Design of new Polymyxins with reduced Nephrotoxicity

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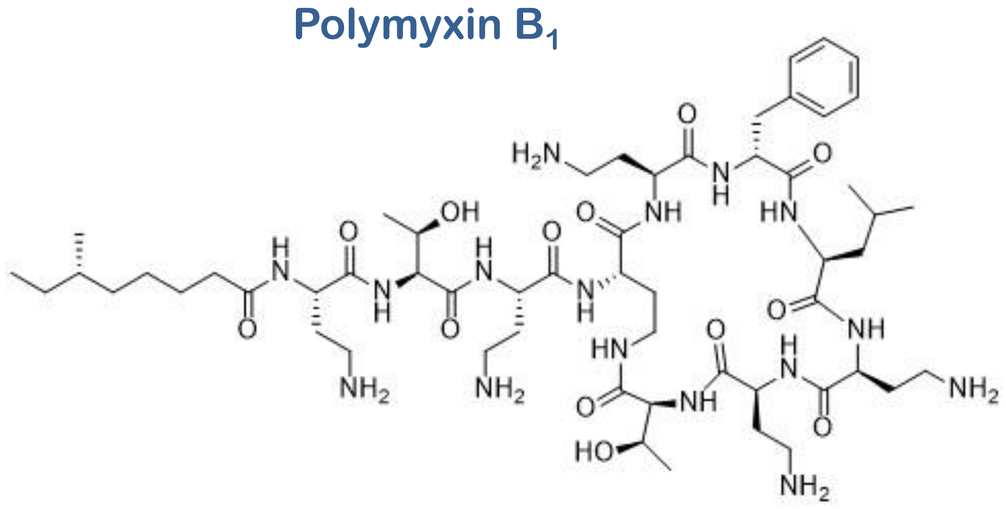
Introduction

There is a clear unmet medical need in the field of infectious diseases: infections caused by resistant bacteria. A major goal to fight resistant bacteria involves the design, discovery and development of new antibiotics particularly against multi-drug-resistant strains. Polymyxins, an old class of antimicrobial cyclic lipopeptides highly potent against therapeutically relevant Gram-negative bacteria, have been rescued and are now used only as last resort antibiotics in hospitals because of their nephrotoxicity and neurotoxicity that require careful monitoring of the patient. Our group has embarked in a project to design and develop new polymyxins devoid of toxicity problems using a versatile and chemically accessible scaffold structure. Compounds show a remarkable activity against Gram-negative bacteria. Herein, the last results of our recently designed polymyxin analogs will be presented.

Polymyxin B_1



Polymyxin Toxicity

The molecular mechanism of polymyxin toxicity is not well understood. It seems to be associated to the presence of the fatty acid tail and the cationic charges of the basic Dab side chain amino groups (Keirstead *et al*. 2013).

In fact, polymyxin B nonapeptide, a deacylated and truncated derivative of polymyxin B exhibits much lower toxic effects (Danner *et al* 1989). In addition, the sulfomethylation of polymyxin reduces its acute toxicity (Barnett *et al.* 1947).

Polymyxins accumulate in the kidney's cortical region and is metabolized with difficulty by renal detoxifying enzymes (Rabanal *et al*. 2017).

Design

Starting from our successful disulfide cyclopeptide scaffold (Rabanal *et al.* 2015), we have recently designed a series of new compounds aiming at reducing toxicity by (see figure):

- ➡ shortening the fatty acid tail
- ➡ reducing basicity of amino groups
- ➡ increasing lability of the scaffold backbone by introducing isosteric bonds (i. e. disulfide or ester) to facilitate metabolization upon accumulation in kidneys to potentially lower renal toxicity.

Canonical analog 1

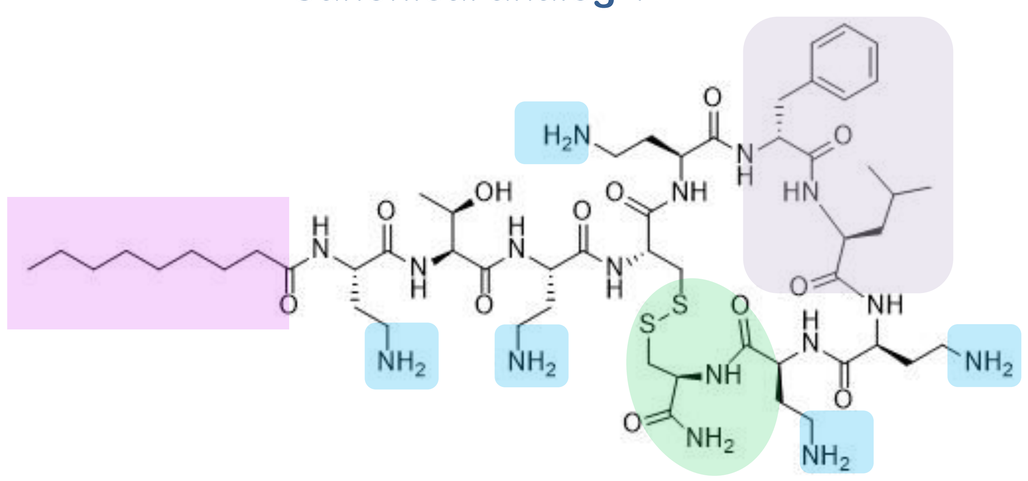


Figure: General structure of designed compounds (canonical analog 1 is shown as an example). The structural features taken into account for the design of the analogs are highlighted. (Rabanal et al. 2015)

Analog	MIC [µg/mL]												
	E. coli				*K. pneumoniae*			*A. baumannii*			*P. aeruginosa*		
	ATCC 25922	MB799	C22	1410	ATCC 13883	MB674	MB1052	ATCC 19606	ATCC 17978	CR17	ATCC 27853	36A	121007
Col	0,5	0,5	8	0,5	4	1	>32	2	1	32	2	1	>32
400	0,5	0,5	16	0,5	32	0,25	>32	2	1	2	2	1	>32
401	1	4	8	0,5	4	0,5	8	1	1	4	1	1	>32
411	2	0,5	32	0,5	>32	0,5	>32	2	1	4	2	2	>32
500	4	4	8	0,5	16	1	32	8	2	>32	1	1	>32
501	1	2	4	1	2	1	4	8	4	2	2	2	32

Table: MIC values with the bacterial inoculum automatically adjusted using a nephelometer (BD PhoenixSpec™ nephelometer) determining the turbidity of microbial suspensions equivalent to McFarland standards from 0.10 to 4.5.

Conclusions

- It is possible to design highly active analogs with shorter fatty acid tail or lower overall cationic charge and having a more easily metabolizable scaffold to potentially lower toxicity. *In vivo* tests in mice are underway.
- Compounds are easily synthesized in good yields.

References

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