Computational Screening and Design of G-quadruplex Ligands Targeting *c-MYC* in Breast Cancer

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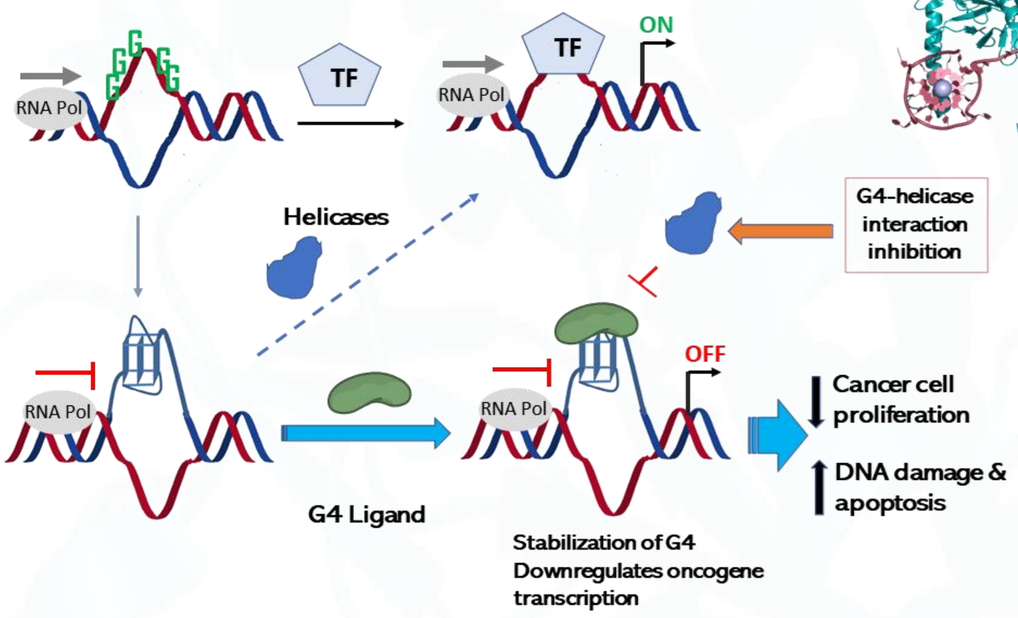
Introduction

- G-quadruplexes (G4) are four-stranded nucleic acid secondary structures formed by guanine-rich sequences of DNA or RNA.
- G4 in *c-MYC* oncogene has biological functions in cancer cells [1].
- G4 in the *c-MYC* promoter is reported to be unwounded by the helicase DHX36, that recognizes specifically G4s and promotes the regulation of DNA transcription[1,2].



Aim of study

In silico identification and chemical synthesis of Indoloisoquinolones derivatives

- G4 Stabilizers
- Inhibitors of Helicase interaction

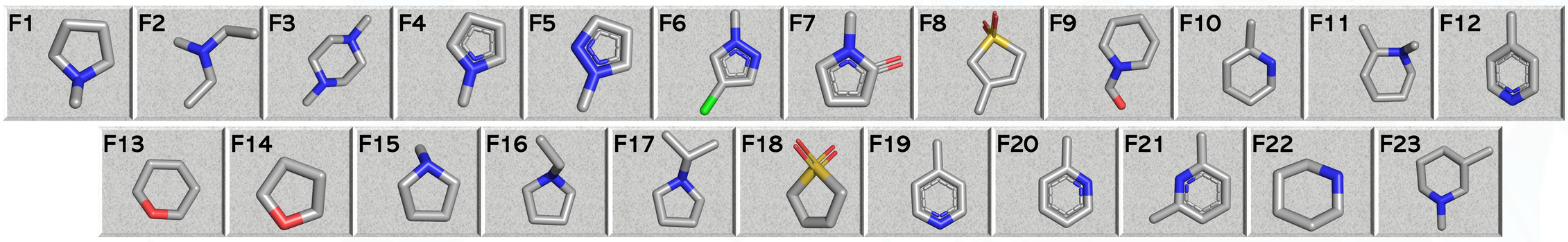
Workflow

SOFTWARES : Vinardo
Autodock Vina 1.1.2
Autodock Vina 1.2.2
DockER ranking

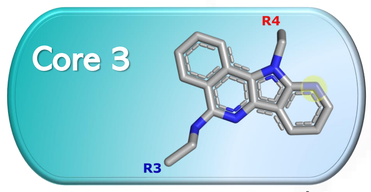
→ Docking with different scoring functions

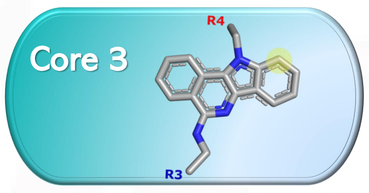
→ Library of (23 fragments with ligands3 cores) 1104

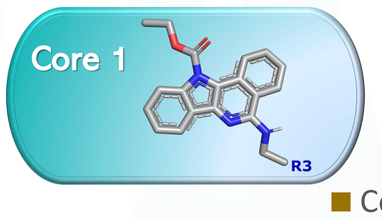
→ Build compounds (smiles and 3D)

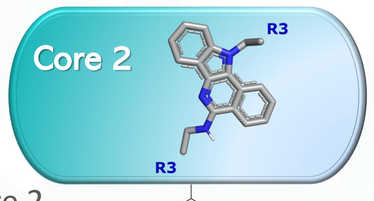


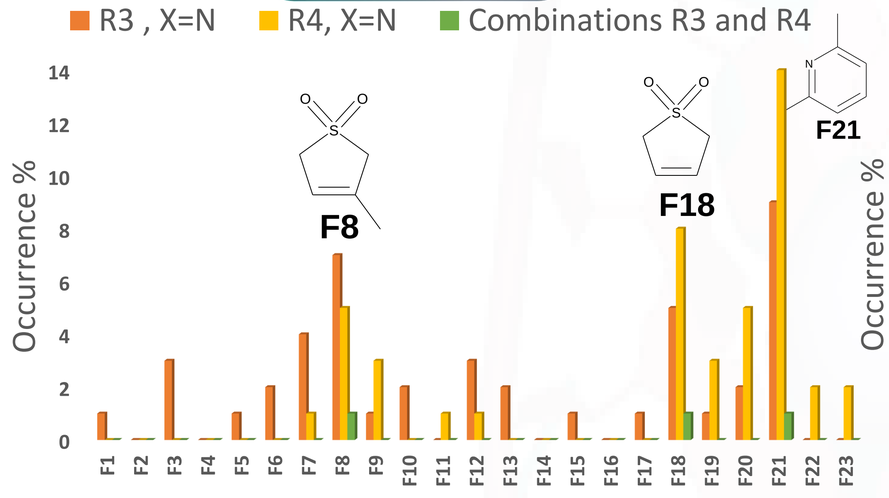
Results

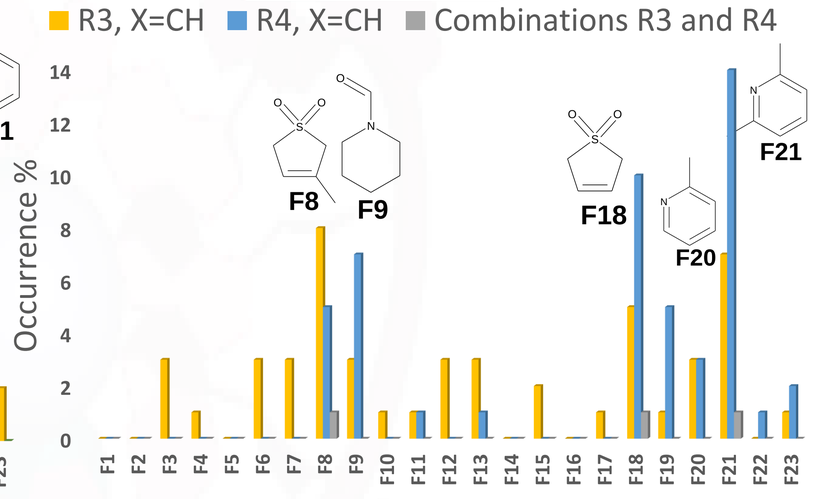


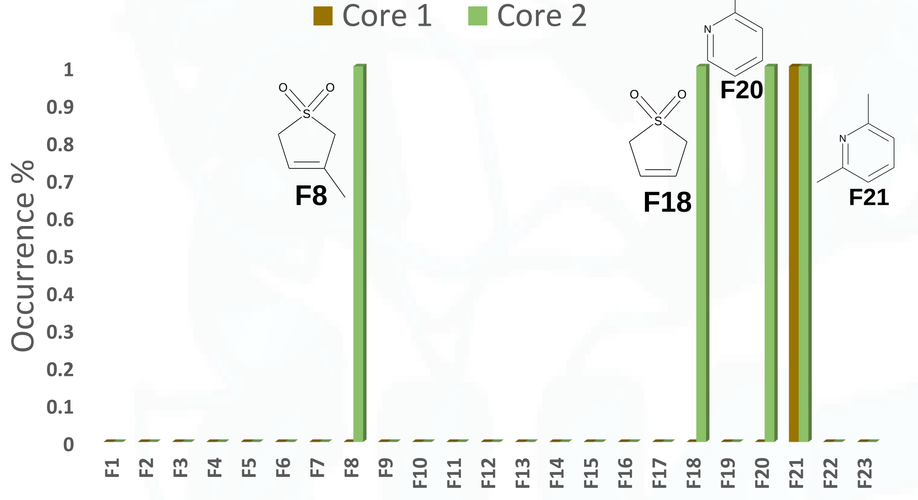






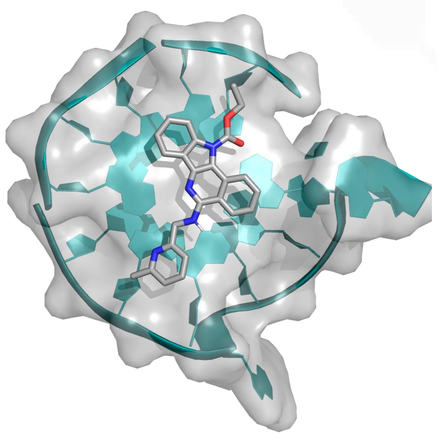




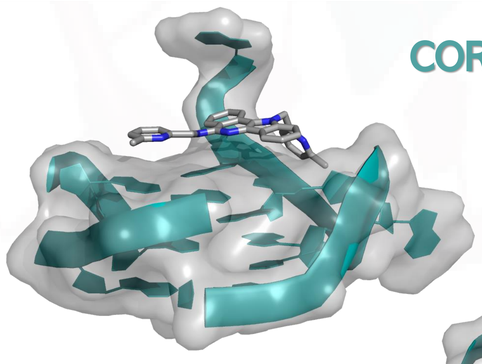


Fragments showing higher occurrence in docking consensus calculations : **F8**, **F18**, **F21**, **F9**, and **F20**

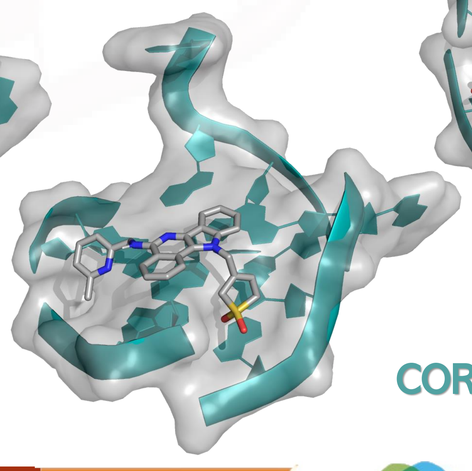
CORE 1_F21



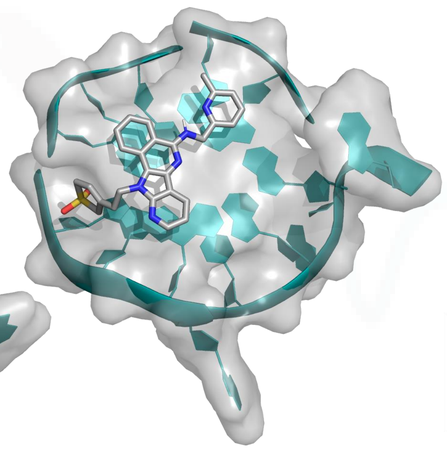
CORE 2_F21



CORE 3_F21_CH_F18



CORE 3_F21_N_F8

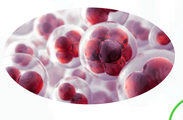


Conclusion

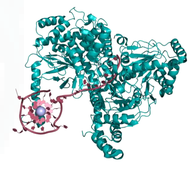
- ✓ Core 3 derivative compounds were the ones showing higher binding affinity to *c-MYC* G4.
- ✓ We have identified the most promising indoloisoquinolones stabilizers of *C-MYC* G4

Next Step …

Chemical synthesis of fragments →



in vitro test. →



Optimization of the compounds with molecular dynamics

References

[1] Paulo, A.; Castillo, C. C.; Neidle, S. *Compr. Med. Chem. III* **2017**, *5–8*, 308–340.
[2] Chen, M. C.; Tippana, R.; Demeshkina, N. A.; Murat, P.; Balasubramanian, S.; Myong, S.; Ferré-D'amaré, A. R. *Nat.* **2018**, *558* (7710), 465–469.

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