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Living Grant for International Graduate Students

Synthesis of Novel Suramin Analogs with Anti-Proliferative Activity via FGF1 and FGFRD2 blockade

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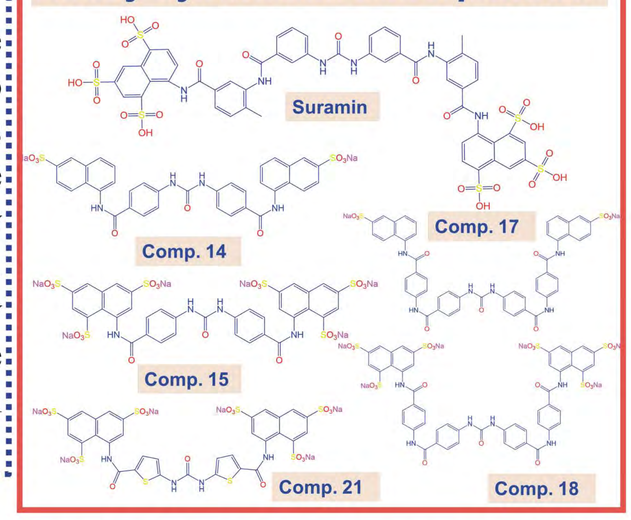
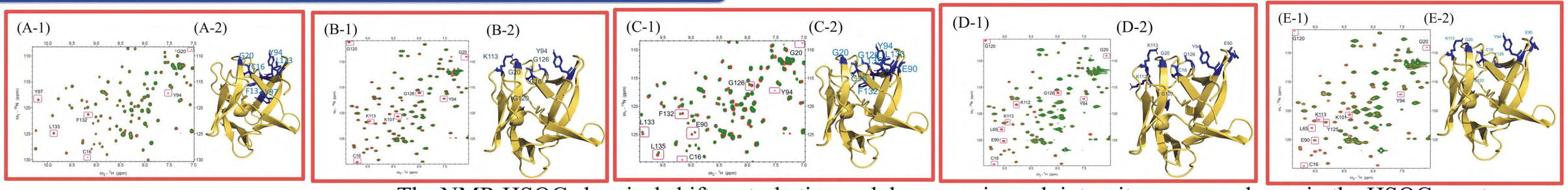
Introduction

A promising approach in cancer therapy is the inhibition of cell proliferation using small molecules. In this study, we report the synthesis of suramin derivatives and their applications. We used NMR spectroscopy and docking simulations to confirm binding sites and three-dimensional models of the ligand-protein complex. The WST-1 assay was used to assess cell viability and cell proliferation in vitro to evaluate the inhibition of protein–protein interactions and to investigate the anti-proliferative activities in a breast cancer cell line. All the suramin derivatives showed anti-proliferative activity by blocking FGF1 binding to its receptor FGFRD2. The dissociation constant was measured by fluorescence spectroscopy. The suramin derivatives synthesized herein show potential as novel therapeutic agents for their anti-proliferative activity via the inhibition of protein–protein interactions. The cytotoxicity of these suramin derivatives was lower than that of the parent suramin compound, which may be considered a significant advancement in this field. Thus, these novel suramin derivatives may be considered superior anti-metastasis molecules than those of suramin.

Newly synthesized compounds

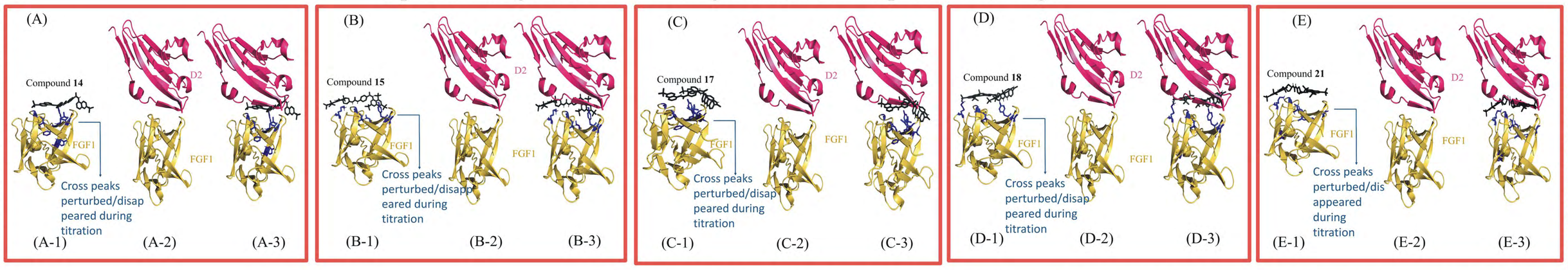


Results and Discussion: HSQC Results

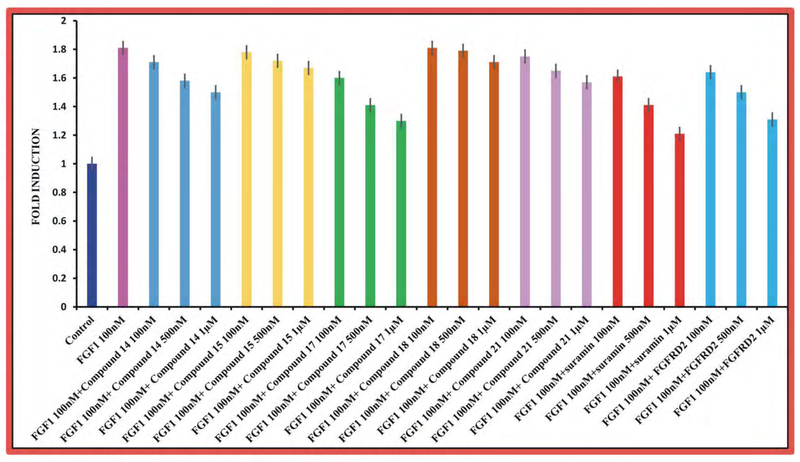


HADDOCK Results

The NMR HSQC chemical shift perturbation and decreases in peak intensity occur as shown in the HSQC spectra upon the addition of suramin derivatives to the protein. These changes provide significant data about protein-drug binding and provide insight about the binding site between the protein and drugs.



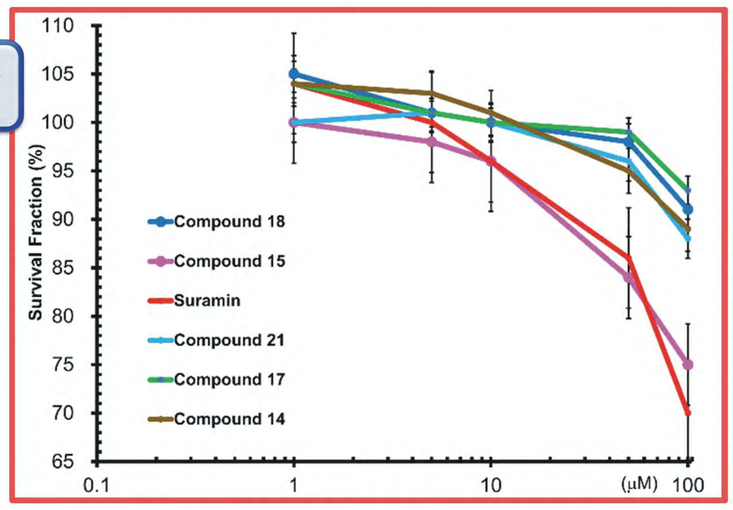
WST-1 Assay for cell proliferation



HADDOCK results revealed that these five suramin derivatives block in between the FGF1 and D2 and interrupted the signal transduction cascade and, thus, could interfere with downstream cell proliferation.

WST-1 Assay for cytotoxicity

The breast cancer cell line MCF-7 was used for both cell proliferation and cytotoxicity assay, which is known to express the FGFR. The cell proliferation results revealed that the FGF1-stimulated cell proliferation could be attenuated by co-treatment with all five suramin derivatives in a dose-dependent manner and the results for the cytotoxicity showed that compounds were less toxic to MCF-7 cells than to suramin.



Conclusion

- A series of signal transduction cascades are triggered by the process of auto-phosphorylation when FGF1 binds to FGF1R2D2 leading to cell proliferation.
- Suramin derivatives directly interacts with the growth factor itself in hydrophobic way and blocked the interaction between FGF1 and FGF1R2D2, thus causes reduction of cell proliferation.
- Thus we conclude that these newly synthesized suramin derivatives act as an anti proliferant by blocking the interaction between FGF1 and FGFRD2.