DESIGN AND SYNTHESIS OF SMALL MOLECULES AS PROTEIN-PROTEIN INTERACTION STABILIZERS.

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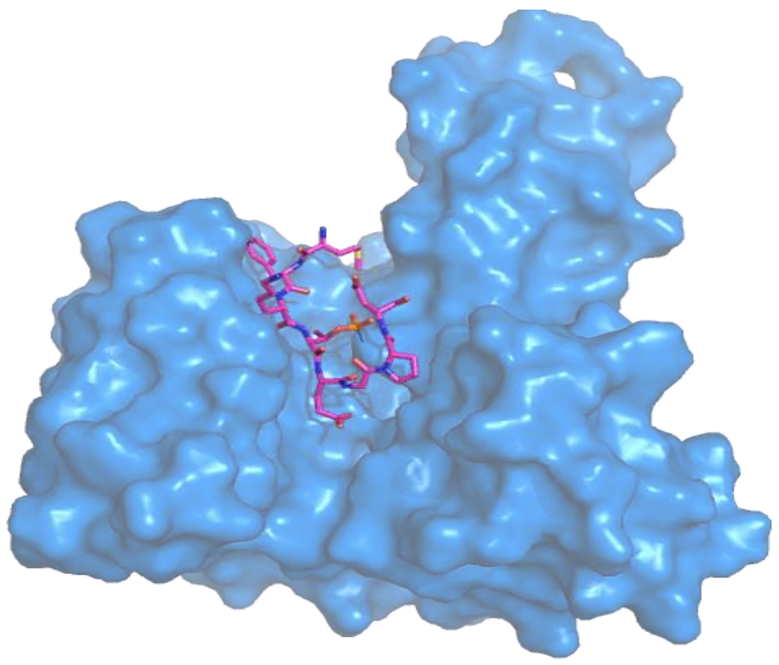
1 Introduction

Targeting protein – protein interactions (PPI) has emerged as a significant strategy in drug discovery. [1] In this project we are focusing on the 14-3-3 protein family and more specifically on the interaction between 14-3-3 and p53.[2] Since 14-3-3 is a positive regulator of p53 and p53 is mutated in 50% of human cancers, stabilization of the PPI is expected to lead to tumor suppression. [3]

2 Design

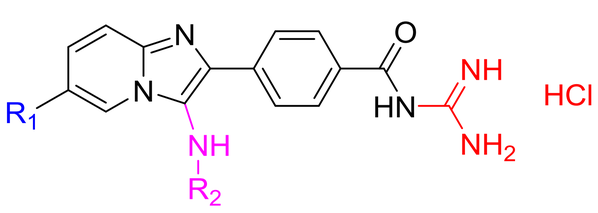
- The 14-3-3/p53 PPI is large, hydrophobic, with no deep pockets
- A polar fragment was co-crystallized with the PPI and showed a stabilization effect
- Having the fragment as starting point, we chose two scaffolds based on multi-component reaction chemistry (MCR) for the rapid generation of diverse libraries
- The scaffolds derive from the Groebke-Blackburn-Bienaymé reaction (GBB), which leads to flat, aromatic structures, with promising shape complementarity

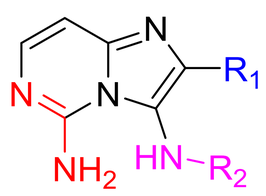


The PPI of 14-3-3 (blue surface) with p53 (magenta sticks).

3 Synthesis

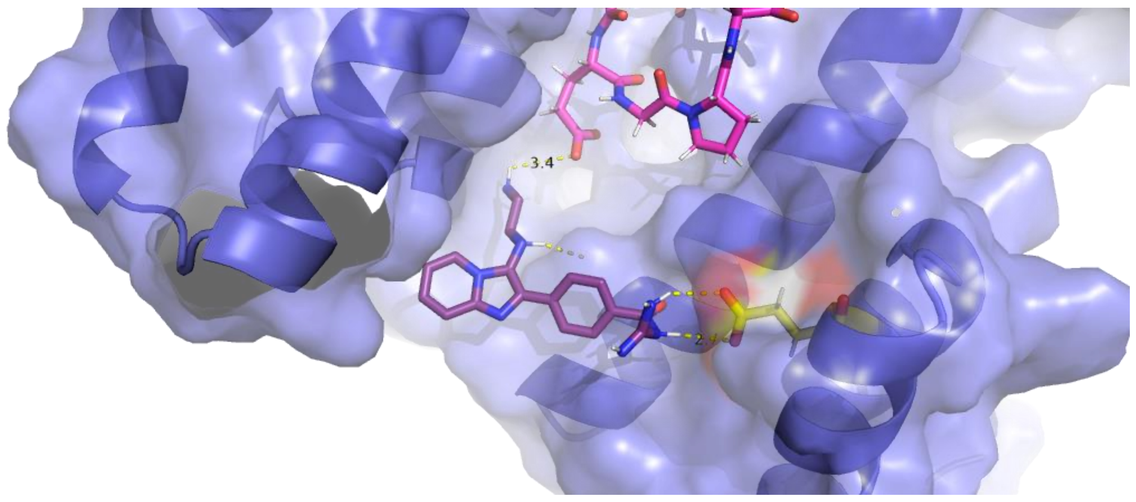
- Derivatives from 2 scaffolds were synthesized after docking studies



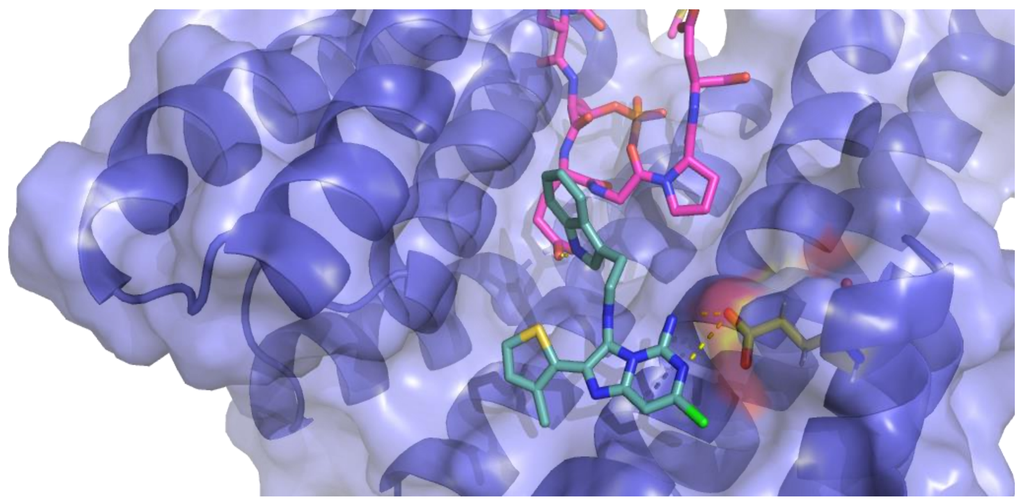


9 derivatives (Scaffold 1), 10 derivatives (Scaffold 2) were synthesized

- The two scaffolds can be accessed through a two step synthesis
- Commercially available starting materials are used
- Diversity is achieved through the two points of variation in each scaffold (blue and magenta substituents)
- The moieties in red are participating in the main interactions with the PPI



Docking pose for derivative of Scaffold 1



Docking pose for derivative of Scaffold 2

4 Biological evaluation

- Isothermal titration calorimetry (ITC)
- Surface plasmon resonance (SPR)
- Fluorescence polarization assay (FP)
- Crystallography

Acknowledgement

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References

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