Design of Indoloisoquinoline derivatives as potential inhibitors of the interaction between c-MYC:G4 and helicase

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Guanine rich DNA or RNA sequences may form a noncanonical higher-order structure called G-quadruplexes (G4). The structural features of G4 have been described to promote genomic instability in DNA replication, modulate transcription and translation and have been found with high prevalence in promoter regions of many cancer-related genes such as *c-MYC* (1). G4s are transient structures that can be unfolded by helicases, a protein family that binds and remodel nucleic acid structures and nucleic acid protein complexes. Some helicases, such as DHX36, prefer binding and unwinding G4 nucleic acid structures (2). In previous reports, G4 structure stabilization by small organic molecules, has shown promising results as anticancer drug target (1,3). However, many difficulties related to lipophilicity and specificity towards different G4s have been found. To overcome these obstacles, in this project, we propose to design, synthesize and evaluate indoloisoquinoline (IDQ) derivatives as potential inhibitors of the *c-MYC*:G4-DHX36 interaction, taking advantage of the recently resolved crystallographic structure of DHX36 helicase in complex with this G4 (2). The IDQ core was combined with a library of purchasable fragments to create a final library of compound derivatives, which was then used in a molecular docking screening campaign targeting the *c-MYC*:G4 structure in complex with DHX36 (5). Different scoring functions from different molecular docking softwares (4-6) were used to derive a final consensus scoring (7), and consequently identify a subset of IDQ fragment substituents shown to be prevalent in the lowest binding affinity docking solutions with *c-MYC*:G4. These results will now guide the synthesis of the most promising ligands, which selectivity and stabilization will afterwards be validated with several *in vitro* assays. The obtained results will guide additional structure-activity *in silico* calculations, to allow the optimization of the most promising inhibitors.

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References:

1. Paulo A. *et. al.* (2017) Third Edition. Vols. 5–8, Comprehensive Medicinal Chemistry III. Elsevier; 308–340 p. 2. Chen, M. C., *et al.* (2018). Nature, 558(7710), 465–483. 3. Cadoni E, *et al.* (2021). *Pharmaceuticals*. 14(7) 669. 4. Trott, O., Olson, A. J. (2009). *Journal of Computational Chemistry*, NA-NA. 5. Eberhardt, J., Santos-Martins, D., Tillack, A. F., & Forli, S. (2021). *Journal of Chemical Information and Modeling*, *61*(8), 3891–3898. 6 Koebel MR, *et al.*. (2016) J Cheminform. May 18;8:27. 7. Ochoa, R. *et al.*, (2021) Journal of Molecular Graphics and Modelling, Volume 109, 108023.