Antibacterial Activity of Cyclam Salts

João F. Portel,[a,b] Luís G. Alves,[a,*] Sílvia A. Sousa,[b] Jorge H. Leitão,[b] Ana M. Martins[a]

[a]Centro de Química Estrutural / [b]IBB - Instituto de Bioengenharia e Biociências

Instituto Superior Técnico, Universidade de Lisboa

Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal

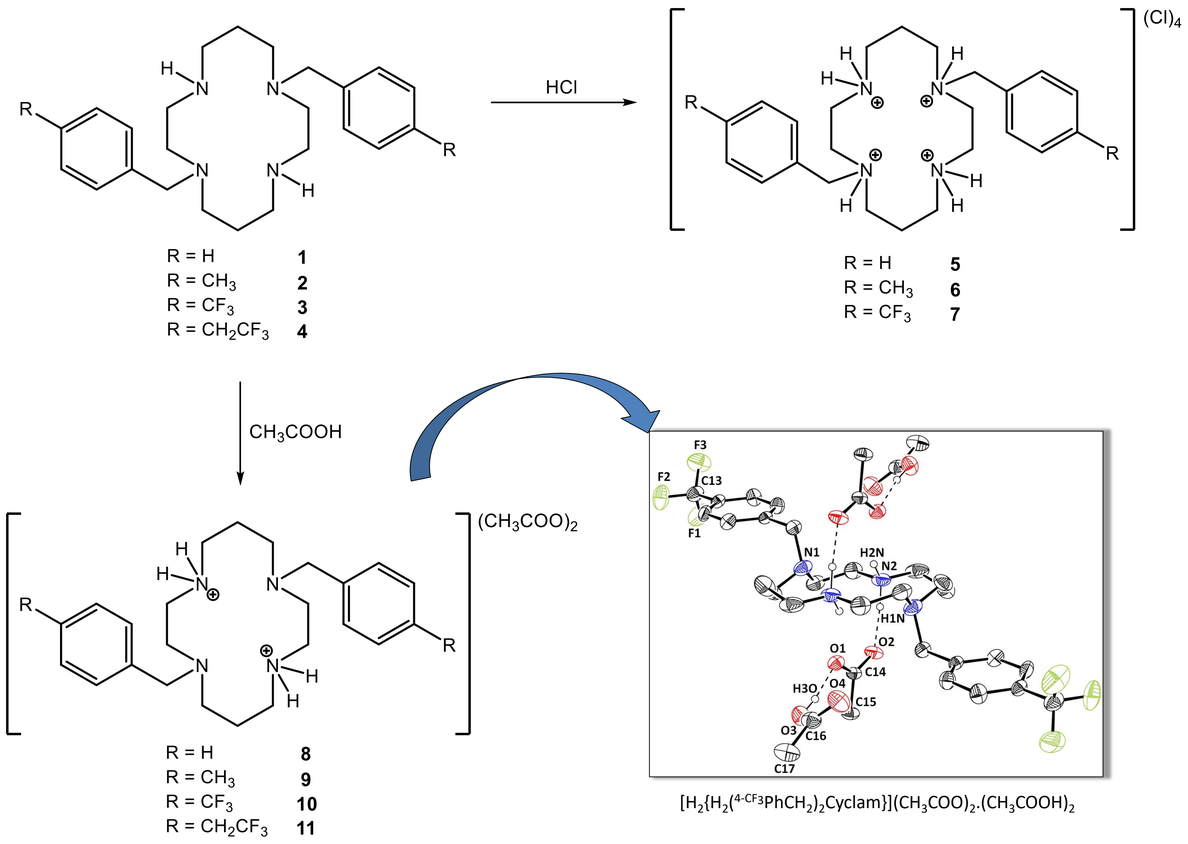
* luis.g.alves@tecnico.ulisboa.pt

INTRODUCTION

The steadily increasing of the resistance of human pathogens to multiple antimicrobials over the last decade is alarming and a serious threat to public health.[1] While the emergence of multidrug resistance has been associated with misuse and abuse of antimicrobials, the number of available effective agents is decreasing and the arrival of new compounds into the market are scarce.[2,3] Tetraazamacrocycles are versatile and readily tunable molecules with potential for the development of compounds having enhanced antimicrobial activity.[4]

RESULTS AND DISCUSSION

Reaction of H_2Bn_2Cyclam, **1**-**4**, with Brønsted acids led to the formation of the corresponding cyclam salts **5**-**11** as shown in Scheme 1. Depending on the pK_a of the acid used, tetracationic (**5**-**7**) or dicationic (**8**-**11**) salts are obtained.



Scheme 1

The estimation of the Minimal Inhibitory Concentration (MIC) values for compounds **5**-**11** to *E. coli and S. aureus* species was assessed by measuring the optical density of the cultures in liquid media (see Figures 1 and 2). The MIC values determined for *E. coli* and *S. aureus* are presented in Table 1.

Table 1 – Minimal Inhibitory Concentration (MIC) values (μg/mL) determined for *S. aureus* Newman and *E. coli* ATCC25922 in liquid media.

	S.aureus	***E. coli***
5	80	124
6	119	43
7	5	5
8	206	80
9	49	55
10	8	7
11	10	10

Toxicity essays were conducted for compound **10** using the nematode *C. elegans* as model. Concentrations lower than 32 μg/mL did not affect the survival and reproduction of the nematodes. However, concentrations equal or above this value significantly affect the nematode survival in a dose dependent mode. No progeny was detected when the worms were exposed to the presence of 128 μg/mL of the cyclam salt.

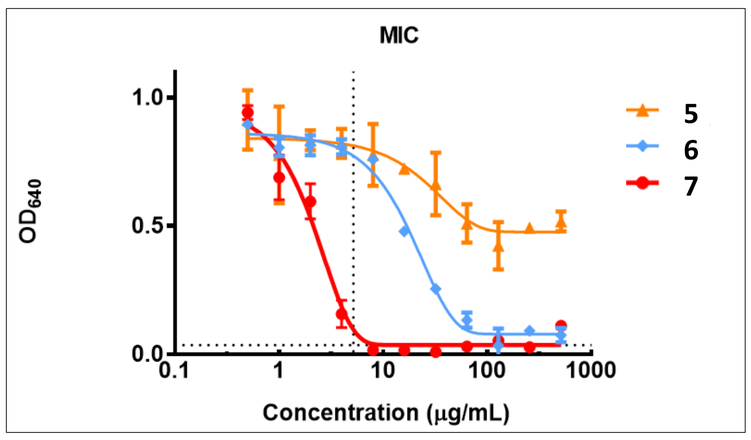


Figure 1 - Antibacterial activity of compounds **5**-**7** towards *S. aureus* Newman. Optical density (OD_{640}) measured in the wells of the microplates after 24 h cultivation at 37 °C in the presence of the respective compound. Data was fitted using a modified Gompertz equation.

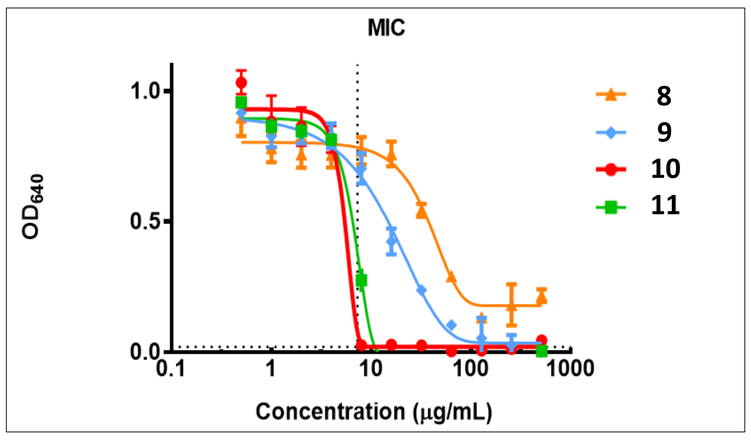


Figure 2 - Antibacterial activity of compounds **8**-**11** towards *E. coli* ATCC25922. Optical density (OD_{640}) measured in the wells of the microplates after 24 h cultivation at 37 °C in the presence of the respective compound. Data was fitted using a modified Gompertz equation.

CONCLUSIONS

The antibacterial activity of several cyclam derivatives was evaluated for selected bacteria strains. The MIC values obtained for *S. aureus* Newman and *E. coli* ATCC25922 reveal that the activity of the compounds is strongly dependent on the nature of the substituent groups of the aromatic rings. Thus, the presence of fluorinated groups in the *para* position seems to be crucial for the antibacterial activity of the compounds. The nature of the anion have almost no influence on the antibacterial activity of the cyclam salts.

REFERENCES

[1] WHO. Antimicrobial Resistance: Global Report on Surveillance 2014; Geneva, 2014

[2] Bax, R.; Mullan, N.; Verhoef, J., *Int. J. Antimicrob. Agents* 2000, *16*, 51-59

[3] Norrby, S. R.; Nord, C. E.; Finch, R., *Lancet Infect. Dis.* 2005, *5*, 115-119

[4] Alves, L. G.; Pinheiro, P. F.; Feliciano, J. R.; Leitão, J. H.; Martins, A. M., *Int. J. Antimicrob. Agents* 2017, *49*, 646-649

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