Cyclam-based compounds as a novel class of antibacterial and antitumoral agents

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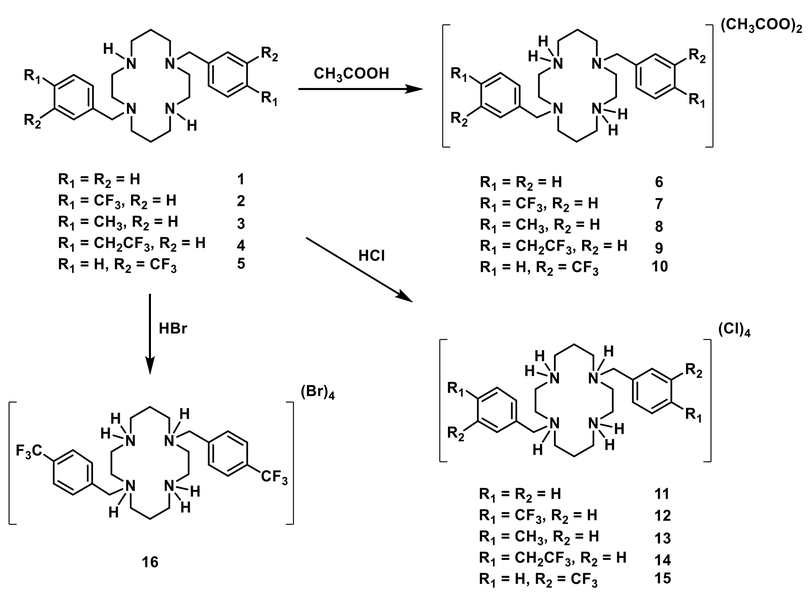
INTRODUCTION

Cyclams are macrocyclic polyamines which medical interest was fueled by the therapeutic potential of a bicyclam derivative in HIV infection, inflammatory diseases, cancer and stem-cell mobilization. [1] Taking advantage of the biocompatibility, the high metal chelation stability constants and the possibility of *N*-functionalization of the cyclam backbone, a variety of compounds have been explored in a wide range of medicinal applications. [2] The use of cyclams and cyclam-based complexes as antimicrobial and antitumoral agents has been recently described. [3-5]

RESULTS AND DISCUSSION

Antibacterial Activity

Reactions of *trans*-disubstituted cyclams of general formula $H_2Bn_2Cyclam$, **1**-**5**, with Brønsted acids led to the formation of the corresponding salts **16** as shown in Scheme 1. Depending on the pK_a of the acid used, dicationic (**6**-**10**) or tetracationic (**11**-**16**) salts are obtained.



Scheme 1

The Minimal Inhibitory Concentration (MIC) values determined for compounds **6**-**16** to *S. aureus and E. coli s*pecies are presented in Figure 1. The structure/activity relationship reveals that the presence of a CF_3 group on the aromatic ring of the cyclam pendant arms is crucial for the antibacterial activity of the compounds.

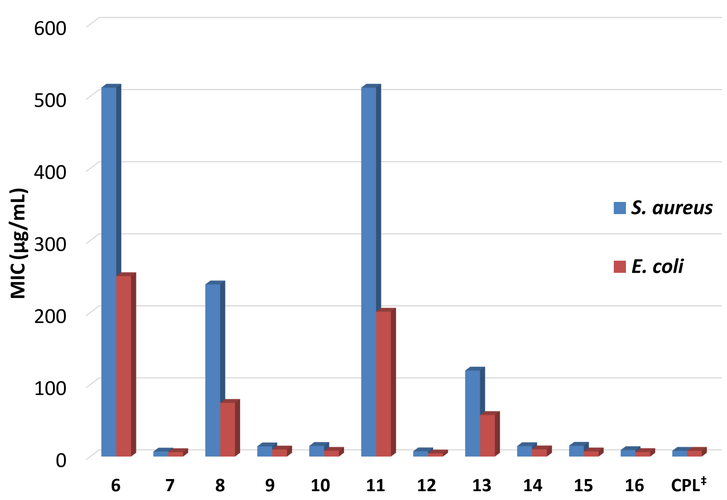
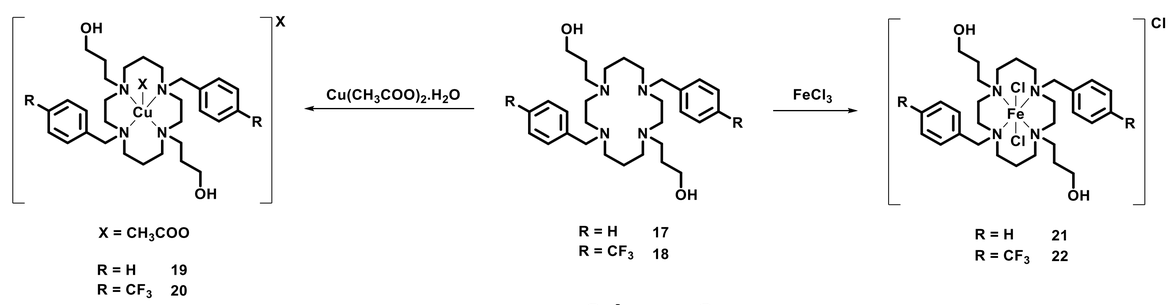


Figure 1. MIC values (µg/mL) for **6**-**16** and chloramphenicol (CPL)‡ determined for *S. aureus* Newman and *E. coli* ATCC25922 in MHB liquid media.

‡Data obtained from EUCAST

Antitumoral Activity

Cyclam derivatives **17** and **18** react with one equiv. of $Cu(CH_3COO)_2.H_2O$ to afford complexes of formula $[Cu\{(HOCH_2CH_2CH_2)_2Bn_2Cyclam\}(CH_3COO)](CH_3COO)$, where Bn = $PhCH_2$, **19**, and $^{4\text{-}CF3}PhCH_2$, **20**, as shown in Scheme 2. Reaction of **17** and **18** with one equiv. of $FeCl_3$ led to the formation of the corresponding Fe(III) complexes **21** and **22** (see Scheme 2).



Scheme 2

The IC_{50} values of **17**-**22** obtained for the growth inhibition of HeLa cells are presented in Figure 2. At 24 h incubation only compound **18** and complexes **20** and **22** are cytotoxic, while at 72 h incubation all the compounds show significant antiproliferative effects. Notably, compounds displaying *p*-CF_3 on the aromatic rings of the macrocyclic pendant arms as well as their Cu(II) and Fe(III) complexes are up to 12 times more cytotoxic than cisplatin at 24 h incubation.

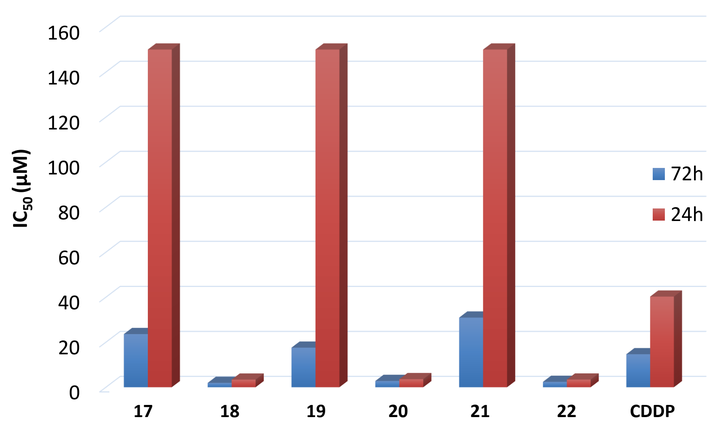


Figure 2. IC_{50} values (µM) for compounds **17**-**22** and cisplatin (CDDP) in HeLa cells.

CONCLUSIONS

The antibacterial and antitumoral activity of cyclams reveals a strong dependence on the presence of the CF_3 group on the aromatic ring of the macrocyclic pendant arms. Remarkably, these compounds display similar antibacterial activity as the commercial available antibiotic chloramphenicol and are up to 12 times better than cisplatin for HeLa cancer cells. As far as we are aware, compounds of formula $[\{(HOCH_2CH_2CH_2)_2Bn_2Cyclam\}FeCl_2]Cl$, are the first Fe-Cyclam compounds to be ever tested as anticancer agents.

REFERENCES

[1] De Clercq, E. *Nat. Rev. Drug Discov*. **2003**, *2*, 581–587
[2] Liang, X. *et. al. Chem. Soc. Rev.* **2004**, *33*, 246-266
[3] Yu, M. *et. al. J. Med. Chem.* **2016**, *59*, 5917–5921
[4] Alves, L. G. *et. al. Int. J. Antimicrob. Agents* **2017**, *49*, 646-649
[5] Pilon, A. *et. al. ChemMedChem* **2019**, *14*, 770-778

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