quadruplex stabilization

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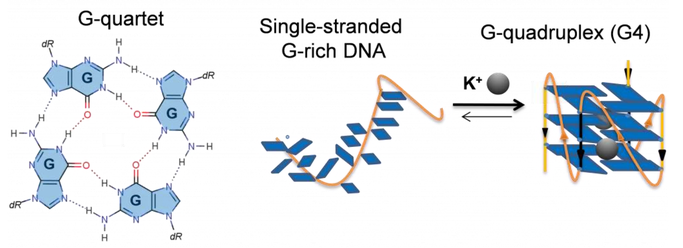
Introduction

Derivates of new aromatic scaffolds as G-quadruplexes ligands

G-quadruplexes (G4s) have received considerable attention in recent years, due to evidence of their occurrence in living cells[1]. Formed by stacks of guanine quartets, G4s belong to the wide class of non-canonical nucleic acid structures. Putative G4 forming sequences are distributed in genomic regions relevant for numbers of pathologies, spanning from cancer to viral infections, where they can act as regulators of genetic information transfer[2]. In this context, G4-targeting is regarded as a novel potential therapeutic approach for the treatment of associated diseases[3].

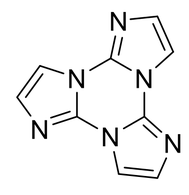


Structural features of a selective G4 ligand

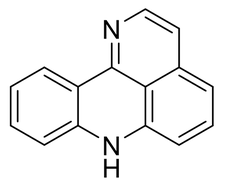
- extended planar aromatic systems
- positively charged tethered substituents

Taking inspiration from the recent literature on G4 ligands[4] and relying on the scaffold hopping strategy,[5] we selected three different heterocyclic frameworks, potentially able to bind G4s by stacking the external G-tetrads. We functionalized these scaffolds with proper polar or positively charged flexible groups for binding to G4 loops/grooves, and/or with alkylating warheads for more selective covalent targeting. To investigate the G4 binding properties of the new molecules. Under preliminary in vitro studies, some ligands proved to inhibit cancer cells proliferation, not affecting healthy cells used as control.

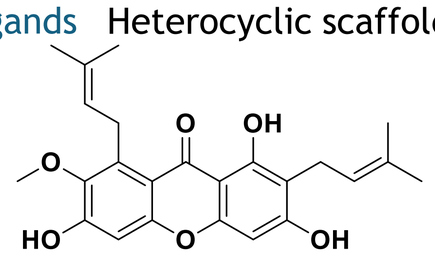
Aromatic scaffolds as G-quadruplexes ligands Heterocyclic scaffolds.



cyclic triimidazole



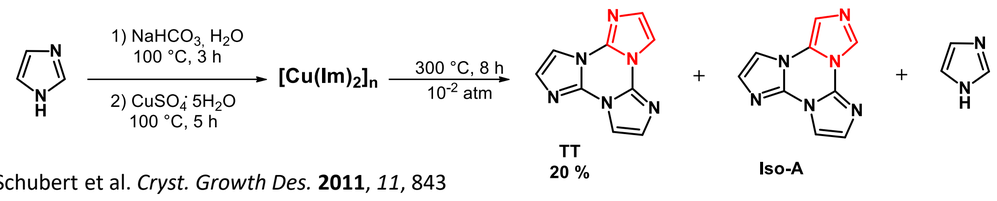
pyridoacridine



α-mangostin

Cyclic Trimidazole

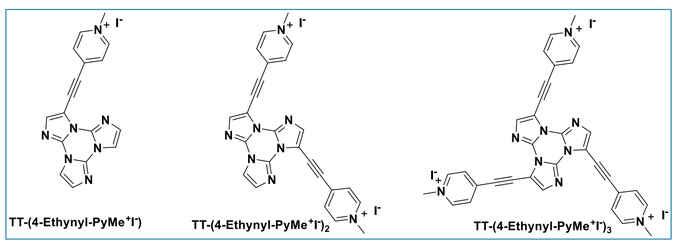
TT synthesis

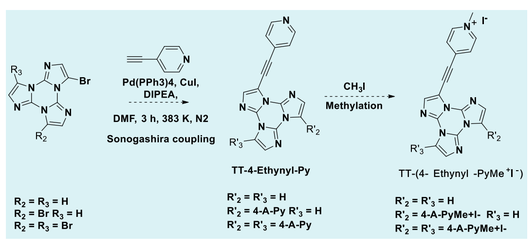


Schubert et al. *Cryst. Growth Des.* **2011**, *11*, 843

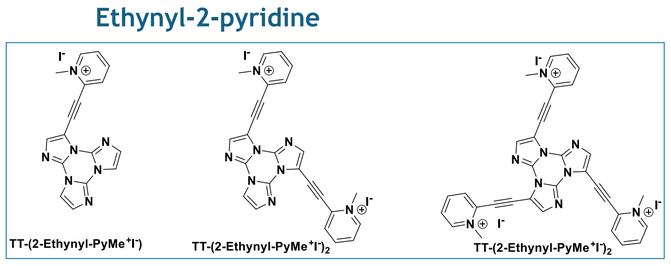
New derivates with side chains TT

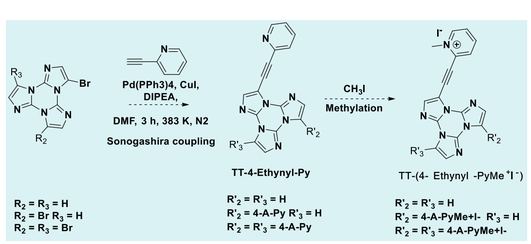
Ethynyl-4-pyridine



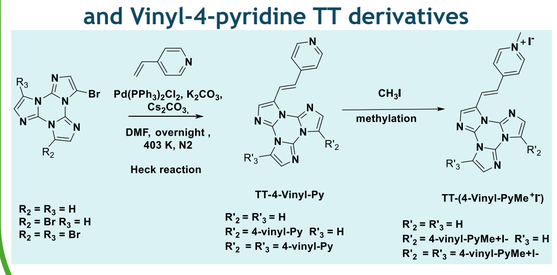


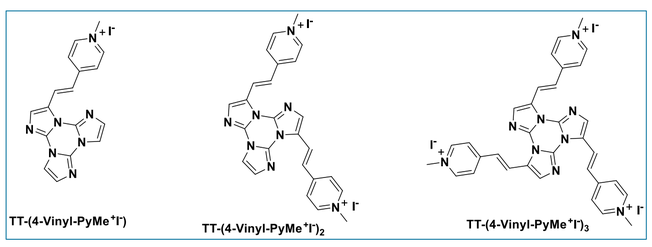
Ethynyl-2-pyridine



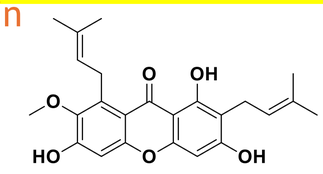


and Vinyl-4-pyridine TT derivatives

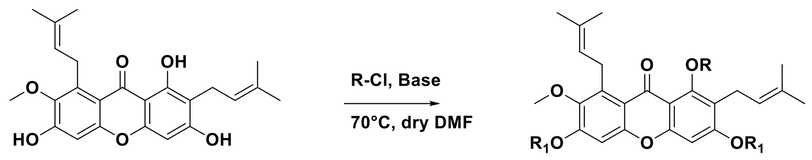




New derivates α-mangostin



Derivates o-Alkilation



Di-sotituted

1 R: H R1:

2 R: H R1:

3 R: H R1:

4 R: H R1:

5 R: H R1:

Tri-sotituted

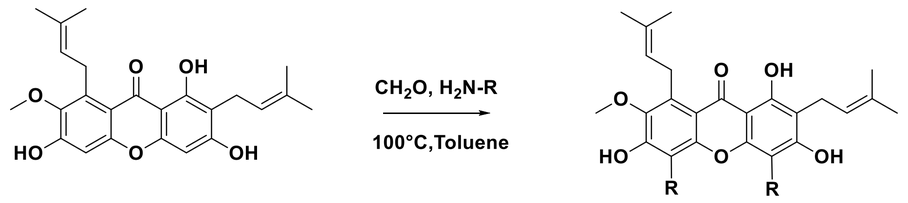
6 R,R1:

7 R,R1:

8 R,R1:

9 R,R1:

Derivates Mannich reaction



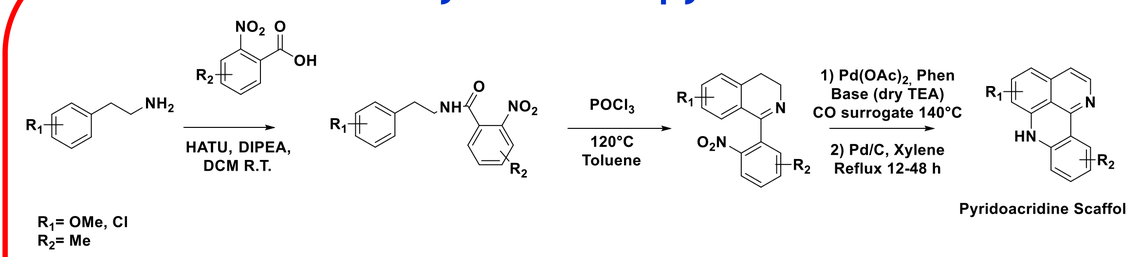
13 R:

14 R:

15 R:

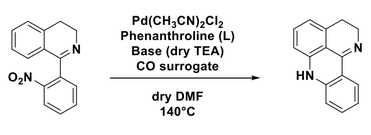
Pyridoacridine

Total Synthesis of pyridoacridine

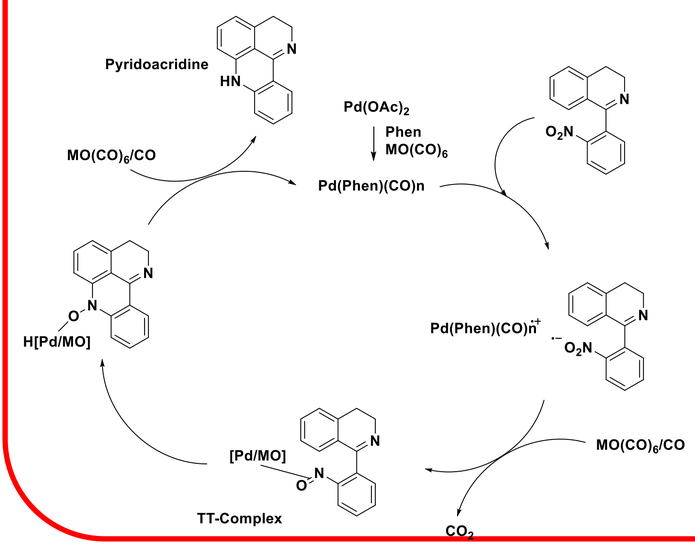


R1= OMe, Cl
R2= Me

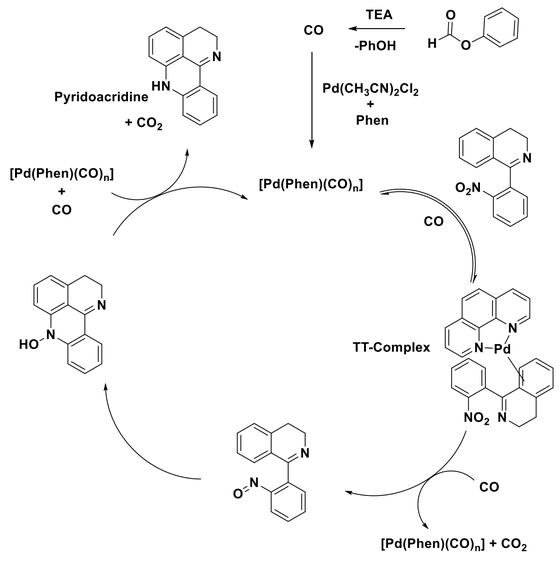
Cyclization reaction into pyridoacridine



Previuos Mechanism with $Mo(CO)_6$



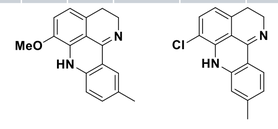
Our Mechanism with CO surrogate



Results of screening and optimization of cyclization into pyridoacridine

Entry	Pd	mol %	L	mol %	HCOOH (eq)	Ac_2O (eq)	dry TEA (eq)	HCOOPh (eq)	solvent	mL	T (°C)	t (h)	Conversion	Selectivity	Calculated Yield	Isolated Mmol	Isolated yield
1	$Pd(CH_3CN)_2Cl_2$	1%	1,10-phenanthroline	5%	3	3	3	/	CH_3CN	5	130	16	30%		0%		
2	$Pd(CH_3CN)_2Cl_2$	1%	1,10-phenanthroline	5%	/	/	1	3	CH_3CN	5	130	16	23%		9%		
3	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	10	10	10	/	CH_3CN	5	140	16	87%		36%		
4	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	/	/	1	14	CH_3CN	5	140	16	49%		33%	0.03	20%
5	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	/	/	1	10	CH_3CN	5	140	24	38%		44%		
6	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	10	10	10	/	CH_3CN	5	140	24	68%		39%		
7	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	10	10	1	/	DMF	5	140	24	89%		66%	0.15	100%
8	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	/	/	10	10	DMF	5	140	24	100%		88%	0.16	100%
9	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	10	10	10	/	DMF	5	140	24	88%		55%	0.091	60%
10	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	/	/	1	10	DMF	5	140	24	100%		93%	0.17	100%
11	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	/	/	1	5	DMF	5	140	24	63%		68%		
12	$Pd(CH_3CN)_2Cl_2$	2%	1,10-phenanthroline	5%	5	5	5	/	DMF	5	140	24	91%		58%	0.10	66%
13	$Pd(CH_3CN)_2Cl_2$	1%	1,10-phenanthroline	2,5%	/	/	0.5	5	DMF	5	140	24	38%		N.I.		

pyridoacridine already synthesized



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