Design and Spectral Validation of RAD51 Inhibitors Based on BRC4 (1523-1546)

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Abstract

RAD51 is a core factor for homologous recombination (HR) to repair DNA double strand breaks and overexpressed in breast cancer cells. Truncated peptide BRC4 (1523-1537) was obtained by computer simulation which had the highest binding free energy targeting RAD51. To enhance the binding affinity to the target protein, six nicotinic acid derivatives were modified at the N-terminal of BRC4 (1523-1537) by Fmoc solid-state synthesis to obtain nicotinamide-modified peptides. The interaction of RAD51 (181-200) with BRC4 (1523-1537) and nicotinamide-modified peptides were verified by circular dichroism (CD) spectroscopy and fluorescence spectroscopy. In conclusion, modifying small molecule pharmacophores can improve binding ability. According to spectral results, 2-chloro-5-fluoronicotinic acid modified BRC4 (1523-1537) has the most significant influence on the secondary structure of RAD51 (181-200); binding constant is 1.1×10^{4} L·mol $^{-1}$. Cell experiments showed that BRC4 (1523-1537) modified with nicotinic acid N-oxide had the best inhibitory effect on the proliferation of MDA-MB-231 cells.

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