Discovery of *O*-Alkylamino-Tethered Niclosamide Derivatives as Potent and Orally Bioavailable Anticancer Agents

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S Supporting Information

ABSTRACT: Niclosamide has been identified to potently inhibit the activation, nuclear translocation, and transactivation of STAT3. Nevertheless, the poor aqueous solubility and bioavailability of niclosamide have hindered its further clinical development for cancer therapy. To discover new molecules with enhanced druglike properties, a series of novel *O*-alkylamino-tethered derivatives of niclosamide have been designed, synthesized, and biologically evaluated. Among them, compound **11** (HJC0152) has been demonstrated to significantly suppress MDA-MB-231 xenograft tumor growth in vivo (ip and po), indicating its great potential as efficacious and orally bioavailable therapeutics for human cancer.

11 (HJC0152)
Improved aqueous solubility (3,300-fold better than niclosamide)
High *in vivo* antitumor efficacy (i.p. & p.o.)

KEYWORDS: *niclosamide derivatives, STAT3, water solubility, orally bioavailable*
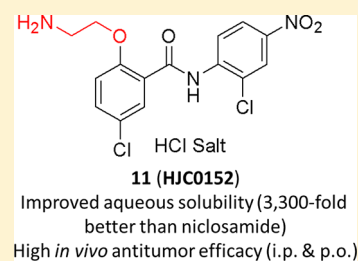
Signal transducers and activators of transcription (STATs) are a family of transcription factors that serve as signaling transmitters for a large number of cytokines and growth factors in the regulation of critical biological processes including cell growth, proliferation, differentiation, and survival.[1−6] Accumulating evidence has demonstrated that persistent activation of STAT3 stimulates tumor angiogenesis, promotes tumor immune evasion, and even confers resistance to apoptosis induced by conventional therapies.[7−13] Therefore, STAT3 represents an attractive therapeutic target for the treatment of various types of human cancer.[14−16]

Despite significant advances in recent discovery efforts targeting STAT3, only several STAT3 inhibitors are advanced into early phase clinical trials.[16] A poor physicochemical property is one of the most significant obstacles in promoting a potent agent into clinical trials.[16] For example, peptide and peptidomimetics inhibitors targeting STAT3 suffer from poor cellular permeability and stability.[17−20] Aqueous solubility plays an essential role in drug disposition and is one of the crucial molecular properties for successful drug development. Although an appropriate formulation could be used to enhance solubility and absorption, the stability and manufacturing difficulties should also be taken into consideration. In addition, oral chemotherapy is obviously a preferred administrative route in cancer treatment due to its convenience, patient compliance, and cost effectiveness.[21,22] Niclosamide, an FDA-approved anticestodal drug, has recently been identified with significant inhibition of the activation, nuclear translocation, and transactivation of STAT3.[19] It inhibits the transcription of STAT3 target genes and induces cell growth inhibition, apoptosis, and cell cycle arrest of cancer cells with constitutively active STAT3.

Nevertheless, niclosamide does not have an ideal pharmacokinetic profile due to its poor water solubility and low oral bioavailability.[23,24] It was of our interest to utilize rational chemical approaches to generate and identify novel derivatives of niclosamide with improved aqueous solubility and bioavailability as potential clinical candidates for cancer therapy. Herein, we report our chemical structural modifications of niclosamide to discover novel molecules aiming at enhanced efficacy and improved druglike properties.

We first directed our optimization effort involving modification of the hydroxyl group on the phenol ring of niclosamide by introduction of an *O*-alkylamino side chain. The amino group-containing scaffolds are important motifs of structural tuning with the capability to form hydrogen bonding like the phenol group for selective protein binding and druglikeness enhancement.[25] These new *O*-alkylamino tethered analogues were expected to provide efficient target binding for a better potency, and as free bases, these molecules could also form salts for the final target compounds to have a better aqueous solubility. As shown in Scheme 1, analogues **2−6** were conveniently prepared by Mitsunobu reaction. Alkylation of the bromide intermediate **2** with a variety of amines including heterocyclic moieties introduced basic functionalities into the molecules, providing niclosamide derivatives **7** and **8**. Mitsunobu coupling of niclosamide with *N*-Boc-protected amino alcohols followed by the Boc deprotection afforded analogues **9−15** with diversified *O*-alkyamino side chains. Both

Scheme 1[a]
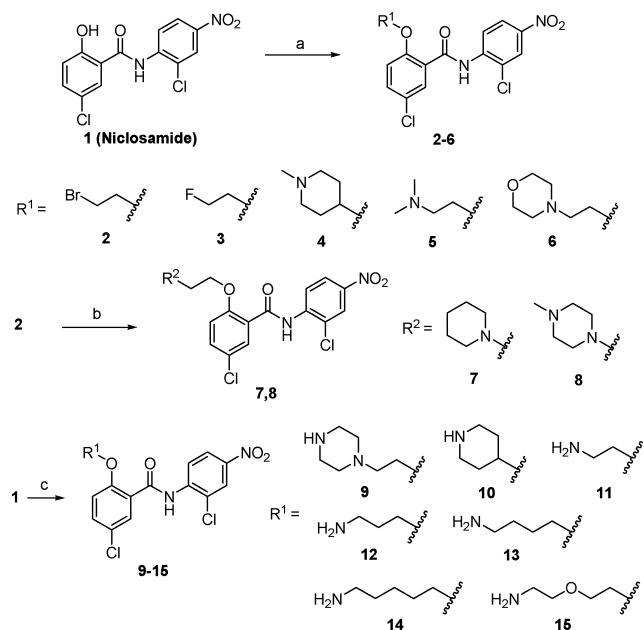
[a]Reagents and conditions: (a) R[1]OH, Ph$_3$P, DIAD, THF, rt, 50−93%. (b) R[2]H, KI, K$_2$CO$_3$, acetone, reflux, 55−91%. (c) (i) Boc-R[1]OH, Ph$_3$P, DIAD, THF, rt; (ii) TFA, CH$_2$Cl$_2$, 0 °C to rt, 34−81% (two steps).

Table 1. Effects of New Niclosamide Analogues on Proliferation of Human Breast and Pancreatic Cancer Cell Lines

		IC$_{50}$ (μM)			
		breast cancer		pancreatic cancer	
compd	cLogP[a]	MCF-7	MDA-MB-231	AsPC1	Panc-1
1	4.05	1.06	0.79	1.47	1.73
3	4.26	>10	>10	ND[b]	ND
4	4.22	4.11	2.69	3.51	>10
5	3.77	>10	>10	ND	ND
6	3.47	9.87	18.0	72.2	>10
7	4.73	>10	>10	ND	ND
8	3.56	>10	>10	ND	ND
9	3.20	12.4	8.7	ND	ND
10	3.91	0.25	0.29	2.76	0.54
11	3.01	0.91	1.64	1.9	1.08
12	3.33	3.11	2.61	4.2	3.11
13	3.76	3.7	2.37	7.4	>10
14	4.15	3.49	3.1	2.08	4.67
15	2.87	9.37	5.3	>10	>10
19	2.95	>10	>10	ND	ND
20	3.13	>10	5.87	ND	ND

[a]cLogP: http://146.107.217.178/lab/alogps/start.html. [b]ND, not determined.

Scheme 2[a]

[a]Reagents and conditions: (a) 16, Ph$_3$P, DIAD, THF, rt, 58%. (b) Zn dust, sat. NH$_4$Cl (aq.), MeOH, rt. (c) MeC(O)Cl or MeSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, rt. (d) TFA, CH$_2$Cl$_2$, 0 °C to rt, 31−66% (three steps).

linear alkyl amines and heterocyclic alkyl amines have been explored for the purpose of comparison.
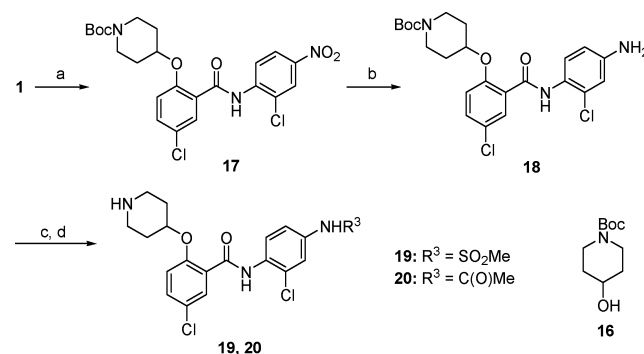
To examine whether the substitution of moiety groups affected biological activities of newly synthesized analogues and explore the structure−activity relationship (SAR), we first evaluated the in vitro anticancer effects of the compounds 3−15 on the proliferation of breast cancer cell lines MCF-7 (ER-positive) and MDA-MB-231 (ER-negative and triple-negative), as well as pancreatic cancer cell lines AsPC1 and Panc-1 using MTS assays. The ability of these new analogues to inhibit the growth of cancer cells is summarized in Table 1. The results revealed that analogues 10−15 bearing the terminal amino group-containing side chain at the phenol moiety showed promising antiproliferative activities with low micromolar to nanomolar IC$_{50}$ values, while the alkyl-substituted derivatives 5−9 at the terminal amino group on the same position displayed moderate to low activities. For example, new analogues 10 and 11 exhibited a similar or significantly higher potency than niclosamide. However, compound 4 with a methylated terminal amino group in 4-O-piperidinyl moiety displayed 10-fold loss of antiproliferative activity in comparison with analogue 10. The same trend of SAR was also found for compounds 5−8, in which the dialkylsubstitution at the terminal amino group resulted in significant loss of activities, while O-ethylpiperazinyl derivative 9 in contrast with 8 regained antiproliferative activity with IC$_{50}$ values of 12.4 and 8.7 μM against two breast cancer cell lines MCF-7 and MDA-MB-231, respectively. The fluorinated compound 3 that was initially designed for potential PET imaging studies displayed no significant effects against the tested cancer cells.

Further modifications of nitro group in compound 10, one of the most potent analogues identified from our first SAR exploration, were also investigated. As outlined in Scheme 2, reduction of the nitro group of the intermediate 17 with zinc dust provided the corresponding amine 18. Further treatment

of 18 with methanesulfonyl chloride or acetyl chloride followed by removal of the Boc group afforded the desired products 19 and 20, respectively. As shown in Table 1, replacement of the nitro group of compound 10 with methanesulfonamide (19) or acetamide (20) resulted in a significant loss of the antiproliferative activity, indicating that the nitro moiety is fairly important for potency.

From the in vitro screening of all tested compounds, analogues 10 (HJC0125) and 11 (HJC0152) stood out with an attractive anticancer profile and were therefore subjected to further biological evaluation. To study the effects of these two compounds on cell growth, cellular morphological changes were examined in MDA-MB-231 breast cancer cells treated with compounds 10, 11, or niclosamide for 48 h, under light microscopy. Like niclosamide, both compounds 10 and 11 significantly inhibited cell proliferation and induced apoptosis accompanying cellular morphological changes at concentrations of 1, 5, and 10 μM, respectively (Supporting Information).

Because one of major goals for our discovery effort was to identify compounds with improved water solubility and oral bioavailability, aqueous solubility of the new analogues **10** and **11** was determined by an HPLC method.[26] As expected, introduction of the *O*-alkylamino-tethered moiety not only enhanced anticancer activity but also significantly increased the aqueous solubility. Both compounds **10** and **11** (in the form of HCl salt) demonstrated excellent water solubility, with a saturated concentration of 248 and 762 μg/mL, respectively (Figure 1). The *O*-ethylamino derivative **11** showed the most
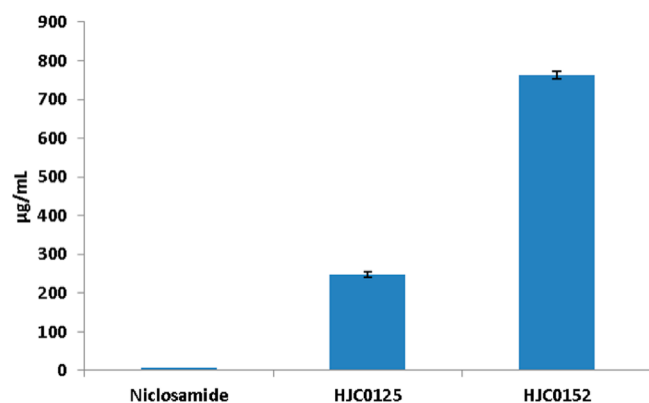

Figure 1. Aqueous solubility of novel niclosamide analogues. Compounds **10** (HJC0125) and **11** (HJC0152) showed significantly improved solubility as compared with niclosamide.

favorable solubility, which is about 3300-fold improvement in comparison with that of niclosamide (0.23 μg/mL).[27] The significant improvement of the aqueous solubility is expected to facilitate these compounds to be more orally bioavailable and efficacious in vivo than niclosamide, which is substantially water insoluble.

Previous studies have demonstrated that niclosamide is a potential inhibitor of STAT3.[19] To determine whether the new derivatives act as potent small-molecule inhibitors of STAT3 activation, we measured the effect of niclosamide and compound **11** on promoter activity using the cell-based transient transfection and dual luciferase reporter assays. MDA-MB-231 cells were pretreated with niclosamide or **11** at different concentrations for 24 h. The STAT3 promoter activity in MDA-MB-231 cells was determined after transient transfecting with pSTAT3-Luc vector. As shown in Figure 2A, treatment with 10 μM compound **11** decreased the STAT3 promoter activity in MDA-MB-231 cells by approximately 32%, and increasing the dose of compound **11** to 20 μM further decreased STAT3 promoter activity by 62% as compared with control. Similarly, STAT3 promoter activity in MDA-MB-231 cells was suppressed after treatment with 20 μM niclosamide, while proliferation of MDA-MB-231 cells (MTT assay)[19] showed comparable to slightly more potent reduction (Figure 2B). These results demonstrate that compound **11** inhibits STAT3 promoter activity in MDA-MB-231 cells in a dose-dependent manner and has a similar effect as niclosamide.

To further investigate the inhibitory activity of compound **11** against the STAT3 pathway, we examined STAT3 phosphorylation and expression of the known STAT3 target genes in MDA-MB-231 cell line. The cells were treated with different doses of compound **11** for 24 h, and levels of total STAT3 and phosphorylated STAT3 at Tyr-705 were then examined by Western blot. As shown in Figure 3, total STAT3 was reduced
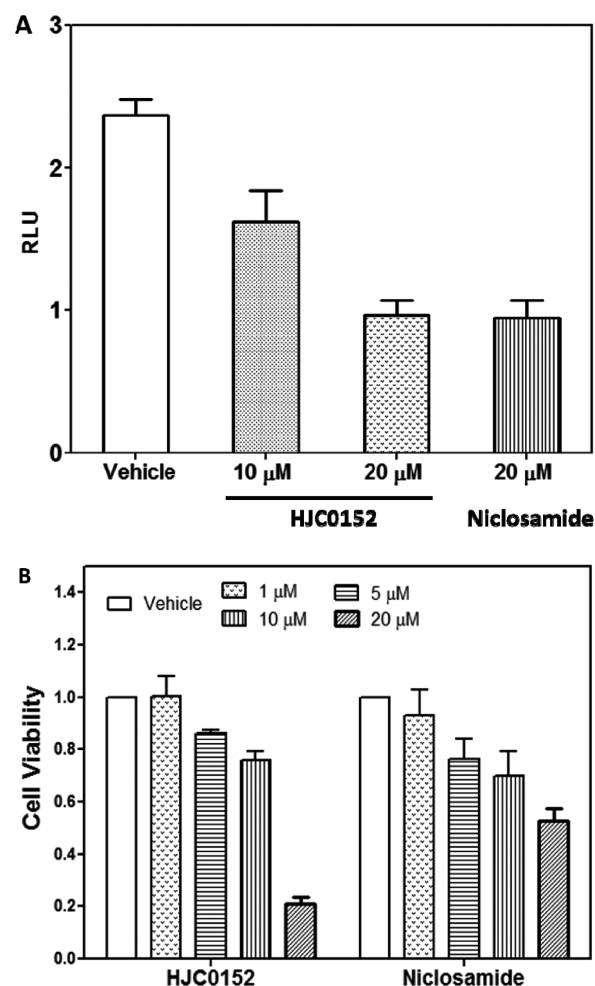
Figure 2. (A) HJC0152 inhibited the STAT3-mediated luciferase reporter activity in MDA-MB-231 cells. (B) Proliferation of MDA-MB-231 cells treated with HJC0152 and niclosamide for 24 h.

after treatment with **11** or niclosamide, suggesting that these compounds may alter transcription and/or translation of STAT3. Similarly, phosphorylated STAT3 (p-STAT3) at Tyr-705 is suppressed by **11** or niclosamide, suggesting that compound **11** has a comparable potency in downregulating STAT3 protein production and phosphorylation at the Tyr-705 site. Blocking STAT3 signaling in many different tumor cells leads to induce growth arrest and apoptosis.[28−30] We observed that compound **11** induced cleaved caspase-3 and down-regulated cyclin D1 in MDA-MB-231 cells. These results suggest that compound **11** inhibits cell cycle progression and promotes apoptosis. We further confirmed these results using annexin V-based measurement using flow cytometry. As depicted in Figure S2 in the Supporting Information, compound **11** and niclosamide activated apoptosis in MDA-MB-231 breast cancer cells in a dose-dependent manner. Other than targeting STAT3, niclosamide has also been found to inhibit NF-kB and Wnt/β-catenin signaling.[19,31,32] Currently, we are investigating the mechanisms of how compound **11** regulates STAT3 upstream targets and related signaling pathways and transcriptional/translational regulation.
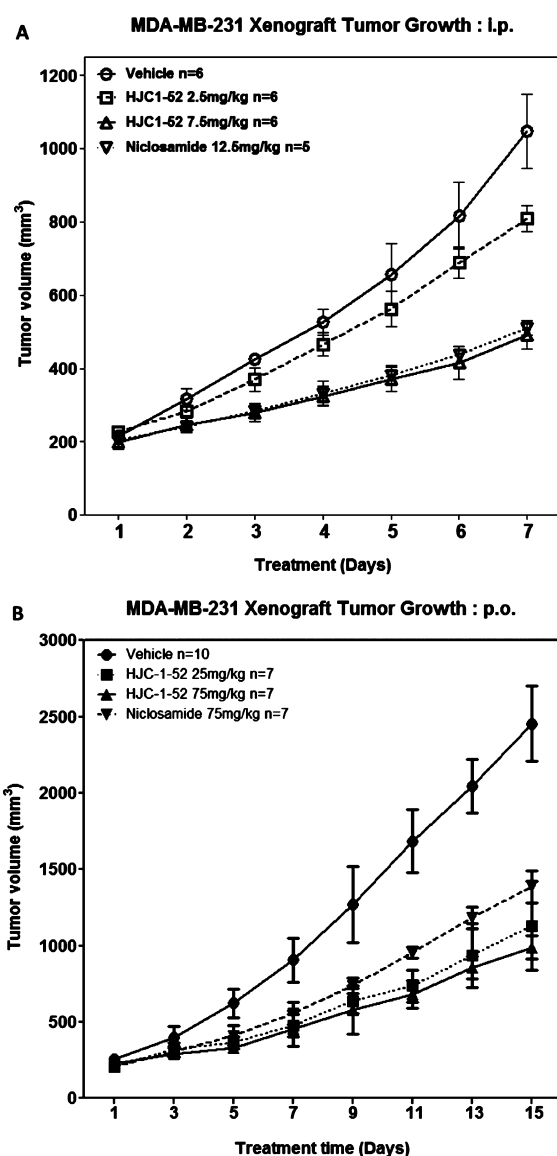
Furthermore, compound **11** was further evaluated for its antitumor activity in inhibition of tumor growth in the MDA-MB-231 xenograft model. As expected, mice treated with 7.5 mg/kg of compound **11** via ip showed a better effect in
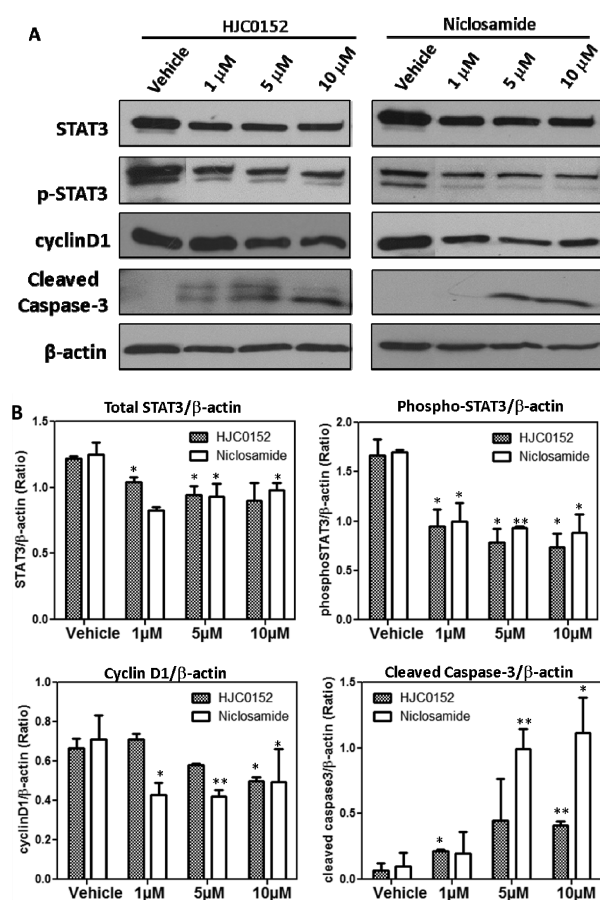
Figure 3. (A) Western blot analysis of biochemical markers for apoptosis induction and inhibition of STAT3 activity by HJC0152 in the MDA-MB-231 cell line. (B) Densitometric analysis of three independent experiments for the expression level of total STAT3, phospho-STAT3, cyclin D1, and cleaved caspase 3. * represents $p < 0.05$, and ** represents $p < 0.01$.

Figure 4. In vivo efficacy of compound **11** (HJC0152) in inhibiting growth of xenograft tumors (breast cancer MDA-MB-231) in mice. (A) ip and (B) po.

inhibiting tumor growth as compared to the mice treated with 12.5 mg/kg niclosamide (Figure 4A). Similarly, we treated the MDA-MB-231 xenograft mice with oral administration of compound **11** and found that the growth of xenograft tumors in mice was significantly reduced by compound **11** at a dose of 25 mg/kg and even more efficacious than niclosamide at 75 mg/kg (Figure 4B). This observation might be attributed to the superior solubility of compound **11**, which might have resulted in an improved oral bioavailability[33−37] and, consequently, an enhanced suppression of tumor growth in mice. It is also noteworthy that compound **11** did not show significant signs of toxicity at a dose of 75 mg/kg. These results have demonstrated that compound **11** (HJC0152) is a promising anticancer drug candidate with excellent aqueous solubility and have significant potential to be developed as an orally bioavailable anticancer agent.

In summary, a series of novel *O*-alkylamino tethered derivatives of niclosamide have been designed, synthesized, and biologically evaluated in this work. New analogues **10** and **11** were identified to exhibit a similar or significantly higher potency than niclosamide against human breast and pancreatic cancer cells. Both compounds **10** and **11** have demonstrated a superior aqueous solubility, especially the compound **11**, which has about 3300-fold improvement in water solubility in comparison with niclosamide. In MDA-MB-231 cells, com-

pound **11** inhibited STAT3 promoter activity, increased the expression of active caspase-3, inhibited cell cycle progression, and promoted apoptosis. In nude mice bearing breast tumor xenografts, compound **11** significantly suppressed MDA-MB-231 xenograft tumor growth in vivo (both ip and po). These results suggest that compound **11** (HJC0152) with remarkably improved aqueous solubility may have great potential to be developed as an orally bioavailable agent for cancer therapy.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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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Author Contributions

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