Stabilization of G-Quadruplex DNA by FRET

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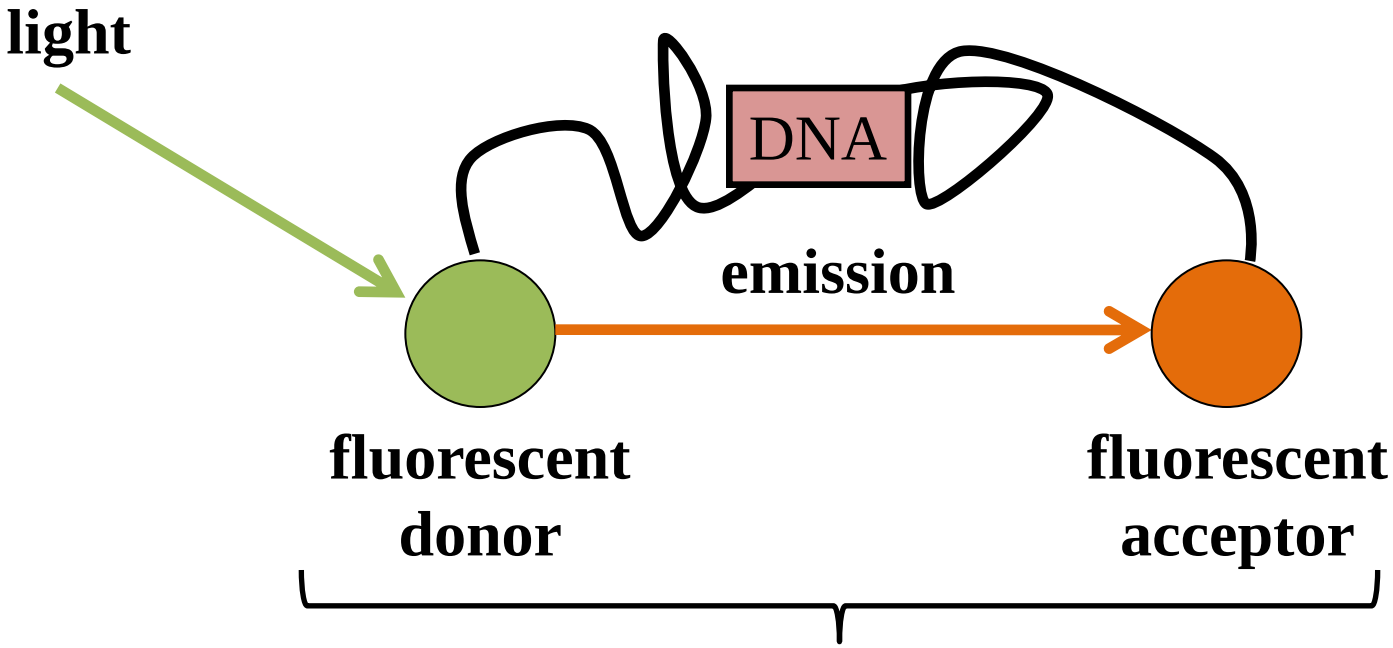
TBIC Meeting – February 7th, 2012

Fluorescence Resonance Energy Transfer (FRET)

Used to obtain data on biomolecular **structure**

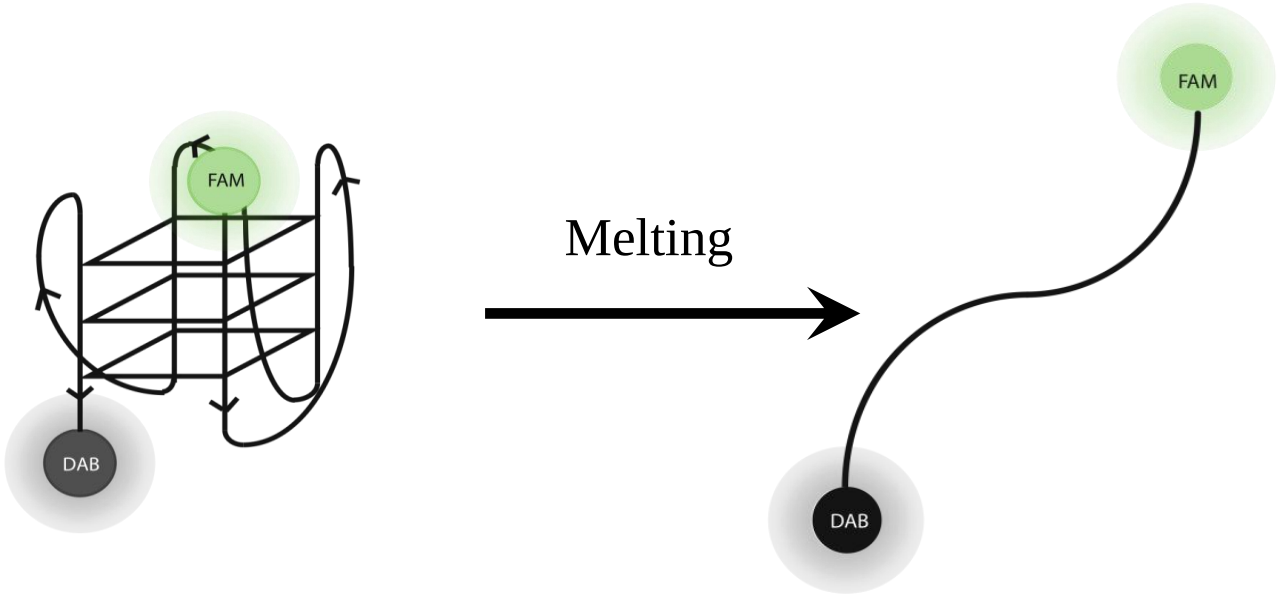
Quick way to assess **stabilization** of GQs by drugs



When probes are close: acceptor absorbs most emitted light

When probes are far apart: acceptor cannot absorb light

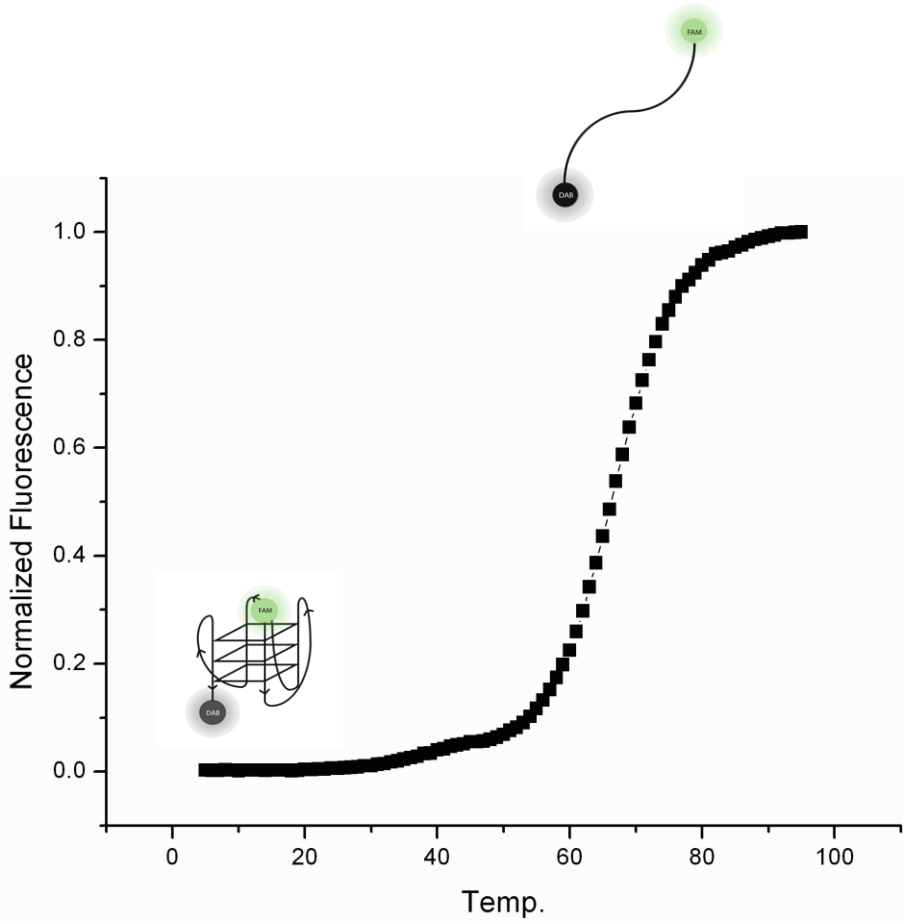
F21D – Fam-GGG(TTAGGG)$_3$-Dabcyl

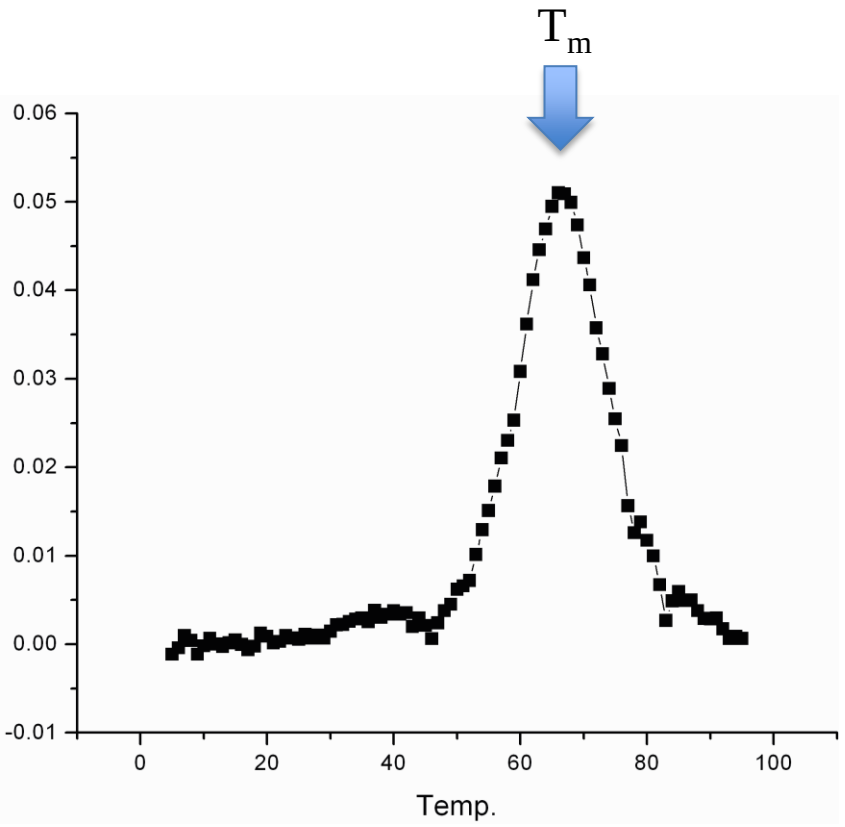


(Probes close)

(Probes far apart)

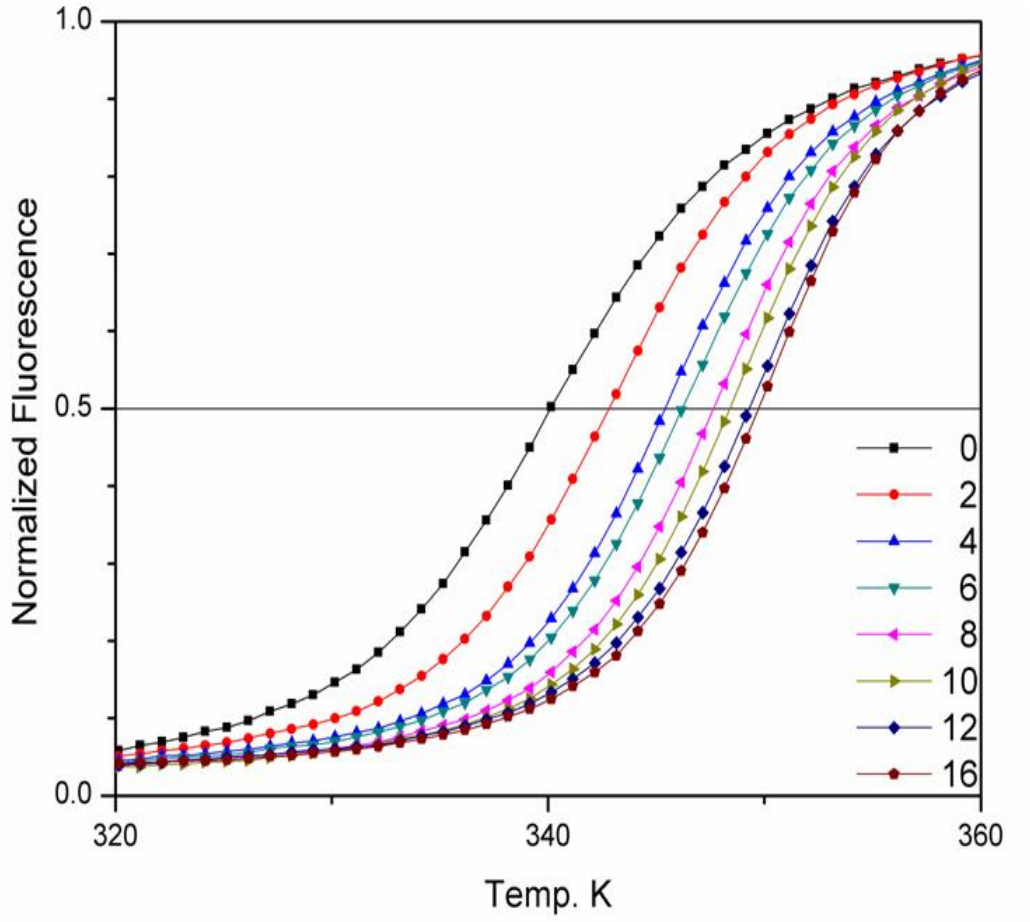
Example of FRET Melting Data





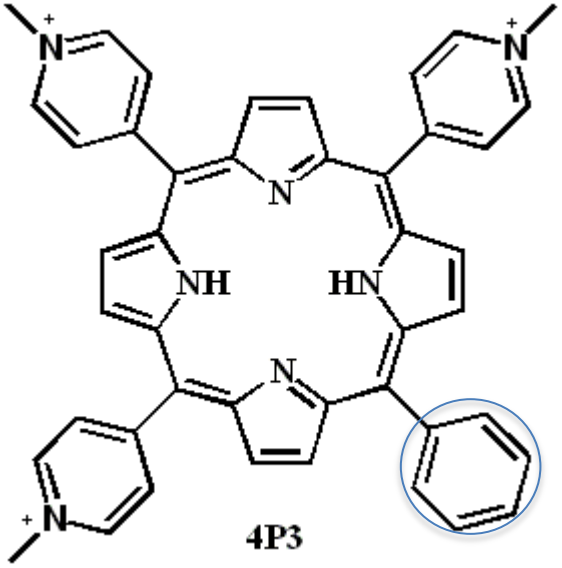
First derivative curve

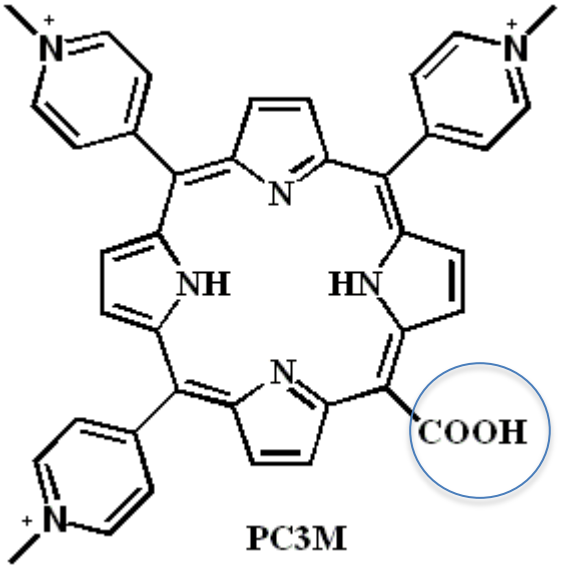
Example Stabilization Data

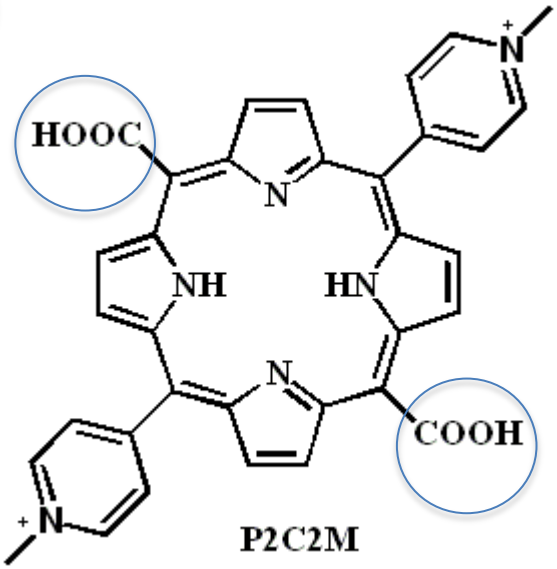


Adding NMM increases the melting temperature of F21D

Porphyrins Currently Under Investigation

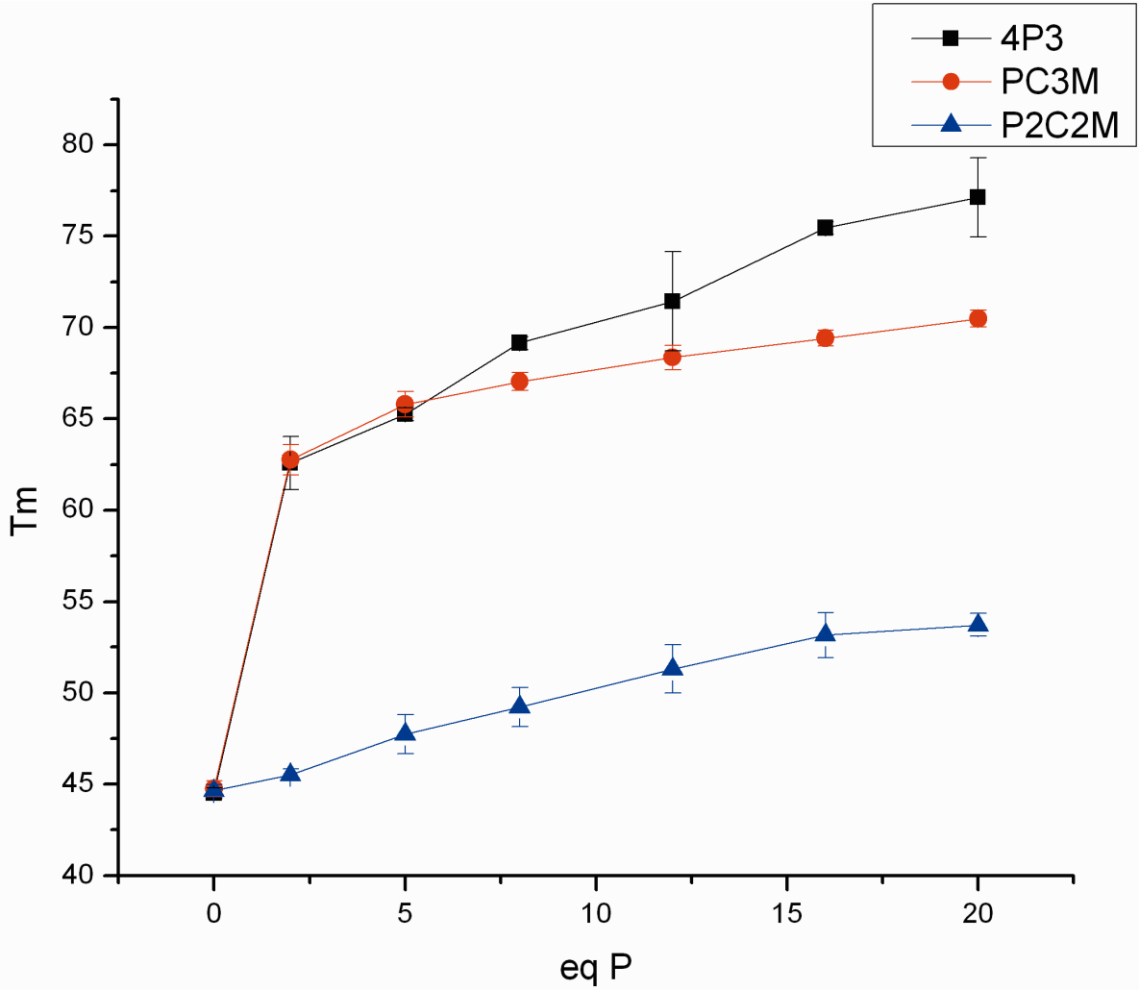






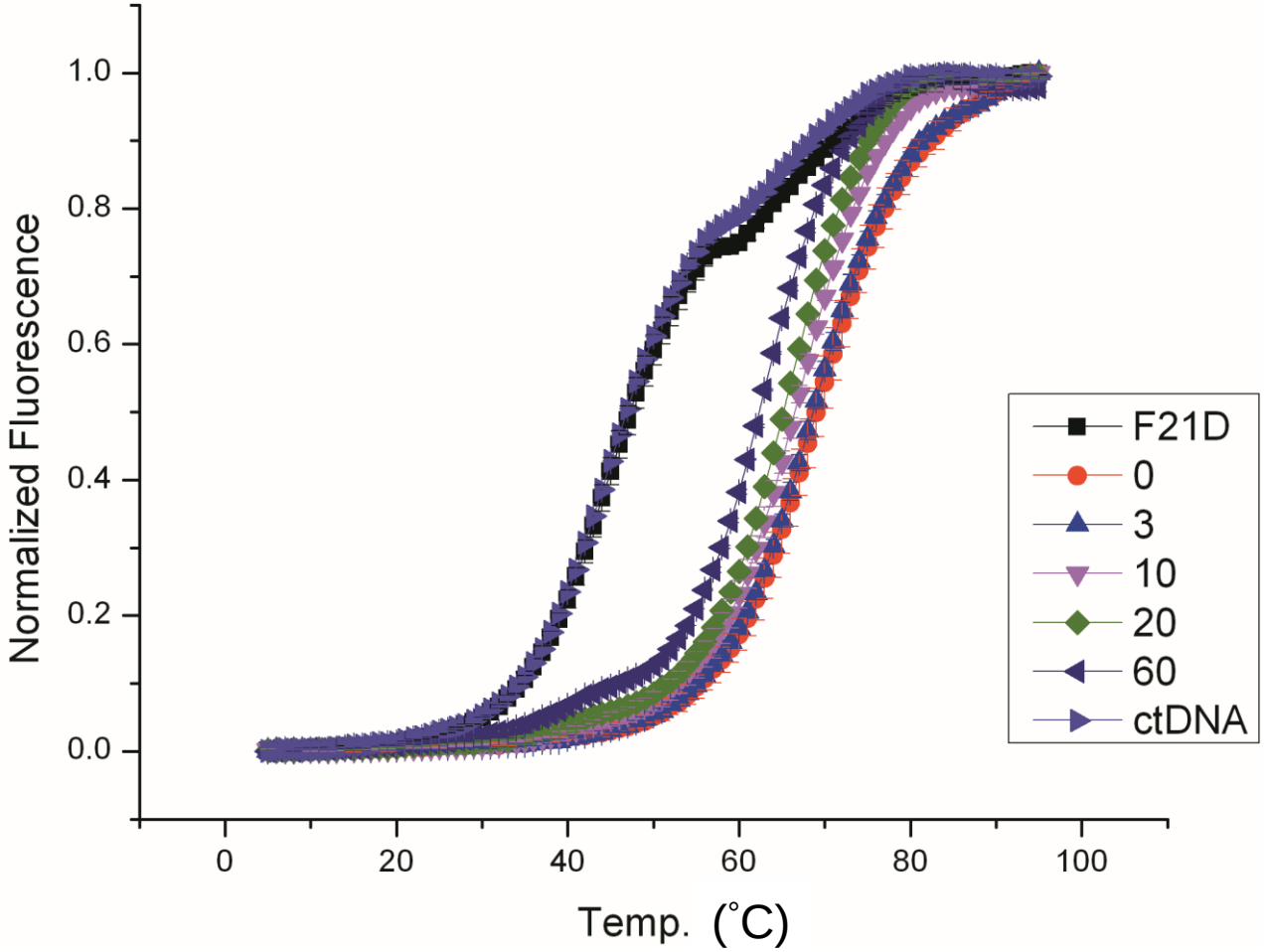
Piotr Habdas
Roberto Purello

Stabilization



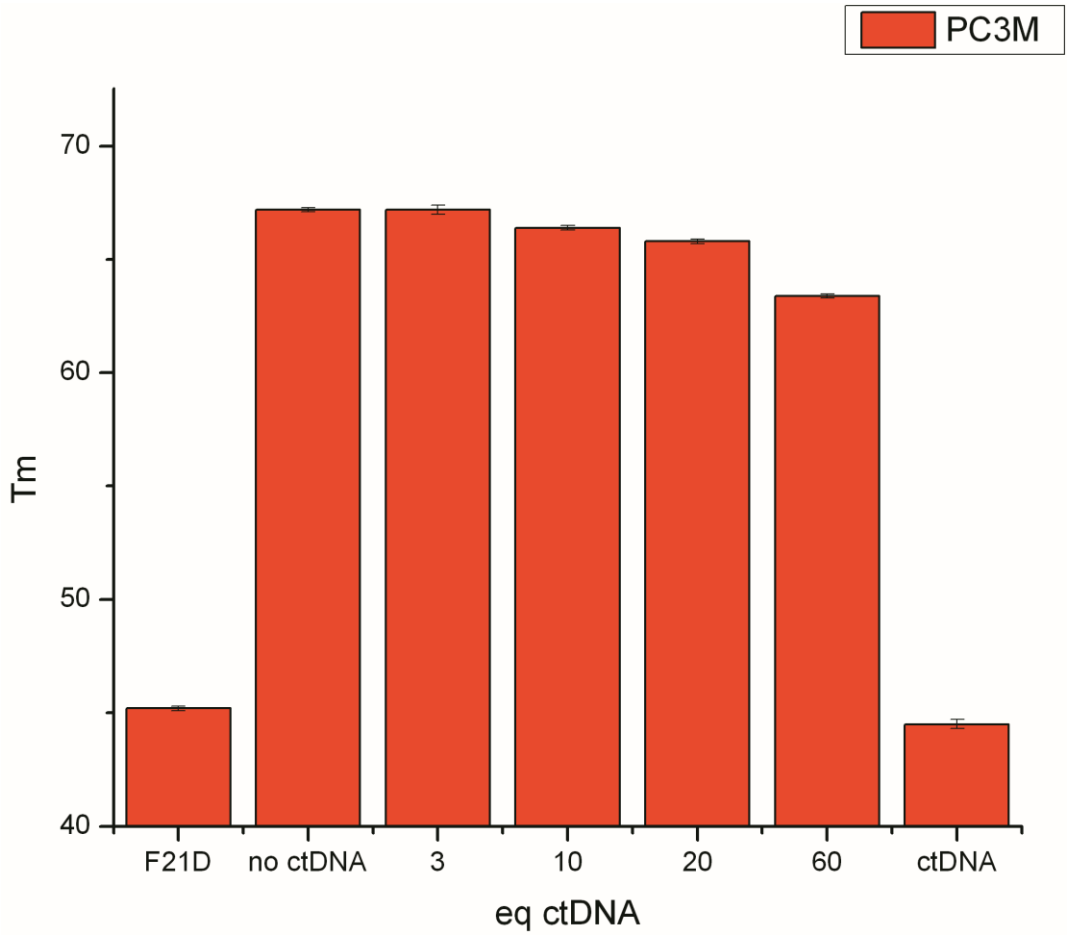
4P3 and PC3M are excellent stabilizers.
P2C2M exhibits some stabilization for GQs.

Competition Data for F21D + 4P3 in the presence of ctDNA



Adding ctDNA decreases the T_m of F21D + 4P3 only slightly

Competition



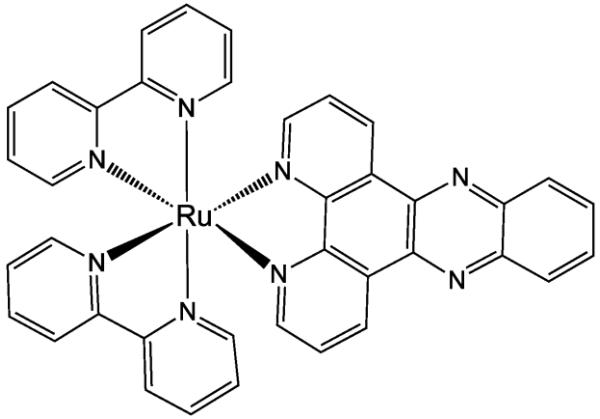
PC3M is highly selective for G-quadruplex DNA

Future Plans

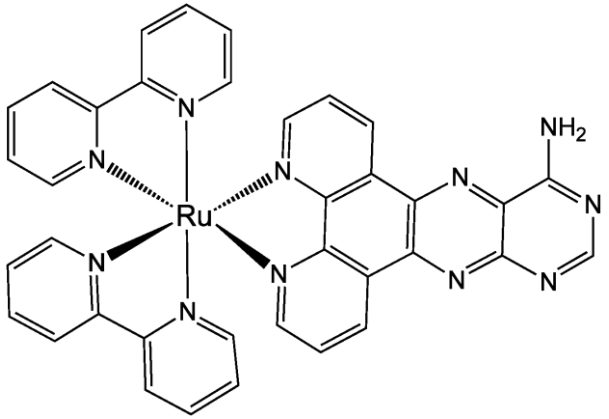
- Repeat competition study with current porphryins
- If competition study is confirmed, perform detailed characterization of porphyrin binding to DNA

Ruthenium complexes as potential quadruplex ligands

$[Ru(bpy)_2L]^{2+}$



dppz

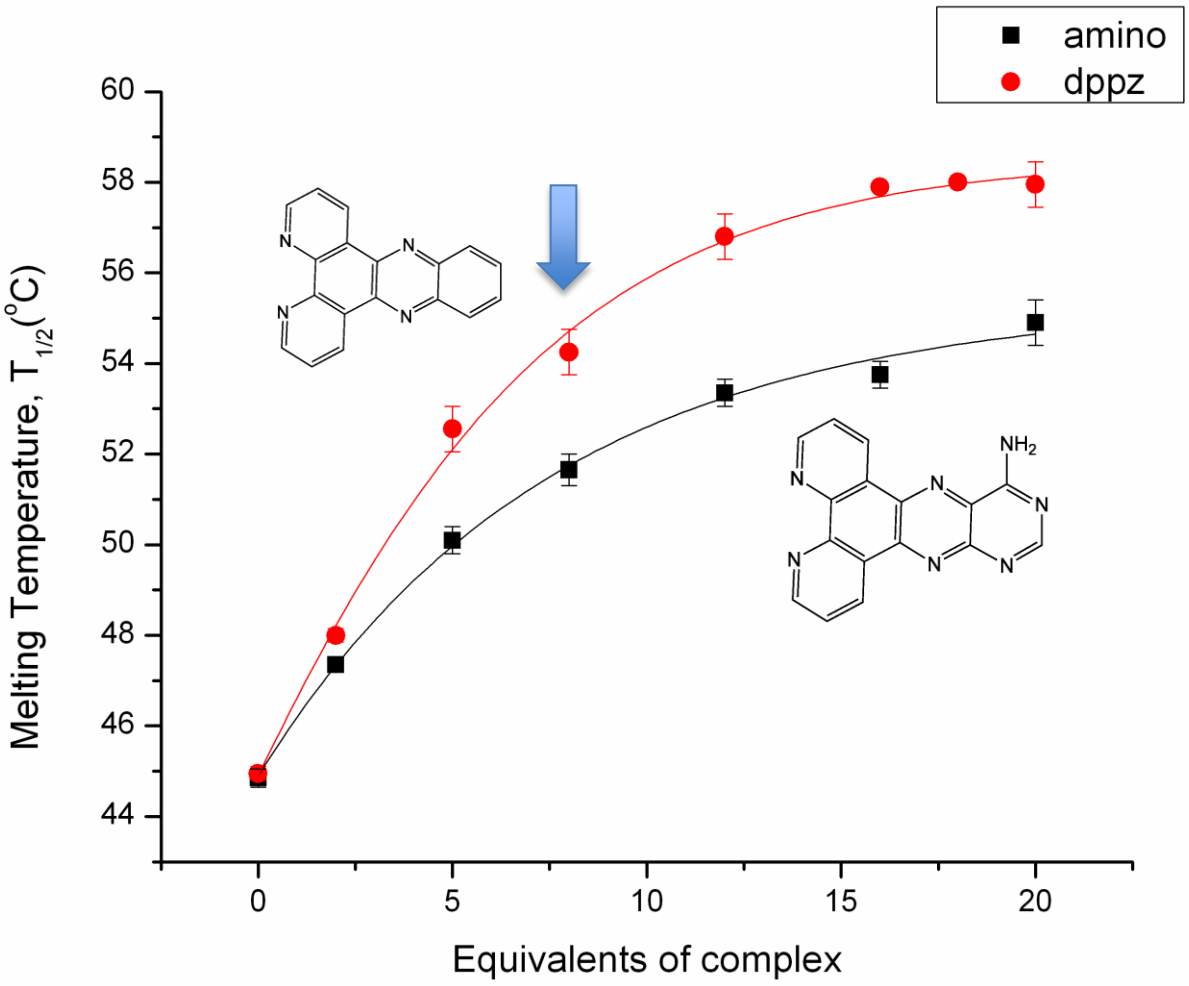


amino

Compounds from Benjamin Williams, Sharon Burgmayer *et al*.

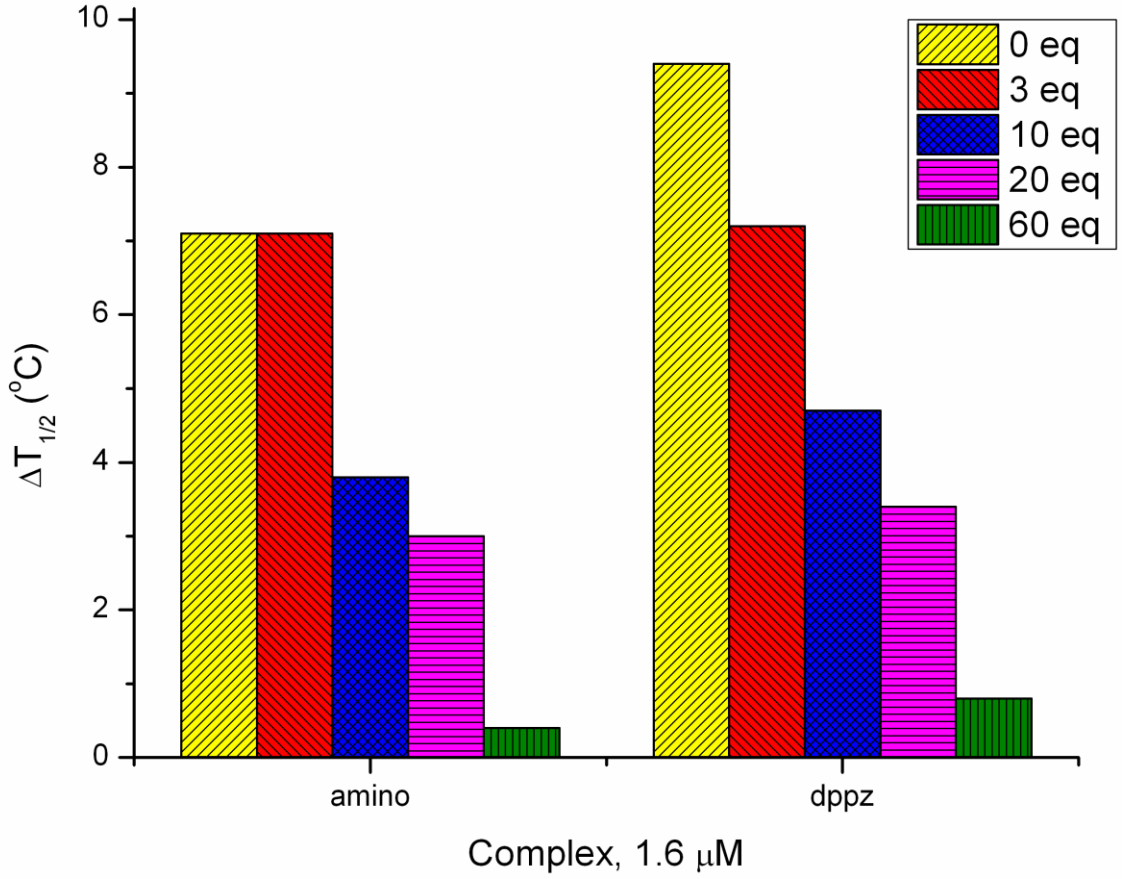
Bryn Mawr

Stabilization

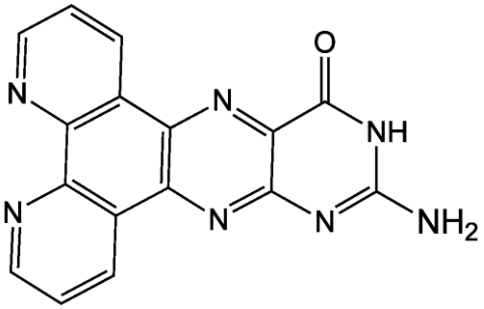


Quadruplex stabilization of these ligands is promising

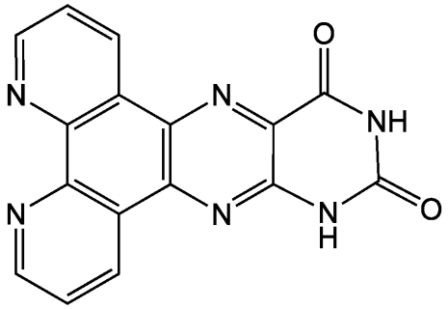
Competition



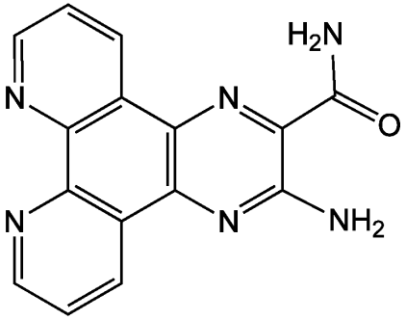
These complexes are weakly selective for GQs

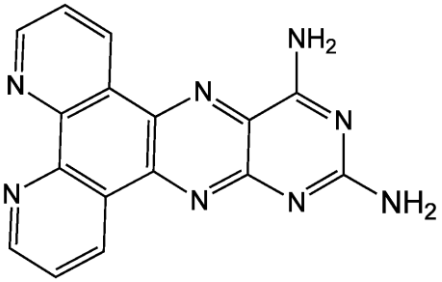


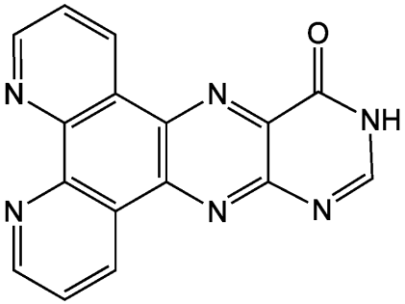
Future Plans

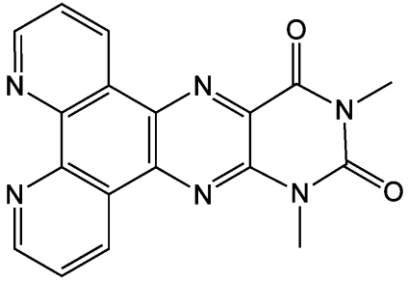


- Continue screening Ru complexes
  - Starting work on allox and pterin ligands
- Detailed characterization of binding









Acknowledgements

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  - Jack Nicoludis
  - Steven Barrett
- Nick Kaplinsky
- Collaborators
  - Burgmayer *et al*
  - Purello and Habdas