

# F1-1514

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# Synthesis and Antibacterial Activities of Aza Tetracyclines: A Novel Class of Tetracycline Analogs

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## Abstract/Introduction

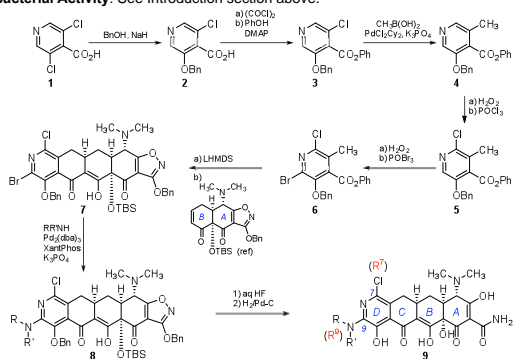
**Background:** A unique fully synthetic platform for tetracycline synthesis provides access to a broad range of tetracyclines that would be inaccessible by semisynthesis. Novel aza tetracycline analogs with a heterocyclic moiety were designed, synthesized and tested. The structure-antibiotic activity relationship (SAR) of diverse aza tetracycline analogs was studied.

**Method:** Novel aza tetracyclic analogs were synthesized from a key bicyclic AB precursor via a single-step tandem Michael-Dieckmann reaction. *In vitro* antibacterial activity was evaluated by susceptibility testing according to CLSI guidelines. *In vivo* efficacy was determined in a mouse systemic infection model against *Staphylococcus aureus* ATCC 13709.

**Conclusion:** Aza tetracyclic analogs exhibit very good *in vitro* and *in vivo* activity against bacterial pathogens including tetracycline-resistant strains with efflux- or ribosomal-mediated resistance. This demonstrates the potential of the total synthetic approach as a platform to overcome known mechanisms of tetracycline resistance.

## Methods

**Chemistry:** A typical synthesis of 7-Cl-8-aza-9-amino-tetracyclines is outlined below. **Antibacterial Activity:** See Introduction section above.



## Results

Table 1. Antibacterial Activity of 7-R-8-Aza-9-H-Tetracyclines

ID	R <sup>7</sup>	MIC (µg/mL)													PD <sub>25</sub> SA10 (mg/kg)		
		SA101 29213	SA100 13709	SA161 MRSA test(K)	SA158 test(K)	EF103 29212	EF159 test(M)	SP106 49619 test(M)	SP160 25922 test(M)	EC107 25922 test(A)	EC155 19606 test(A)	AB110 27853	PA111 13047	EC108 13883 test(A)		KP109 test(A)	KP153 test(A)
01	H	0.5	1	32	16	16	>32	0.25	32	0.5	>32	2	8	1	1	>32	1
02	CH <sub>3</sub>	0.5	1	32	0.5	>32	>32	0.25	>32	1	>32	1	16	1	1	>32	
03	Ph	0.063	0.063	32	1	4	>32	0.031	4	0.5	>32	0.13	>32	2	2	>32	
04	OCH <sub>3</sub>	0.13	0.13	8	4	8	>32	0.063	16	0.25	>32	0.5	>32	1	1	>32	
05	N(CH <sub>3</sub> ) <sub>2</sub>	0.031	0.25	32	1	1	32	0.063	8	0.13	>32	0.5	8	0.5	0.25	>32	<0.3
06	F	0.031	0.063	8	8	4	32	0.016	8	0.25	>32	0.25	8	0.5	0.5	>32	
07	Cl	1	1	32	32	32	>32	1	32	2	>32	32	>32	8	4	>32	

Table 2. Antibacterial Activity of 7-Cl-8-Aza-9-R-Tetracyclines

ID	R <sup>9</sup>	MIC (µg/mL)													PD <sub>25</sub> SA10 (mg/kg)		
		SA101 29213	SA100 13709	SA161 MRSA test(K)	SA158 test(K)	EF103 29212	EF159 test(M)	SP106 49619 test(M)	SP160 25922 test(M)	EC107 25922 test(A)	EC155 19606 test(A)	AB110 27853	PA111 13047	EC108 13883 test(A)		KP109 test(A)	KP153 test(A)
07	H	1	1	32	32	>32	1	32	2	>32	32	>32	8	4	>32		
08	H <sub>3</sub> C-CH <sub>2</sub> -X	1	1	4	4	4	4	1	4	16	32	4	>32	32	32	>32	
09	Ph	1	1	2	1	1	1	8	8	>32	>32	16	>32	>32	>32	>32	
10	NH <sub>2</sub>	0.063	0.016	4	8	1	32	0.016	4	0.25	>32	0.5	8	1	0.5	>32	
11	H <sub>3</sub> C-CH <sub>2</sub> -NH <sub>2</sub>	0.031	0.031	1	0.5	0.063	4	0.031	4	0.5	16	0.031	16	4	2	32	
12	Ph-NH <sub>2</sub>	2	1	4	2	1	0.5	16	>32	>32	>32	16	>32	>32	>32	>32	
13	H <sub>3</sub> C-CH <sub>2</sub> -NH-CH <sub>2</sub> -CH <sub>2</sub> -NH <sub>2</sub>	0.25	0.5	2	0.25	2	4	0.031	4	8	>32	0.25	>32	32	16	>32	
14	H <sub>3</sub> C-CH <sub>2</sub> -NH-CH <sub>2</sub> -NH-CH <sub>2</sub> -NH <sub>2</sub>	0.25	0.5	2	0.13	0.25	2	0.016	0.13	0.5	8	2	32	2	2	8	0.36
15	H <sub>3</sub> C-CH <sub>2</sub> -NH-CH <sub>2</sub> -NH-CH <sub>2</sub> -NH-CH <sub>2</sub> -NH <sub>2</sub>	2	2	32	32	8	>32	1	16	4	>32	8	>32	8	8	>32	

## Results

Table 3. Antibacterial Activity of 7-F-8-Aza-9-R-Tetracyclines

ID	R <sup>9</sup>	MIC (µg/mL)														
		SA101 29213	SA100 13709	SA161 MRSA test(K)	SA158 test(K)	EF103 29212	EF159 test(M)	SP106 49619 test(M)	SP160 25922 test(M)	EC107 25922 test(A)	EC155 19606 test(A)	AB110 27853	PA111 13047	EC108 13883 test(A)	KP109 test(A)	KP153 test(A)
06	H	0.031	0.063	8	8	4	32	0.016	8	0.25	>32	0.25	8	0.5	0.5	>32
16	NH <sub>2</sub>	0.063	0.063	2	8	0.5	16	0.063	2	0.25	>32	0.5	4	0.5	1	>32
17	H <sub>3</sub> C-CH <sub>2</sub> -X	0.25	0.25	2	0.25	0.5	4	4	4	2	16	0.13	16	8	8	32
18	Ph-NH <sub>2</sub>	0.25	0.5	2	0.13	0.5	2	0.031	0.25	2	8	2	32	4	4	8
19	H <sub>3</sub> C-CH <sub>2</sub> -NH-CH <sub>2</sub> -NH <sub>2</sub>	1	1	2	0.5	0.5	2	0.5	1	1	8	4	32	2	2	8
20	H <sub>3</sub> C-CH <sub>2</sub> -NH-CH <sub>2</sub> -NH-CH <sub>2</sub> -NH <sub>2</sub>	4	4	16	16	8	32	2	8	8	>32	16	>32	16	16	>32

SA: *Staphylococcus aureus*; EF: *Enterococcus faecalis*; SP: *Streptococcus pneumoniae*; EC: *Escherichia coli*; AB: *Acinetobacter baumannii*; PA: *Pseudomonas aeruginosa*; EC1, *Enterobacter cloacae*; KP: *Klebsiella pneumoniae*.

## Conclusions

- Novel 8-aza tetracycline analogs were prepared via a total synthetic approach and evaluated for antibacterial activity.
- A variety of substituents were installed at C7 and C9 leading to unique analogs with promising antibacterial activity *in vitro* and *in vivo* (see poster F1-1515 for additional data).
- Series will be further optimized for spectrum, potency, and physicochemical properties.

## Reference

M.G. Charest, C.D. Lerner, J.D. Brubaker, D.R. Siegel, A.G. Myers, *Science*, **308**, 395 (2005).