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Abstract

FOXM1 Inhibitors: Emergence of a Neglected Binding Force †

Seyed Amirhossein Tabatabaei Dakhili, David Javier Perez, Keshav Gopal, John Reyes Ussher and Carlos Alberto Velázquez Martínez *

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB T6G 2R3, Canada

* Correspondence: Velazque@ualberta.ca

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Abstract: The Forkhead boX M1 (FOXM1) is an essential transcription factor for normal activation of the cell cycle and cell replication. However, increasing evidence suggests that overexpression of this protein correlates with cancer development and poor patient prognosis, which makes FOXM1 a promising drug target in medicinal chemistry. Based on a computer-based molecular modeling protocol reported by our group, we hypothesized that FOXM1 inhibitors bind to the FOXM1 DNA binding domain (DBD) by (i) a pi-sulfur interaction with His287, and (ii) a halogen bonding with Arg297 within the FOXM1 DNA binding domain. To test this hypothesis, we modified the chemical structure of a known "forkhead domain inhibitor" (FDI) to synthesize and screen a series of FDI-derivatives. In this regard, we removed or replaced two essential groups in FDI-6, namely (i) the 4-fluorophenyl position and (ii) the heterocyclic sulfur atoms. We determined the inhibitory effects of test molecules on the protein expression of FOXM1 using a triple negative breast cancer cell line (MDA-MB-231), and then we measured their binding affinity to DNA by electrophoretic mobility shift assay (EMSA). Next, using a site-directed mutagenesis technique, we confirmed specific binding interactions exerted by these molecules. These results validate the role of essential binding interactions (pi-sulfur binding) predicted by computer simulations and provide preliminary evidence to postulate a mechanism of action exerted by "direct" FOXM1 inhibitors.

Keywords: FOXM1; transcription factor inhibitor; FDI-6