

## Drugging the “Undruggable” DNA-binding Domain of STAT3 for Inhibition of Cancer Cell Migration and Invasion

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Signal transducer and activator of transcription 3 (STAT3) is constitutively activated in malignant tumors, and its activation is associated with high histological grade and advanced cancer stage. STAT3 has been shown to play important roles in multiple aspects of cancer aggressiveness including migration, invasion, survival, self-renewal, angiogenesis, and tumor cell immune evasion by regulating the expression of multiple downstream target genes. Thus, inhibiting STAT3 promises an attracting strategy for treatment of advanced tumors with metastatic potential. Previously, we identified a STAT3 inhibitor, inS3-54, by targeting the “undruggable” DNA-binding site of STAT3 using an improved in-silico screening approach. To further develop this inhibitor, we identified 79 analogues of inS3-54 for the structure-activity relationship analysis. Further study of five effective analogues shows that four analogues (#1, 18, 26, and 69) inhibit STAT3-dependent colony formation of hematopoietic progenitor cells, indicating a higher selectivity for STAT3 than their parental compound, inS3-54 and another analogue #74. These compounds also (1) inhibit STAT3-specific DNA binding activity; (2) suppress proliferation of cancer cells that have constitutively activated STAT3; and (3) inhibit migration and invasion of cancer cells. In addition, analogue #26-conjugated Sepharose beads could also pull down STAT3, revealing a possible direct binding between STAT3 and the inhibitor. Taken together, we conclude that it is possible to inhibit STAT3 by targeting its DNA-binding domain for discovery of anticancer therapeutics and for treatment of metastatic cancers.

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