Hydrosoluble pyrenyl-dendrimers and arene ruthenium metalla-cages: Synergic enhancement of cytotoxicity

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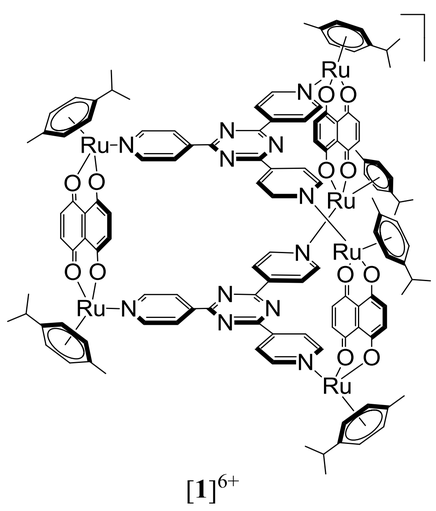
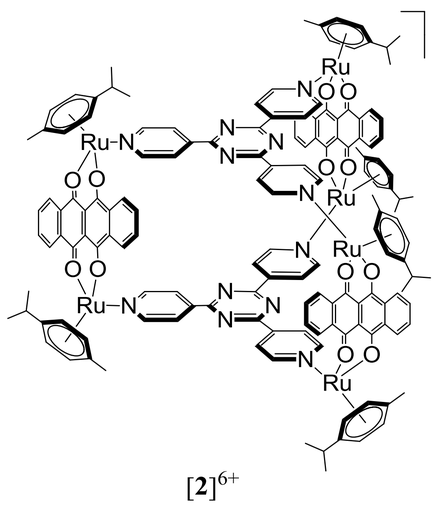
Introduction

Water-soluble dendrimers have been shown to improve drug solubility, increase drug circulation time and prolong drug residence in tumors, thus reducing toxicity.[1] Biodegradability is an important criteria in order to avoid cellular accumulation leading to lysosomal storage disease in patients.[2] Different generations of biodegradable water-soluble dendrimers were synthesised[3] and functionalised by a pyrenyl unit. This unit was then encapsulated into the hydrophobic cavity of hexanuclear arene ruthenium metallacages $[Ru_6(p\text{-cymene})_6(OO\cap OO)_3(tpt)_2]^{6+}$ ($OO\cap OO$ = 5,8-dioxydo-1,4-naphtoquinonato (donq) [**1**]$^{6+}$, 6,11-dioxydo-5,12-naphtocenedionato (dotq) [**2**]$^{6+}$; tpt = 2,4,6-tri(pyridin-4-yl)-1,3,5-triazine).[4] The physical and chemical behavior as well as the biological activity of the host-guest systems are presented.[5]

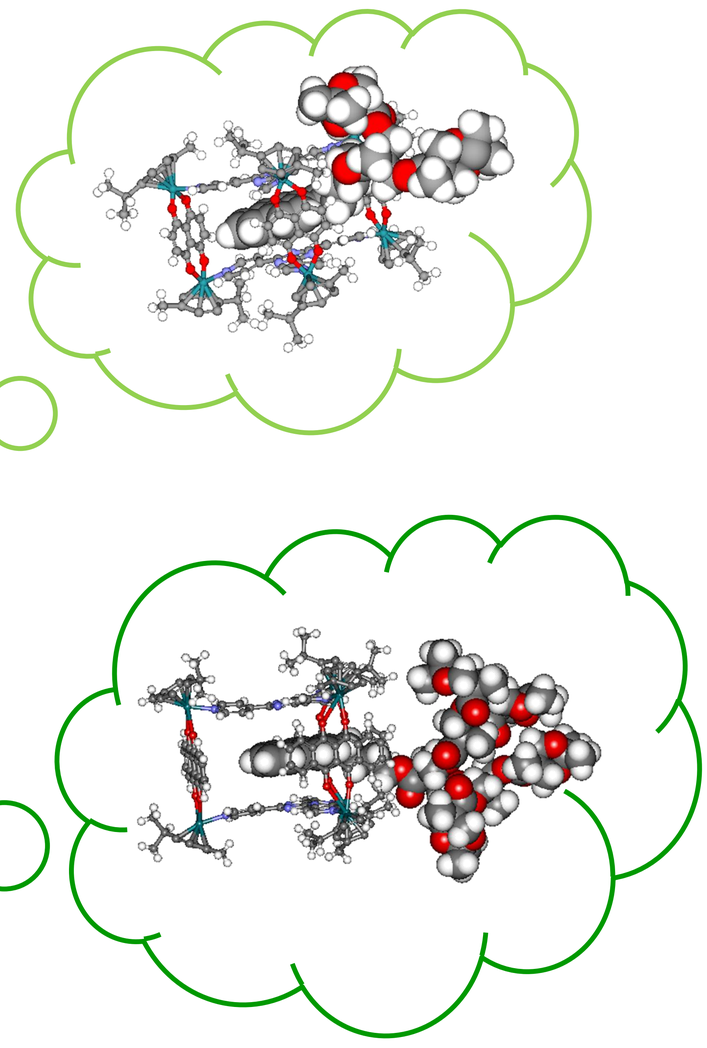


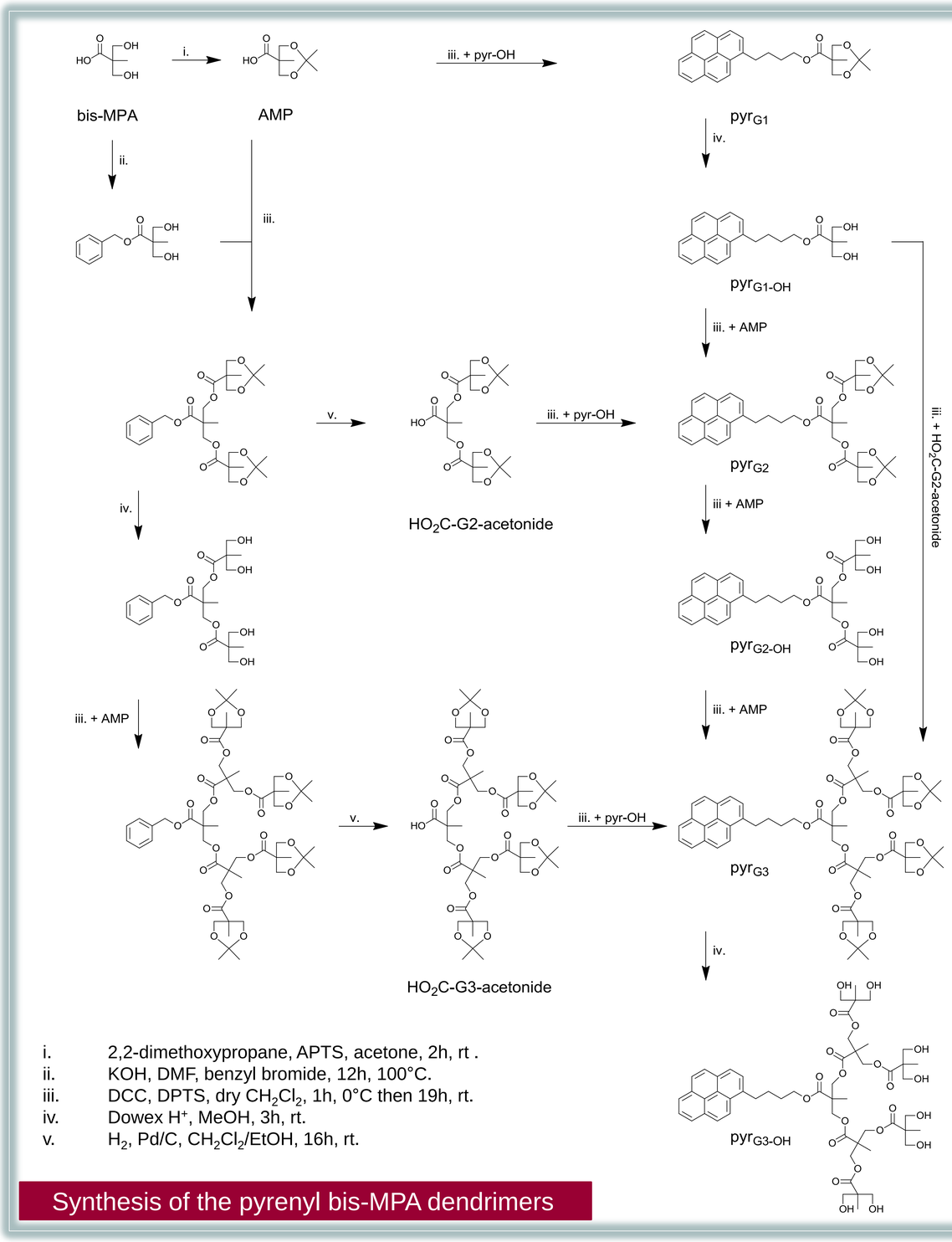


Hexaruthenium metallacages

Biological studies

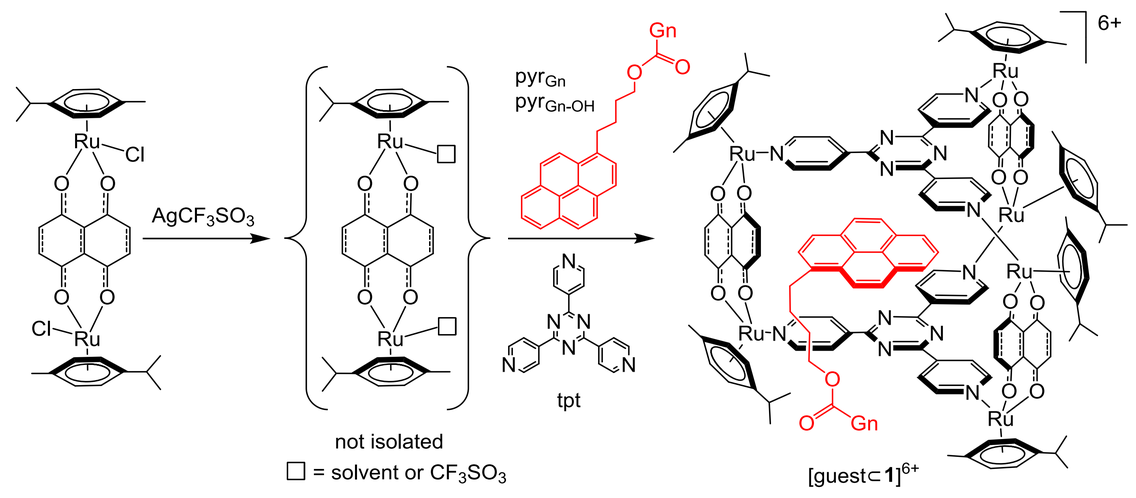
Compound	A2780 (IC_{50} [μM])	A2780cisR (IC_{50} [μM])
pyr_{G1}	n.d.	n.d.
pyr_{G2}	n.d.	n.d.
pyr_{G3}	n.d.	n.d.
$pyr_{G1\text{-}OH}$	n.d.	n.d.
$pyr_{G2\text{-}OH}$	5.9±0.6	7.4±0.8
$pyr_{G3\text{-}OH}$	8.7±0.9	8.7±1.0
[**1**][CF_3SO_3]$_6$	3.1±1.0	4.6±0.5
[**2**][CF_3SO_3]$_6$	4.1±0.07	6.5±1.0
[pyr_{G1}⊂**1**][CF_3SO_3]$_6$	1.2±0.1	0.9±0.08
[pyr_{G2}⊂**1**][CF_3SO_3]$_6$	0.3±0.02	0.2±0.02
[pyr_{G3}⊂**1**][CF_3SO_3]$_6$	0.7±0.3	0.8±0.2
[$pyr_{G1\text{-}OH}$⊂**1**][CF_3SO_3]$_6$	1.4±0.1	0.9±0.08
[$pyr_{G2\text{-}OH}$⊂**1**][CF_3SO_3]$_6$	2.0±0.5	1.3±0.4
[$pyr_{G3\text{-}OH}$⊂**1**][CF_3SO_3]$_6$	0.7±0.1	0.8±0.1
[pyr_{G1}⊂**2**][CF_3SO_3]$_6$	2.1±0.4	1.6±0.2
[pyr_{G2}⊂**2**][CF_3SO_3]$_6$	1.9±0.4	0.9±0.3
[pyr_{G3}⊂**2**][CF_3SO_3]$_6$	1.1±0.3	1.5±0.4
[$pyr_{G1\text{-}OH}$⊂**2**][CF_3SO_3]$_6$	0.8±0.3	2.2±0.8
[$pyr_{G2\text{-}OH}$⊂**2**][CF_3SO_3]$_6$	4.1±0.6	1.9±0.3
[$pyr_{G3\text{-}OH}$⊂**2**][CF_3SO_3]$_6$	1.5±0.03	1.5±0.4
cisplatin	1.6±0.6	8.6±0.6





Synthesis of the pyrenyl bis-MPA dendrimers

Encapsulation of guest in the metallaprism [**1**]$^{6+}$



Conclusion

The combined host-guest systems are significantly more active than either the host or the guest alone. The enhanced cytotoxicity of the [guest⊂**cage**]$^{6+}$ systems compared to the guest or host alone implies that intact [guest⊂**cage**]$^{6+}$ systems are entering the cells together, and are responsible for the overall cytotoxicity observed.

The entrapment of water-soluble dendrimer guests within metalla-prism hosts leads to apparent enhancements in cytotoxicity. The host-guest system is also quite stable in biological media. These features, combined with their potential to preferentially accumulate in tumors, make them interesting candidates for further *in vivo* study and development.

1. M. E. Fox, F. C. Szoka, J. M. J. Fréchet, *Acc. Chem. Res.* **2009**, *42*, 1141. **2.** M. A. Mintzer, M. W. Grinstaff, *Chem. Soc. Rev.* **2011**, *40*, 173. **3.** a) H. Ihre, J. M. J. Fréchet, I. Gitsov, A. Hult, *Macromolecules* **1998**, *31*, 4061; b) A. Würsch, M. Möller, T. Glauser, L. S. Lim, S. B. Voytek, J. L. Hedrick, C. W. Frank, J. G, Hilborn, *Macromolecules* **2001**, *34*, 6601; c) M. Malkoch, K. Hallman, S. Lutsenko, A. Hult, E. Mälmström, C. Moberg, *J. Org. Chem.* **2002**, *67*, 8197. **4:** a) N. P. E. Barry, B. Therrien, *Eur. J. Inorg. Chem.* **2009**, 4695; b) J. Freudenreich, N. P. E. Barry, G. Süss-Fink, B. Therrien, *Eur. J. Inorg. Chem.* **2010**, 2400; c) F. Schmitt, J. Freudenreich, N. P. E. Barry, L. Juillerat-Jeanneret, G. Süss-Fink, T. Therrien, *J. Am. Chem. Soc.* **2012**, *134*, 754. **5:** A. Pitto-Barry, O. Zava, P. J. Dyson, R. Deschenaux, B. Therrien, *Inorg. Chem.*, **2012**, *51*, 7119.