

# F1-1516

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# Synthesis and Antibacterial Activities of Pentacyclines: 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 semisynthetic methods. Novel analogs with a pentacyclic backbone were designed, synthesized and tested. The structure-activity relationship of diverse pentacyclic analogs was studied.

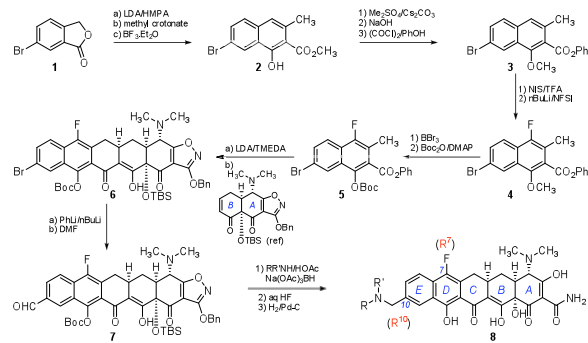
**Method:** Novel pentacyclic analogs were synthesized from a key bicyclic AB precursor via a tandem Michael-Dieckmann reaction. Susceptibility testing was by CLSI guidelines. Testing included strains expressing ribosomal protection gene *tet(M)*, or efflux pump genes, *tet(K)* or *tet(A)*. *In vivo* efficacy was determined in a mouse septicemia model against *Staphylococcus aureus* ATCC 13709.

**Conclusions:** The novel pentacyclic analogs exhibit very good *in vitro* and *in vivo* activity against bacterial pathogens including methicillin- and tetracycline-resistant strains. This demonstrates the potential of the total synthetic approach as a powerful engine for the discovery and development of new tetracycline antibiotics.

## Methods

**Chemistry:** A typical synthesis of 7-F-10-aminomethyl pentacyclines is outlined below.

**Antibacterial Activity:** See Introduction section above.



## Results

**Table 1. Antibacterial Activity of 7-R-10-Azetidinomethyl Pentacyclines**

ID	R <sup>7</sup>	MIC ( $\mu\text{g/mL}$ )													SA10 (mg/kg)		
		SA101	SA100	SA161	SA158	EF103	EF159	SP106	SP160	EC107	EC155	AB110	PA111	EC108		KP109	KP153
		29213	13709	MRSA tet(K)	29212	29212	49619	25922	25922	19606	27853	13047	13883	tet(A)			
01	H	0.5	1	2	0.5	0.5	4	0.13	0.25	1	8	1	32	2	4	8	
02	F	0.25	0.5	1	0.25	0.25	2	0.063	0.13	1	4	0.5	32	2	2	4	0.3
03	Cl	1	1	2	1	0.25	2	0.25	0.5	2	16	2	>32	8	4	8	
04	N(CH <sub>3</sub> ) <sub>2</sub>	0.13	0.25	2	0.06	0.13	2	<0.016	0.13	2	8	1	32	8	4	16	1.7
05	OCH <sub>3</sub>	0.063	0.063	0.5	0.063	0.063	1	0.016	0.063	0.25	8	1	32	1	1	8	0.36
06		8	16	32	32	8	32	1	4	32	>32	>32	>32	>32	>32	>32	

**Table 2. Antibacterial Activity of 7-CH<sub>3</sub>O-10-Aminomethyl Pentacyclines**

ID	R <sup>10</sup>	MIC ( $\mu\text{g/mL}$ )													SA10 (mg/kg)		
		SA101	SA100	SA161	SA158	EF103	EF159	SP106	SP160	EC107	EC155	AB110	PA111	EC108		KP109	KP153
		29213	13709	MRSA tet(K)	29212	29212	49619	25922	25922	19606	27853	13047	13883	tet(A)			
07		0.25	0.5	2	0.016	0.063	2	0.016	0.13	1	4	0.25	16	2	1	8	<0.3
08		0.063	0.25	2	0.031	0.062	2	0.016	0.13	0.5	8	0.25	16	4	2	8	0.6
09		0.063	0.13	4	0.13	0.25	4	0.016	0.25	1	16	1	32	4	2	16	
10		0.25	0.5	2	0.25	0.25	2	0.016	0.5	1	8	2	16	2	2	8	
11		0.25	0.5	2	0.25	0.25	4	0.016	0.25	1	8	1	32	4	4	8	
12		0.25	1	1	0.13	0.13	2	0.016	0.031	2	8	0.25	32	8	4	8	
13		0.25	0.5	2	0.13	0.25	4	0.016	0.25	1	8	1	16	4	4	8	

## Results

**Table 3. Antibacterial Activity of 7-F-10-Aminomethyl Pentacyclines**

ID	R <sup>10</sup>	MIC ( $\mu\text{g/mL}$ )													SA10 (mg/kg)		
		SA101	SA100	SA161	SA158	EF103	EF159	SP106	SP160	EC107	EC155	AB110	PA111	EC108		KP109	KP153
		29213	13709	MRSA tet(K)	29212	29212	49619	25922	25922	19606	27853	13047	13883	tet(A)			
14		0.5	0.5	2	0.25	0.25	2	0.031	0.25	1	8	1	16	2	4	8	
15		0.25	0.25	1	0.25	0.13	1	0.016	0.031	1	8	0.25	32	2	2	8	
16		0.5	0.5	1	0.063	0.13	2	0.016	0.13	1	4	0.25	16	1	1	4	
17		0.13	0.13	1	0.13	0.25	2	0.063	0.063	1	4	0.25	32	2	2	4	
18		0.5	0.5	1	0.016	0.031	1	0.016	0.031	2	4	0.25	16	2	2	4	0.35
19		0.5	1	2	0.25	0.5	2	0.063	0.063	2	8	1	32	8	4	8	
20		0.5	1	1	0.25	0.25	1	0.25	0.5	4	8	1	>32	8	4	8	
21		0.25	0.25	1	0.13	0.13	1	0.03	0.03	1	4	0.25	32	4	2	4	
22		1	1	2	0.5	1	2	0.5	0.5	16	32	4	>32	32	32	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 pentacyclic 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 F1-1219 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).