
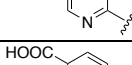
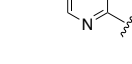
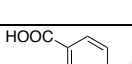
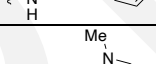
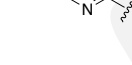
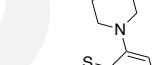
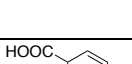
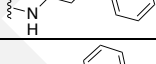
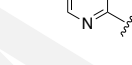
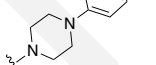
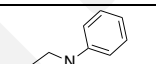
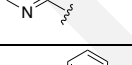
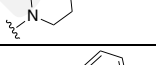
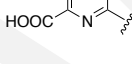
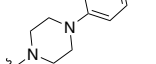
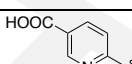
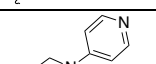


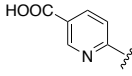
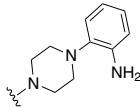
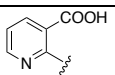
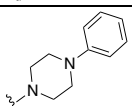
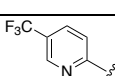
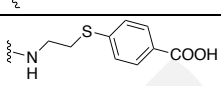
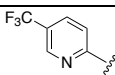
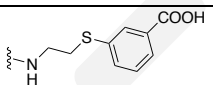
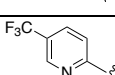
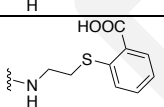
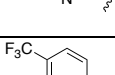
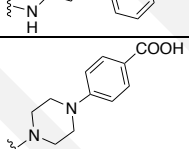
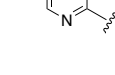
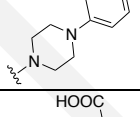
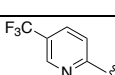
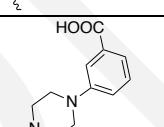
Compound #	R ₂	R ₃
CC4-4-P57	H	
CC4-4-P58	H	
CC4-4-P59	H	
CC4-4-P60	H	
CC4-4-P61	H	
CC4-4-P62	H	

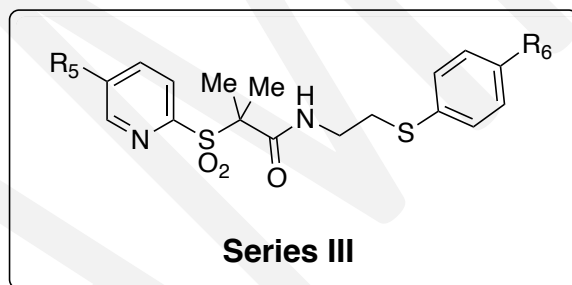
CC4-4-P63	H	
CC4-4-P64	H	
CC4-4-P65	Me	
CC4-4-P66	Me	
CC4-4-P67	Me	
CC4-4-P68	Me	
CC4-4-P69	Me	
CC4-4-P70	Me	
CC4-4-P71	Me	
CC4-4-P72	Me	

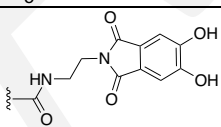
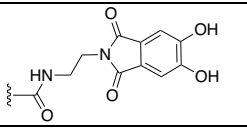


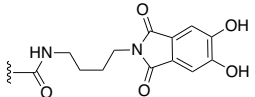
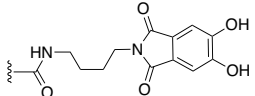
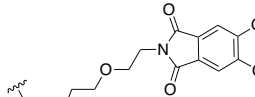
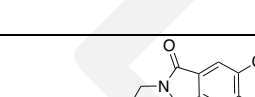
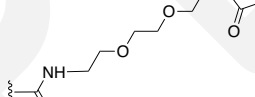
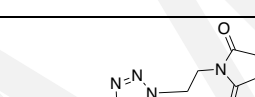
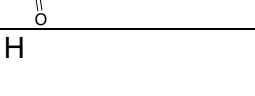
Compound#	Ar ₂	R ₄
CC4-4-P73		
CC4-4-P74		
CC4-4-P75		
CC4-4-P76		

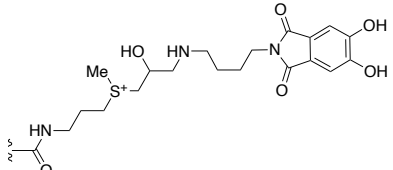
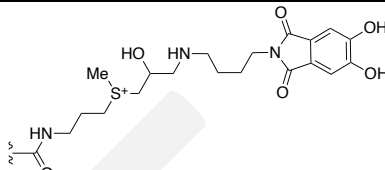
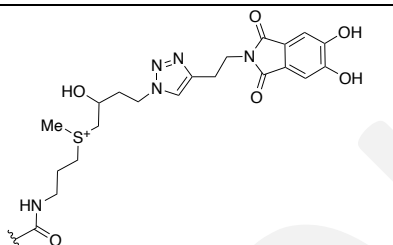
CC4-4-P77		
CC4-4-P78		
CC4-4-P79		
CC4-4-P80		
CC4-4-P81		
CC4-4-P82		
CC4-4-P83		
CC4-4-P84		
CC4-4-P85		
CC4-4-P86		
CC4-4-P87		
CC4-4-P88		
CC4-4-P89		
CC4-4-P90		
CC4-4-P91		
CC4-4-P92		
CC4-4-P93		

CC4-4-P94		
CC4-4-P95		
CC4-4-P96		
CC4-4-P97		
CC4-4-P98		
CC4-4-P99		
CC4-4-P100		
CC4-4-P101		



Compound#	R ₅	R ₆
CC4-4-P102		H
CC4-4-P103	CF ₃	
CC4-4-P104		H
CC4-4-P105	CF ₃	

CC4-4-P106		H
CC4-4-P107	CF ₃	
CC4-4-P108		H
CC4-4-P109	CF ₃	
CC4-4-P110		H
CC4-4-P111	CF ₃	
CC4-4-P112		H
CC4-4-P113	CF ₃	
CC4-4-P114		H
CC4-4-P115	CF ₃	
CC4-4-P116		H
CC4-4-P117	CF ₃	

CC4-4-P118		H
CC4-4-P119	CF ₃	
CC4-4-P120		H
CC4-4-P121	CF ₃	