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Identification of a New Series of STAT3 Inhibitors by Virtual Screening

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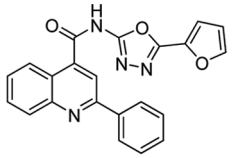
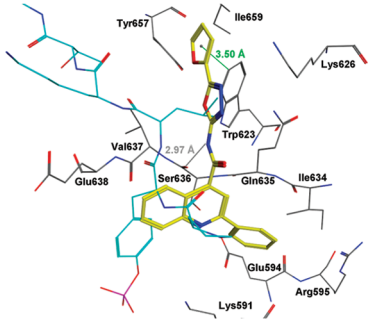
ABSTRACT The signal transducer and activator of transcription 3 (STAT3) is considered to be an attractive therapeutic target for oncology drug development. We identified a *N*-[2-(1,3,4-oxadiazolyl)]-4-quinolinecarboxamide derivative, STX-0119, as a novel STAT3 dimerization inhibitor by a virtual screen using a customized version of the DOCK4 program with the crystal structure of STAT3. In addition, we used in vitro cell-based assays such as the luciferase reporter gene assay and the fluorescence resonance energy transfer-based STAT3 dimerization assay. STX-0119 selectively abrogated the DNA binding activity of STAT3 and suppressed the expression of STAT3-regulated oncoproteins such as c-myc and survivin in cancer cells. In contrast, a truncated inactive analogue, STX-0872, did not exhibit those activities. Oral administration of STX-0119 effectively abrogated the growth of human lymphoma cells in a SCC-3 subcutaneous xenograft model without visible toxicity. Structure−activity relationships of STX-0119 derivatives were investigated using the docking model of the STAT3-SH2 domain/STX-0119.

KEYWORDS STAT3, dimerization, inhibitor, virtual screening, protein−protein interaction, antitumor





The signal transducers and activators of transcription (STATs) are a class of transcription factor proteins that regulate cell growth and survival by modulating the expression of specific target genes. They are activated by various extracellular signaling proteins such as cytokines (e.g., IL-6) or growth factors. Upon activation of cytokine receptors or growth factor receptors, STATs are recruited and phosphorylated at a tyrosine residue adjacent to the SH2 domain by receptor-associated tyrosine kinases [e.g., Janus kinase (JAK)] or the intrinsic kinase activity of growth factor receptors [e.g., platelet-derived growth factor receptor (PDGFR)]. Once activated, phosphorylated STATs form homo- or heterodimers by reciprocal phosphotyrosine-SH2 interactions [i.e., protein−protein interaction (PPI)], and then, the dimers translocate to the nucleus, where they bind to their respective DNA binding motifs within the promoter elements of target genes and induce transcription.[1,2]

STATs consist of seven isoforms (STAT1−4, STAT5a, STAT5b, and STAT6), and among these, STAT3 is considered to be a good target for the treatment of cancer.[2−5] STAT3 drives the malignant progression of tumors through dysregulation of the expression of target proteins, including transcription factors, cell cycle regulators, survival proteins, and inducers of angiogenesis.[6] In addition, aberrant constitutive STAT3 activation is observed in a broad spectrum of solid and hematopoietic tumors.

Recently, several STAT3 inhibitors have been reported, and some of these were capable of inducing apoptosis in cancer cell lines, that is, Phaeosphaeride A,[7] Cucurbitacin Q,[8] CDDO-Im,[9] and 4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylic acid ester.[7,10] Most of these compounds function through inhibition of STAT3 signaling; however, few inhibitors of STAT3 dimerization are known (Chart S-1). Only peptide mimetics,[11] STA-21,[12] Stattic,[13] S3I-201 (NSC74859),[14] and 5,15-DPP[15] have been reported to inhibit STAT3 dimerization. Herein, we report the identification of STX-0119 as a new class of STAT3 dimerization inhibitors by virtual screening and in vitro assays. We also describe the synthesis, structure−activity relationships (SARs),

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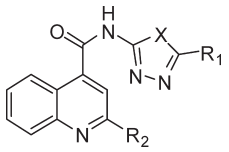
Table 1. Inhibitory Activity on STAT3 Transcription and STAT3 Dimerization



				STAT3 transcription[a]		STAT3 dimerization[b]	
compd no.	R_1	R_2	X	100 μM (%)	IC_{50} (μM)	50 μM (%)	10 μM (%)
1a (STX-0872)	2-furyl	H	O	−5		−4	−2
1b	2-furyl	Cl	O	43		NT[c]	NT[c]
1c (STX-0119)	2-furyl	Ph	O	99	74	62	9
1d	2-furyl	1-naphthyl	O	121	55	70	14
1e	2-furyl	2-furyl	O	129	66	NT[c]	NT[c]
1f	2-furyl	2-thienyl	O	91	63	56	18
1g	2-furyl	2-pyridyl	O	5		NT[c]	NT[c]
1h	2-furyl	3-pyridyl	O	12		NT[c]	NT[c]
1i	2-furyl	piperidino	O	−7		NT[c]	NT[c]
1j	Me	Ph	O	14		NT[c]	NT[c]
1k	Et	Ph	O	33		NT[c]	NT[c]
1l	COOEt	Ph	O	38		NT[c]	NT[c]
1m	Ph	Ph	O	105	66	60	43
1n	2-ClPh	Ph	O	5		NT[c]	NT[c]
1o	4-ClPh	Ph	O	115	61	NT[c]	NT[c]
1p	CH_2Ph	Ph	O	82	75	61	25
1q	3-furyl	Ph	O	103	72	55	8
1r	2-thienyl	Ph	O	86	75	56	36
1s	2-furyl	Ph	S	26		NT[c]	NT[c]

[a] STAT3-dependent luciferase reporter gene assay in HeLa cells. Percent inhibition at 100 μM or IC_{50}. [b] FRET-based STAT3 dimerization assay. Percent inhibition at 50 and 10 μM. [c] Not tested.

and biological evaluations including in vivo efficacy of STX-0119 derivatives.

We conducted virtual screening for inhibitors of STAT3 dimerization using CONSENSUS-DOCK,[16] a customized version of the DOCK4[17] program, in which three scoring functions (DOCK4, FlexX,[18] and PMF[19]) and consensus scoring[20] were utilized. The crystal structure of DNA-bound STAT3β homo dimer (PDB code 1BG1[21]) was used for the docking study. The Ala703-Pro704-pTyr705-Leu706-Lys707-Thr708 residues in the binding region of the STAT3-SH2 domain from which the DNA and the dimerization partner of STAT3 had been removed were determined to be the docking region.[12,14] We virtually screened approximately 3.6×10^5 molecules (2.7×10^5 compounds). After docking of the 3.6×10^5 3D molecules into the STAT3-SH2 domain using CONCENSUS-DOCK was completed, we selected 136 compounds by consensus scoring (see the Supporting Information) and visual inspection (for detecting the compounds that still had some hydrogen bonds or ionic interactions following removal of the improperly strained conformers). Then, using a STAT3-dependent luciferase reporter gene assay (HeLa cells) of these 136 compounds purchased from commercial sources, we identified STX-0119 as a STAT3 inhibitor (99% inhibition at 100 μM, Table 1). A truncated analogue lacking the 2-Ph, STX-0872, was inactive in this reporter gene assay (no inhibition at 100 μM, Table 1). To examine the ability of STX-0119 to inhibit STAT3 dimerization in cells, a fluorescence resonance energy transfer (FRET) assay[22] was performed. As shown in Figure 1A, pretreatment of the cells with STX-0119 prior to IL-6 stimulation resulted in the reduction of FRET signals. In addition, a chromatin immunoprecipitation (ChIP) assay of STX-0119-treated MDA-MB-468 cells revealed a reduction in amplification of the c-myc promoter, which is one of the targets for transcriptional activation by STAT3 (Figure 1C). Inhibitory activities were not exhibited by the inactive analogue STX-0872 in those assays. These results suggest that the DNA binding activity of STAT3 was effectively inhibited by STX-0119 presumably due to disruption of STAT3 dimerization in cells. To further evaluate the effects of STX-0119 against downstream transcriptional activation by STAT3, we investigated the expression of its target proteins in human breast cancer MDA-MB-468 cells. Western blotting analysis of lysate from MDA-MB-468 cells treated with STX-0119 showed that STX-0119 reduced the expression of STAT3 target proteins, namely, c-myc, cyclin D1, and survivin, in a concentration-dependent manner (Figure 1C). STX-0872, however, did not suppress the expression of those STAT3-regulated oncoproteins (data not shown). It is noteworthy that STX-0119 has no effect on the level of STAT3 or Tyr705-phosphorylated STAT3

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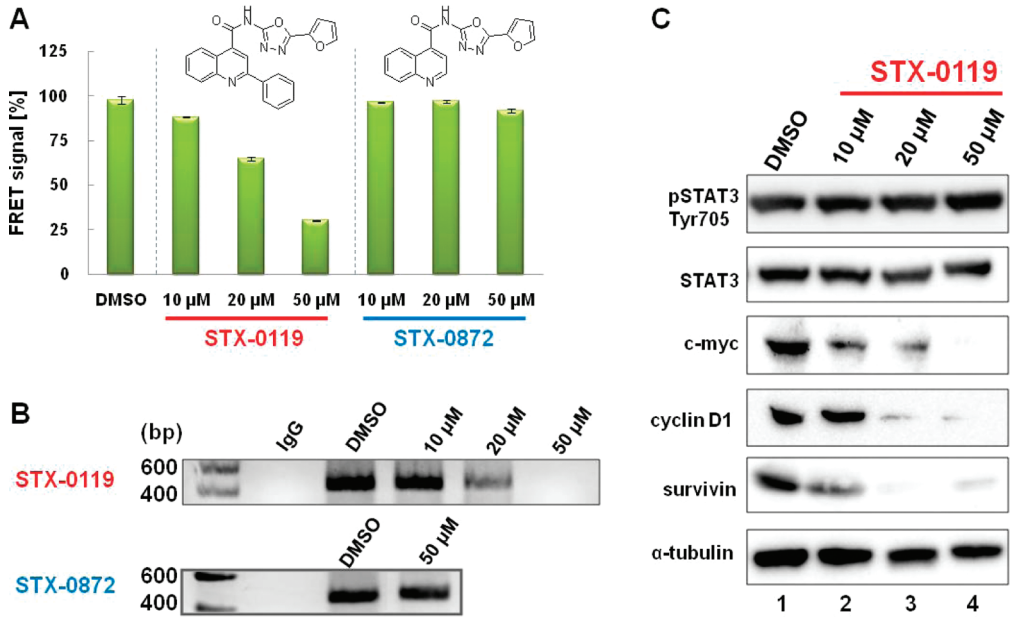


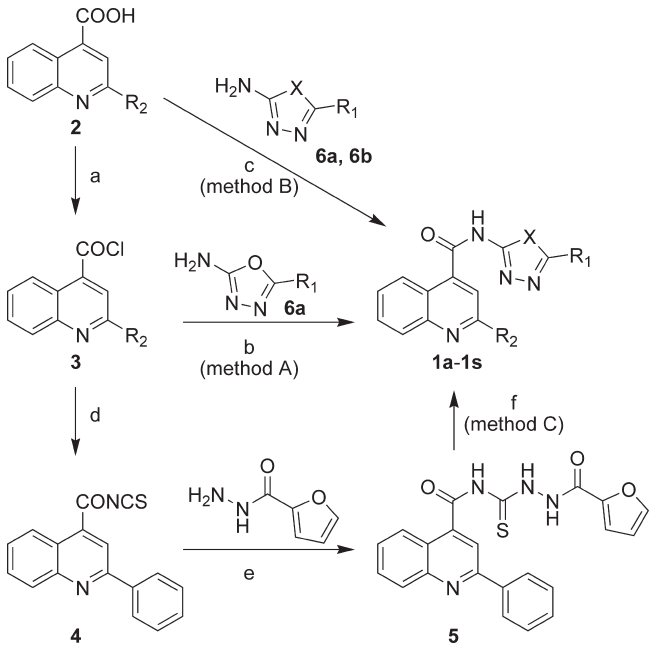
Figure 1. Functional evaluation of STAT3 inhibition in cells by STX-0119 and its inactive analogue STX-0872. (A) FRET assay: Effect of compounds on the FRET signals generated from interactions between STAT3-CFP and STAT3-YFP in HEK293 cells. (B) ChIP assay: Effect of compounds on the c-myc promoter binding by STAT3 in MDA-MB-468 cells. (C) Western blotting analysis: Effect of STX-0119 on Tyr705 phosphorylation of STAT3 and expression of STAT3-regulated oncoproteins in MDA-MB-468 cells.

(Figure 1B). This suggests that STX-0119 inhibits STAT3 dimerization through a direct interaction with the STAT3 protein and not via the modulation of upstream regulators such as JAK.

We next examined the selectivity of STX-0119 against STAT3. Nuclear lysates from MDA-MB-468 cells treated with STX-0119 were analyzed. As shown in Figure S-1A, the DNA binding activity of STAT3 was suppressed by STX-0119 treatment. No inhibition of DNA binding activity of other STAT family members, namely, STAT1, STAT5a, and STAT5b, was observed. Selective induction of apoptosis against cancer cells harboring constitutively activated STAT3 was further examined by measuring the caspase-3/7 activity in cells treated with STX-0119. The human breast cancer cell line MDA-MB-468 was shown to harbor the constitutively activated pSTAT3 (Tyr705), but MDA-MB-453 did not (data not shown). STX-0119 induced apoptosis in MDA-MB-468 cells (Figure S-1B). However, STX-0119 had a minimal effect on MDA-MB-453 cells. Taken together, the results suggest that STX-0119 selectively disrupted STAT3 dimerization and the subsequent transcriptional activity of STAT3, followed by the induction of apoptosis of cancer cells with constitutively active STAT3.

Next, we synthesized *N*-[2-(1,3,4-oxadiazolyl)]-4-quinolinecarboxamide analogues (**1**) to explore the SARs of STX-0119. The methods of synthesis are outlined in Scheme 1. Condensation of 2-amino-1,3,4-oxadiazole (**6a**) with acid halide (**3**), which was prepared from the corresponding carboxylic acid (**2**) and $SOCl_2$, provided the desired compounds (method A); however, the purification was difficult in several cases due to the formation of various byproduct. An alternative method was employed with condensation of carboxylic acid (**2**) using HATU-HOAt providing the desired compounds (method B).

Scheme 1. Preparation of Compound **1** Series[a]



[a] Reagents and conditions: (a) $SOCl_2$, reflux. (b) Pyridine, room temperature, then 60 °C. (c) HATU, HOAt, Huenig base, DMF. (d) KSCN, MeCN. (e) MeCN. (f) TsCl, pyridine.

STX-0119 (**1c**) was also synthesized by the following procedure to confirm the expected acylation at the *exo*-amino position; bis(acyl)thiosemicarbazide (**5**), which was obtained from acylisothiocyanate (**4**) and 2-furoylhydrazide, was cyclized by TsCl in pyridine to afford STX-0119 (**1c**) (method C). The NMR and

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liquid chromatography−mass spectrometry spectra were in agreement by all three methods and the originally purchased STX-0119. Also, the synthesized STX-0119 demonstrated similar inhibitory activity on the STAT3-dependent luciferase reporter gene assay (data not shown). Compounds **6a** and **6b** were prepared by cyclization of acylthiosemicarbazide (**8**) by iodine oxidation and sulfuric acid, respectively (Scheme S-1). Almost all of the synthesized compounds were of >95% purity, except compound **1b** with 91% purity (see the Supporting Information).

The inhibitory activity of the synthesized compounds on STAT3-dependent luciferase reporter gene assay is listed in Table 1. Among the analogues with various 2-substituents on the quinoline ring (**1a**−**i**), **1c**−**f** showed a similar degree of inhibitory activity, whereas 2-H (**1a**) and 2-Cl (**1b**) were inactive. Thus, an aromatic or bulky substituent at this position is essential for inhibition of STAT3. Also, replacement of the 2-phenyl group on the quinoline ring with a pyridyl (**1g**,**h**) or piperidino (**1i**) group completely abolished activity, suggesting that the nitrogen atom on the pyridine or piperidine ring might have a detrimental effect on inhibitory activity. Regarding the 5-substituent on the 1,3,4-oxadiazole ring (**1j**−**r**), 3-furyl (**1q**), 2-thienyl (**1r**), phenyl (**1m**), and benzyl (**1p**) groups were tolerated. The incorporation of 4-Cl (**1o**) in the phenyl ring retained activity; however, the incorporation of 2-Cl (**1n**) rendered the compound inactive. As analogues with lower alkyl groups (**1j**,**k**) and COOEt (**1l**) were inactive, an aromatic or bulky hydrophobic substituent is also essential at this position. In addition, 1,3,4-thiadiazole (**1s**) was completely inactive. We speculated that the reason for such a considerable difference in activity between **1c** and **1s** might be due to the conformational difference, namely, an unique intramolecular C═O···S interaction for acylamino-1,3,4-thiadiazole.[23] Most of the compounds that showed inhibitory activity in the luciferase-based reporter assay also inhibited STAT3 dimerization in cells (Table 1).

A docking model of STX-0119 bound to the STAT3-SH2 domain was generated on the basis of the crystal structure of the STAT3β homo dimer (PDB code 1BG1[21]) by CONSENSUS-DOCK. As illustrated in Figure 2, the 2-Ph ring is inserted into the hydrophobic cleft where it comes into proximity with the phospho-tyrosine binding pocket, providing a strong rationale for the lack of activity of analogues bearing a smaller substituent such as H (**1a**) or Cl (**1b**) at this position. The amide-NH participates in a hydrogen bond interaction with the backbone amide−C═O of Ser636. In addition, a hydrophobic interaction around the furan ring and a CH−π interaction with the indole moiety of Trp623 is observed, in accordance with the finding that inactive analogues contained a lower alkyl group at this position.

Finally, we evaluated the antitumor activity of STX-0119 in vivo. We selected the human lymphoma cell line SCC-3 that had been characterized as a cell line that expresses constitutively activated STAT3 and the most sensitive to STX-0119 in vitro among cell lines used.[24] SCC-3 was implanted into the hind flank of male BALB/cA-nu/nu nude mice and allowed to establish sizable tumors. Oral gavages of STX-0119 at 160 mg/kg sid for 4 days suppressed the growth of SCC-3 cells significantly (p < 0.05) on the fourth day, as shown in Table 2. Pharmacokinetic analysis showed that the plasma concentration of STX-0119 was maintained at >100 μg/mL (>260 μM), even at 8 h after administration (Supporting Information). No obvious body weight loss or toxicological effects were observed during the evaluation. To our knowledge, this is the first demonstration of in vivo efficacy following oral administration of a STAT3 dimerization inhibitor.

In this study, we have demonstrated that a combination of virtual screening and in vitro assays is an effective approach for the identification of PPI modulators and that STAT3 inhibitors could provide a new therapeutic approach for cancer treatment. Further optimization of the compound **1** series is underway.

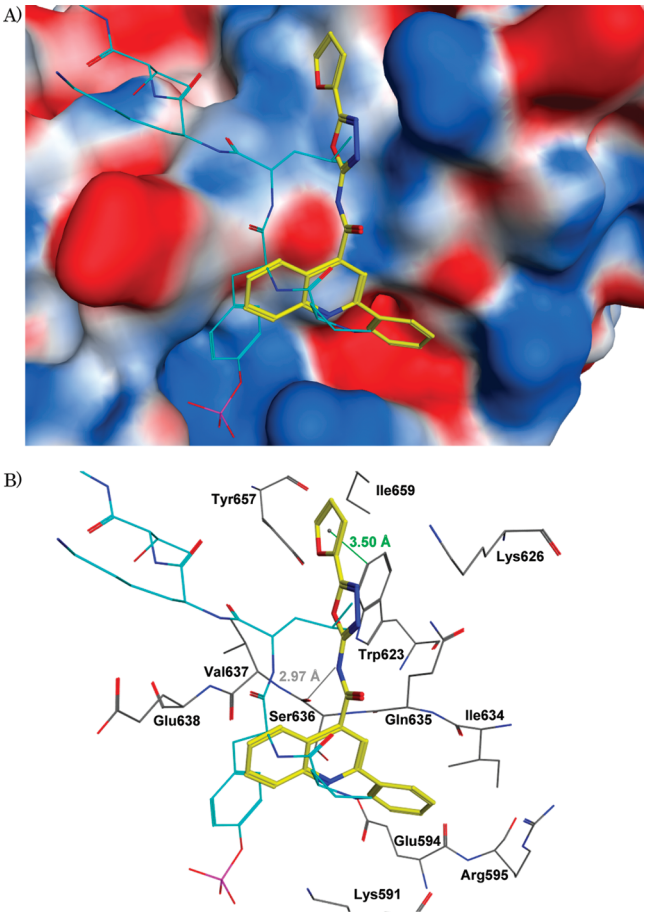

Figure 2. Docking model of STX-0119 with the STAT3-SH2 domain generated by CONSENSUS-DOCK. Visible by MOE. (A) Surface of the electrostatic map. (B) Residues of STAT3. Carbon atoms of STX-0119 are colored yellow, and those of the phosphotyrosine peptide (Pro704-pTyr705-Leu706-Lys707-Thr708) are colored cyan.

Table 2. Antitumor Activity upon Treatment with STX-0119 in the SCC-3 Lymphoma Xenograft Model

T/C (%)	significance	body weight change (g)	mortality
40	p < 0.05	+0.3	0/5

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SUPPORTING INFORMATION AVAILABLE Supplemental data, spectroscopic data with methods of synthesis for all compounds, and methods of biological evaluation. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS STAT, signal transducers and activators of transcription; JAK, Janus kinase; PDGFR, platelet-derived growth factor; VEGF, vascular endothelial growth factor; PPI, protein−protein interaction; SARs, structure−activity relationships; PCA, principle components analysis; MACCS, Molecular ACCess System; MOE, molecular operating environment; FRET, fluorescence resonance energy transfer; ChIP, chromatin immunoprecipitation.

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