

## **Development of antibiotics that dysregulate the *Neisserial* ClpP protease**

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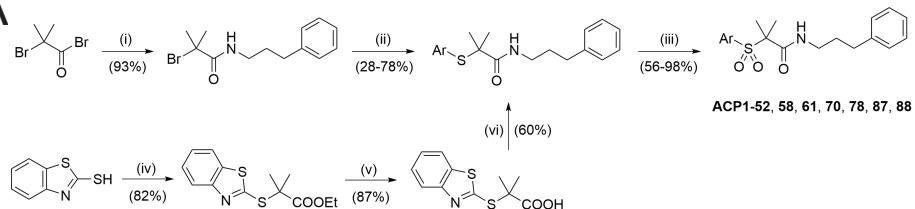
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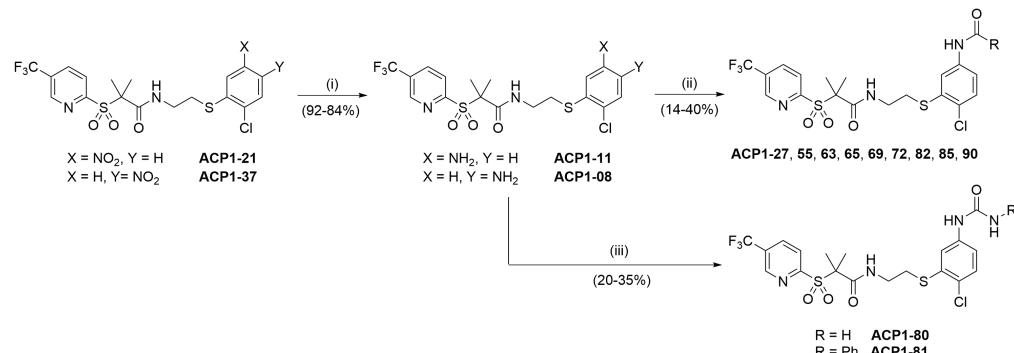
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A



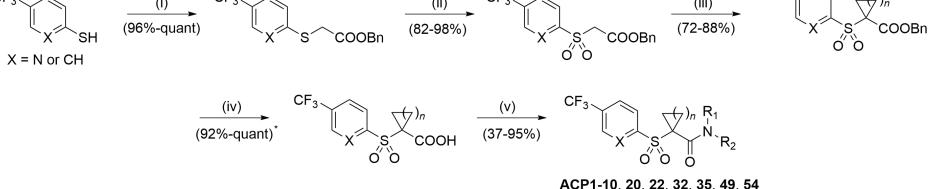
Reagents and conditions: (i)  $\text{H}_2\text{N}(\text{CH}_2)_3\text{Ph}$  (1.0 equiv),  $i\text{-PrNEt}_2$  (1.2 equiv), THF, 0 °C to rt, 24 h; (ii) Ar-SH (1.0 equiv), KOH (1.0-1.2 equiv) or  $\text{K}_2\text{CO}_3$  (1.3-1.6 equiv), EtOH, reflux, 17-67 h; (iii) *m*CPBA (2.2-2.7 equiv),  $\text{NaHCO}_3$  (3.5-12.7 equiv),  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 24-29 h; (iv)  $\text{BrC}(\text{CH}_2)_3\text{COOEt}$  (1.0 equiv), KOH (1.0 equiv), EtOH, reflux, 24 h; (v)  $\text{LiOH H}_2\text{O}$  (7.1 equiv), THF: $\text{H}_2\text{O}$  (3:2), rt, 24 h then  $\text{HCl}$  (aq); (vi)  $\text{H}_2\text{N}(\text{CH}_2)_3\text{Ph}$  (1.0 equiv), PyBOP (1.1 equiv),  $i\text{-PrNEt}_2$  (2.2 equiv), DMF, 0 °C to rt, 24 h.

D



Reagents and conditions: (i)  $\text{SnCl}_2 \cdot 2 \text{H}_2\text{O}$  (10.5 equiv), EtOAc, reflux, 4-19 h; (ii) CDI (1.05 eq),  $\text{CH}_2\text{Cl}_2$ , rt, 20 h then amine (1.0 equiv) or  $\text{PhSH}$  (1.0 equiv) or  $\text{PhOH}$  (1.0 equiv), 0 °C to rt, 5 min; (iii) Phenyl isocyanate (1.2 equiv) or trimethylsilyl isocyanate (1.4 equiv),  $\text{CH}_2\text{Cl}_2$ , rt, 5 h.

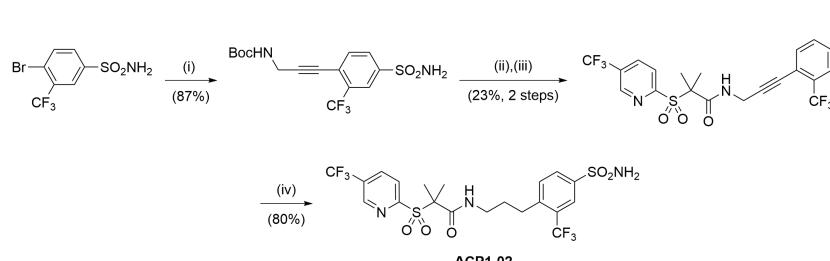
B



Reagents and conditions: (i)  $\text{NaH}$  (1.1-1.2 equiv), THF, 0 °C, 20 min then  $\text{BrCH}_2\text{COOBn}$  (1.0 equiv), 0 °C to rt, 2-17 h; (ii) *m*CPBA (2.2-2.4 equiv),  $\text{NaHCO}_3$  (2.1-7.6 eq),  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 24 h; (iii)  $\text{BrCH}_2(\text{CH}_2)_n\text{Br}$  (1.1-1.2 equiv, where  $n = 0-3$ ),  $\text{K}_2\text{CO}_3$  (5.9-8.0 equiv), MeCN, reflux, 6-24 h; (iv) Pd/C (11-29 mol %),  $\text{H}_2$  (1 atm), MeOH, rt, 24-39 h. (v)  $\text{R}_1\text{R}_2\text{NH}$  (1.0-1.4 equiv), PyBOP (1.2-1.3 equiv),  $i\text{-PrNEt}_2$  (1.1-2.4 equiv), DMF, 0 °C to rt, 12-24 h.

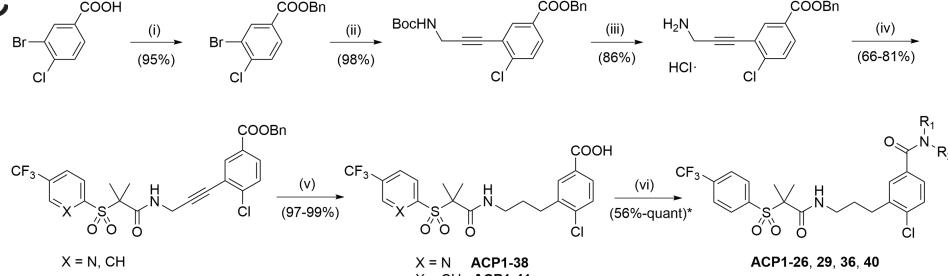
\* Note: MeOH:THF (3:1) was used as the solvent system for  $\text{X} = \text{N}$  and  $n = 3$ . THF was used as the solvent for  $\text{X} = \text{CH}$  and  $n = 2$ .

E



Reagents and conditions: (i) N-Boc-propargylamine (1.1 equiv),  $\text{Pd}(\text{PPh}_3)_4$  (11 mol %),  $\text{CuI}$  (19 mol %),  $\text{NEt}_3$  (2.0 equiv), THF, 80 °C, 24 h, sealed tube; (ii) TFA (30 equiv),  $\text{CH}_2\text{Cl}_2$ , rt, 14 h; (iii)  $\text{ArSO}_2\text{C}(\text{CH}_3)_2\text{COOH}$  (1.1 equiv), PyBOP (1.1 equiv),  $i\text{-Pr}_2\text{NEt}$  (2.3 equiv), DMF, 0 °C to rt, 15 h; (iv) Pd/C (17 mol %),  $\text{H}_2$  (1 atm), THF, rt, 4 h.

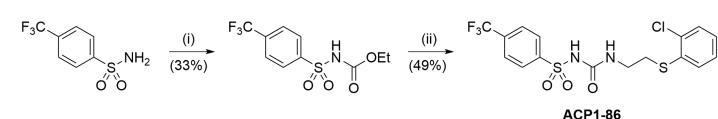
C



Reagents and conditions: (i)  $\text{NBu}_4\text{I}$  (10 mol %),  $\text{BrN}$  (1.1 equiv),  $\text{NEt}_3$  (1.2 equiv), THF, rt, 12 h; (ii)  $\text{N-Boc-propargylamine}$  (1.0 equiv),  $\text{Pd}(\text{PPh}_3)_4$  (10 mol %),  $\text{Cul}$  (5 mol %),  $\text{NEt}_3$  (2.1 equiv), THF, 60 °C, 38 h, sealed tube; (iii)  $\text{HCl}$  (10.0 equiv), dioxane, rt, 24 h; (iv)  $\text{ArSO}_2\text{C}(\text{CH}_3)_2\text{COOH}$  (1.0 equiv), PyBOP (1.1 equiv),  $i\text{-Pr}_2\text{NEt}$  (2.1 equiv), DMF, 0 °C to rt, 15 h; (v) Pd/C (10-12 mol %),  $\text{H}_2$  (1 atm), THF, rt, 15-17 h; (vi)  $\text{R}_1\text{R}_2\text{NH}$  (1.1-2.1 equiv), PyBOP (1.1 equiv),  $i\text{-Pr}_2\text{NEt}$  (2.5-2.7 equiv), DMF, 0 °C to rt, 15 h.

\* Note: ACP1-36 was isolated as the formic acid salt following reversed-phase HPLC purification.

F



Reagents and conditions: (i) ethyl chloroformate (1.1 equiv), DMAP (13 mol %),  $\text{NEt}_3$  (1.3 eq),  $\text{CH}_2\text{Cl}_2\text{-THF}$  (2:1), rt, 18 h; (ii) 2-(2-chlorophenyl)thioethan-1-amine (1.1 equiv), toluene, reflux, 24 h.

**Figure S1. Detailed synthetic scheme for the remainder of the ACP1 analogs.**  
(A-E) Shown are the detailed synthetic routes for the remainder of the ACP1 analogs.

**Table S2. Naming of ACP1 and ADEP analogs.**

This table correlates our naming of the compounds with the previously published names.

Compound	Common Name	Reference
ACP1-06	ACP1b	1
ACP1-44	ACP1a	1
ACP1-45	ACP1	1
ADEP-01	n/a	2
ADEP-02	n/a	2
ADEP-03	A54556 Factor C (ADEP1C)	3
ADEP-04	A54556 Factor D (ADEP1D)	3
ADEP-05	A54556 Factor A (ADEP1A)	3
ADEP-06	n/a	2, 4
ADEP-07	n/a	5
ADEP-08	A54556 Factor B (ADEP1B)	3
ADEP-11	ADEP 4	4
ADEP-13	n/a	5
ADEP-14	n/a	5
ADEP-15	n/a	2, 6
ADEP-16	n/a	3
ADEP-17	n/a	5
ADEP-18	n/a	4
ADEP-20	n/a	6
ADEP-21	n/a	2
ADEP-22	n/a	3
ADEP-25	n/a	2
ADEP-26	A54556 Factor E (ADEP1E)	3
ADEP-28	n/a	7
ADEP-29	n/a	5
ADEP-30	n/a	5
ADEP-31	n/a	3
ADEP-32	n/a	5
ADEP-34	n/a	3
ADEP-35	n/a	3
ADEP-36	A54556 Factor H (ADEP1H)	3
ADEP-37	n/a	2
ADEP-38	n/a	5
ADEP-40	n/a	3
ADEP-41	n/a	7
ADEP-42	n/a	2
ADEP-43	n/a	2
ADEP-45	n/a	2
ADEP-46	n/a	3

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