New Cross-Bridged Cyclam Ligands and Their Transition Metal Complexes as CXCR4 Antagonists

Dustin J. Davilla[1], Shay L. Klassen[1], Brittany M. Epley[1], Justin G. Le[1], Dr. Timothy J. Hubin[1]

1. Department of Chemistry, Southwestern Oklahoma State University, 100 Campus Drive, Weatherford, OK 73096

Introduction

1. CXCR4 is a co-receptor on the surface of immune cells that has been proven to facilitate the entry of HIV into the cells. (**fig 1**)

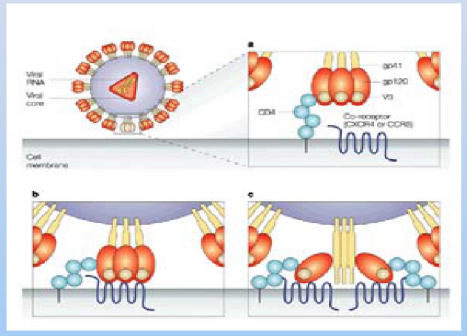


Figure 1. HIV cell entry. (Reproduced from Nature Reviews Drug Discovery).[1]

Within the last 15 years the CXCR4 and CCR5 co-receptors have influenced new therapeutic approaches to the treatment of HIV via fusion inhibitor drugs that target these receptors.

Our aim is to develop new antagonists for the CXCR4 co-receptor. Specifically, the goal was the synthesis of Propyl Cross-Bridged, linked analogues of the known CXCR4 antagonist AMD-3100.

2. AMD 3100 is a known CXCR4 binding fusion inhibitor. Each macrocycle can bind to metal ions giving rise to six possible configurations. (**fig 2**)

3. Previously synthesized Ethylene Cross-Bridged analogues have proven to be even more potent antagonists than AMD3100. A potential problem with these complexes is stability. The Propyl Cross-Bridged versions may be more stable.

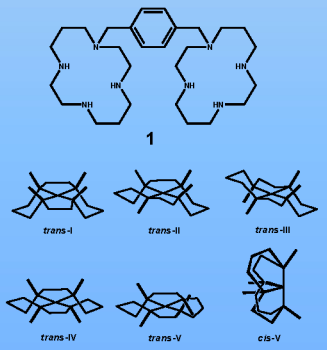


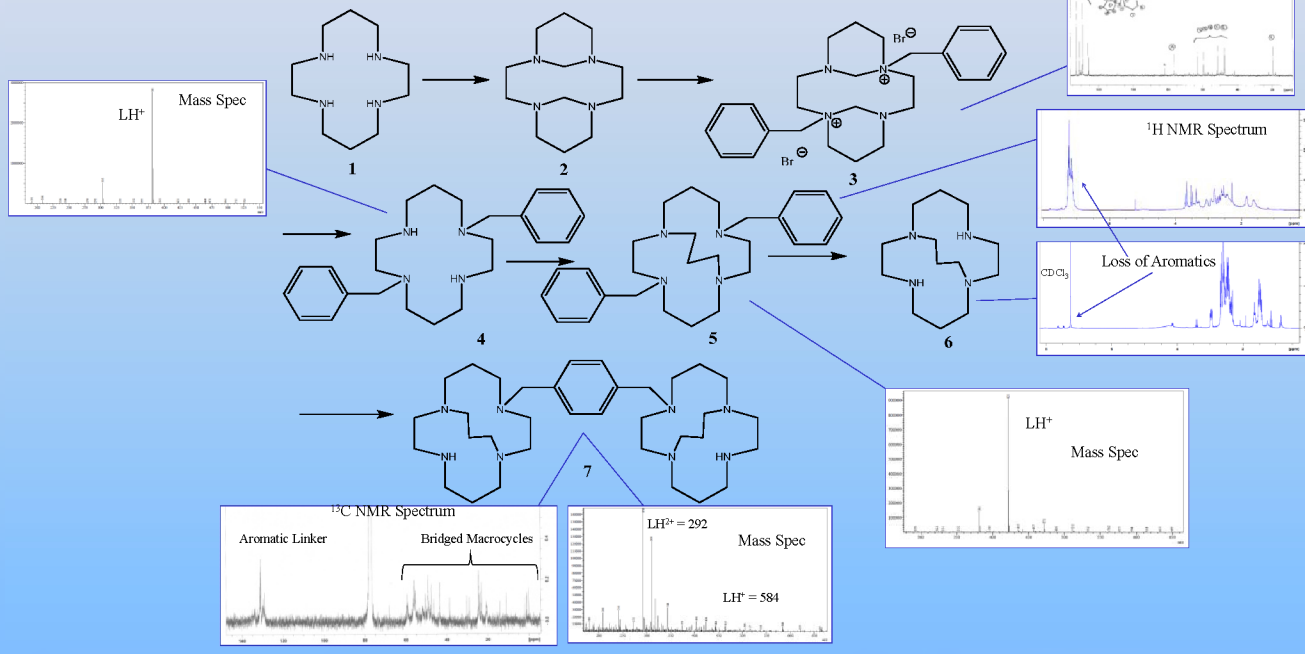
Figure 2. AMD3100 and the six possible macrocyclic configurations.

Conclusion

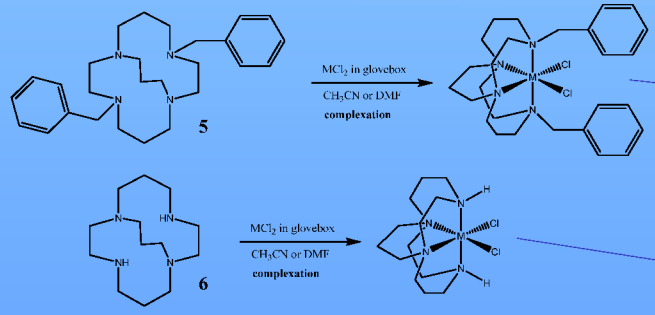
Propyl Cross-Bridged bis-linked bridged tetraazamacrocycles are difficult, but possible to produce. Metal ion complexation with single-macrocycle analogues proceeds smoothly following known procedures. The resulting complexes will inform our understanding of the requirements for producing even more efficient CXCR4 antagonists of this class. Chemical characterization of the complexes produced need to be completed prior to complexation with the bis-linked analogues and biological testing of the CXCR4 binding ability of these new compounds.

Synthesis and Characterization of the Propyl Cross-Bridged Ligands

Methods: Synthetic routes extending our bis-linked ligand syntheses to synthesize and link a propyl cross-bridged cyclam were developed. The propyl cross-bridged cyclam is a challenging synthesis with rather low yields. Linking two of these macrocycles with a xylene group proceeded efficiently.



Synthesis and Characterization of the Transition Metal Complexes



Results: The ligand syntheses of the Propyl Cross-Bridged ligands proceeded similarly to the previously developed bis-ligand routes. Complexation with desired metal ions for single-macrocycle analogues proceeded as expected.

Elemental Analyses of Propyl Bridged Cyclam Complexes

	%C	%H	%N
$[Mn(C_{27}H_{40}N_4)][MnCl_4]$			
Calculated	48.23	6.00	8.33
Found	49.56	6.47	9.47
$[Fe(C_{27}H_{40}N_4)][FeCl_4] \bullet H_2O$			
Calculated	46.85	6.11	8.10
Found	46.97	5.71	7.85
$[Cu(C_{27}H_{40}N_4)(C_2H_3O_2)](PF_6) \bullet 2.5H_2O$			
Calculated	47.50	6.60	7.64
Found	47.54	5.93	7.66
$[Co(C_{13}H_{28}N_4)(C_2H_3O_2)](PF_6) \bullet NH_4PF_6 \bullet H_2O$			
Calculated	26.33	5.45	10.23
Found	26.42	5.06	9.49
$Mn(C_{13}H_{28}N_4)Cl_2 \bullet 3H_2O$			
Calculated	34.26	7.52	12.29
Found	34.36	6.66	12.41
$Fe(C_{13}H_{28}N_4)Cl_2 \bullet H_2O$			
Calculated	37.12	7.19	13.32
Found	37.23	7.15	13.28

Acknowledgements

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