Sulfonamide Anilides, a Novel Class of Histone Deacetylase Inhibitors, Are Antiproliferative against Human Tumors

Marielle Fournel, Marie-Claude Trachy-Bourget, P. Theresa Yan, Ann Kalita, Claire Bonfils, Carole Beaulieu, Sylvie Frechette, Silvana Leit, Elie Abou-Khalil, Soon-Hyung Woo, Daniel Delorme, A. Robert MacLeod, Jeffrey M. Besterman, and Zuomei Li

MethylGene, Inc., St. Laurent, Quebec, H4S 2A1 Canada

ABSTRACT

Inhibition of histone deacetylases (HDACs) is emerging as a new strategy in human cancer therapy. We have designed and synthesized novel non-hydroxamate sulfonamide anilides that can inhibit human HDAC enzymes and can induce hyperacetylation of histones in human cancer cells. These compounds selectively inhibit proliferation and cause cell cycle blocks in various human cancer cells but not in normal cells. The growth inhibitory activity of sulfonamide anilides against human cancer cells in vitro is reversible and is dependent on the induction of histone acetylation. One of these compounds (Compound 2) can significantly reduce tumor growth of implanted human colon tumors in nude mice. Unlike another anilide-based HDAC inhibitor, MS-275, which decreases both red and white blood counts and reduces spleen weights in mice, Compound 2 does not exhibit noticeable toxicity. By using cDNA array analysis, we have identified downstream genes whose expression is altered by Compound 2 in human cancer cells. In correlation with its antitumor activity both in vitro and in vivo, Compound 2 induces expression of p21WAF1/Cip1, gelsolin, and keratin 19, while down-regulating expression of cyclin A and cyclin B1 in human cancer cells in a dose-dependent manner. Our results suggest that sulfonamide anilides are novel HDAC inhibitors and may be useful as antiproliferative agents in cancer chemotherapy.

INTRODUCTION

In eukaryotic cells, histone acetylation/deacetylation is important in transcriptional regulation (1). Transcriptionally active genes associate with hyperacetylated chromatin, whereas transcriptionally silent genes associate with hypoacetylated chromatin (2). Chromatin acetylation is controlled by the opposite effects of two families of enzymes, histone acetyltransferases and HDACs2 (3, 4). Histone acetyltransferases, as transcription coactivators, catalyze the addition of acetyl groups on the ε-amino group of lysine residues in the NH2-terminal tails of core histones. Conversely, HDACs, as transcription corepressors, remove the acetyl groups from the acetylated lysines in histones (3, 4).

There are three subclasses of HDAC enzymes in humans (5). Class I enzymes (HDAC1, HDAC2, HDAC3, and HDAC8; Refs. 6–9) are homologues of yeast Rpd3 deacetylase, whereas class II enzymes are homologues of yeast Hda1 deacetylase (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, HDAC10, and HDAC11; Refs. 10–15). Class III enzymes are homologues of yeast Sir2 (16). Unlike class I and class II enzymes, class III HDAC activities require NAD+, and they are not sensitive to TSA (16). Deregulation of HDAC activity can cause malignant diseases in humans (17, 18).

Small molecule inhibitors of HDACs have emerged as antiproliferative agents because of their ability to inhibit proliferation, induce apoptosis, and/or cell differentiation in cancer cells (5, 19, 20). These HDAC inhibitors include sodium butyrate, TSA, suberoylanilide hydroxamic acid, oxamflatin, MS-275 (21), trapoxin, all-trans retinoic acid, apicidin, and FR901228 (see Refs. 5, 19, 20 for reviews). It is believed that induction of p21WAF1/Cip1 and blockade of tumor cell cycle progression are critical for antitumor activities of all of the HDAC inhibitors (22–25).

In the course of developing agents with antitumor activities, we aimed to develop novel HDAC inhibitors with potency and safety. In previous publications, we described our efforts to develop novel hydroxamates as HDAC inhibitors (26, 27). As nonhydroxamates generally have more pharmaceutically desirable properties than hydroxamates (19), we developed a novel class of HDAC inhibitors, sulfonamide anilides, based on their corresponding hydroxamates (28). The results presented here show that sulfonamide anilides exhibit antitumor activity both in vitro and in vivo, and compared with MS-275, another anilide-based HDAC inhibitor in clinical trial, our compound (Compound 2) does not exhibit gross toxicity in mice. Thus, sulfonamide anilides could be potential therapeutic agents in treating human cancers.

MATERIALS AND METHODS

Chemicals. All sulfonamide anilides and MS-275 were prepared in-house (26, 28, 29). Compound 1 (N-2-aminophenyl-3-[4-(3,4-dimethoxy benzene-sulfonfonylamin)-phenyl]-2-propanamide), Compound 2 (N-2-aminophenyl-3-[4-(4-methyl benzene-sulfonfonylamin)-phenyl]-2-propanamide), Compound 3 (N-2-aminophenyl-3-[4-(4-phenyl benzene-sulfonfonylamin)-phenyl]-2-propanamide), and Compound 4 (N-phenyl-3-[4-(4-phenylbenzene-sulfonfonylamin)-phenyl]-2-propanamide) were all prepared with >95% purity. Other chemicals were purchased from Sigma. Each compound’s cLogP was calculated using Pallas program.

Cell Culture. HMEC cells were obtained from BioWhittaker (Walkersville, MD). All other cell lines used were from American Type Culture Collection (Manassas, VA). Human normal and cancer cells were all cultured after the vendor’s instructions. In growth curve analysis, cells were plated 24 h before treatment with HDAC inhibitors. Cells were counted by trypan blue exclusion in triplicates at various time points.

Production of Recombinant HDAC1 Enzyme and HDAC Enzyme Assay. Human HDAC1 cDNA was generated by reverse transcriptase-PCR reactions based on human HDAC1 coding sequence (GenBank accession no. U50079). Insect High Five cells (Invitrogen) were used to produce recombinant Flag-tagged HDAC1 using pBlueBAC vector (Invitrogen). HDAC1 recombinant enzymes were partially purified by a Q-Sepharose column (Pharmacia) followed by purification with anti-Flag M2 affinity gels (Sigma). Deacetylase enzyme assays were carried out in the assay buffer [40 mM Tris-Cl (pH 7.6), 20 mM EDTA, and 50% glycerol] using [3H]-labeled acetylated histones as described in literatures (30). The IC50 for inhibitors were determined by analyzing dose-response inhibition curves.

Western Blot Analysis. Whole cell extracts or acid extracted histones prepared from inhibitor-treated cells were analyzed by SDS-PAGE. Proteins were transferred on the polyvinylidene difluoride membrane and probed with various primary antibodies. Primary antibodies were ordered from Santa Cruz Biotechnology, except for acetylated H4 or acetylated H3 antibodies (Upstate Biotechnology), or antibodies against p21WAF1/Cip1 (Transduction Laboratories). Horse-radish peroxidase-conjugated secondary antibodies (Sigma) were used, and the enhanced chemiluminescence (Amersham) was followed for detection.

MTT Assay. Cells seeded in 96-well plates were incubated for 72 h at 37°C in a 5% CO2 incubator. MTT (Sigma) was added at a final concentration of 2 mg/mL, and then plates were incubated for 4 h at 37°C. The purple formazan was dissolved with dimethyl sulfoxide, and OD was read at 540 nm.
of 0.5 mg/ml and incubated with the cells for 4 h before an equal volume of
salubration buffer [50% N,N-dimethylformamide, 20% SDS (pH 4.7)] was
added onto cultured cells. After overnight incubation, solubilized dye was
quantified by colorimetric reading at 570 nm using a reference at 630 nm. A
values were converted to cell numbers according to a standard growth curve of
the relevant cell line. The concentration, which reduces cell numbers to 50%
of those of DMSO-treated cells, is determined as MTT IC50.

Flow Cytometric Analysis. Cells were treated with inhibitors for 16 h,
harvested, and fixed by 70% ethanol at −20°C. Nucleic acids from fixed cells
were stained with propidium iodide (50 µg/ml). DNA content was measured
by using a fluorescence-activated cell sortor.

In Vivo Antitumor Efficacy Studies. Female BALBc nude mice (obtained
from Charles River Laboratories) were used at ages 8–10 weeks. Human colon
carcinoma HCT116 cells (2 million) were injected s.c. in the animal flank and
allowed to form solid tumors. Tumor fragments were serially passaged a minimum
of three times before use in the experiments described. Tumor fragments (∼30
mg) were implanted s.c. through a small surgical incision under general anesthesia.
HDAC inhibitors were dissolved as clear solutions in vehicles (either 100%
DMSO or 20% DMSO, 15% ethanol, and 65% PBS acidified with 0.2 N HCl).
The pH value for the latter vehicle was 2.0. Vehicles alone and HDAC inhibitors
in vehicles were administered daily i.p. by injection. The maximum volume for
daily injection was 100 µl/animal. Tumor volumes and gross body weight of
animals were monitored twice weekly for up to 3 weeks. Each experimental group
contained at least 8 mice. At the end of each experiment, blood and spleen were
collected from mice. Spleens were weighed and routine hematological parameters
were determined. Student’s tests were used to analyze the statistical significance
between numbers in data sets.

cDNA Expression Array Analysis. Total RNAs from HCT116 human
cancer cells were extracted using RNaseasy mini kit (Qiagen). Generally, 50 µg
of total RNA were used to synthesize cDNA probes using Atlas Pure Total
RNA Labeling System (Clontech) before their hybridization on the Atlas
Human Cancer cDNA Expression Array membranes (Clontech). After hybrid-
ization and washing, array membranes were exposed to Cyclone Phosphor-
Human Cancer cDNA Expression Array membranes (Clontech). After hybrid-
ization in cultured human cancer cells, human bladder carcinoma T24
cells, which do not express p53, were treated with escalating doses of
these compounds. T24 cells were chosen because their basal levels of
these compounds are presented. Because HDAC1 is ubiquitously
expressed in many cancer cell lines and is important for transcriptional regulation, Compounds 1–4 were tested against partially purified
recombinant human HDAC1 enzymes. As shown in Table 1, Compounds 1–3 can all significantly inhibit human HDAC1 activity
in vitro with IC50 between 1 and 6 µM, whereas MS-275 can inhibit
HDAC1 with an IC50 of 1.2 µM. Compound 4, the des-amino ana-
logue of Compound 3, has an IC50 > 100 µM against the human
HDAC1 enzyme, suggesting that the integrity of the aniline group is
essential for the inhibitory activity of this class of compounds.

Induction of Core Histone Acetylation in Human Cancer Cells.
To determine whether Compounds 1–4 can induce core histone acety-
lation in cultured human cancer cells, human bladder carcinoma T24
cells, which do not express p53, were treated with escalating doses of
these compounds. T24 cells were chosen because their basal levels of
histone acetylation are low. As shown in Fig. 1, Compounds 1–3 can
all induce core histone H4 or H3 acetylation in a dose-dependent
manner. Compound 4, which did not inhibit HDAC1, did not induce
histone acetylation even at 25 µM (Fig. 1). Among Compounds 1–3,
Compound 2 can induce histone acetylation most strongly, whereas
the ability of MS-275 in induction of histone acetylation in cells is
about 2–3 times stronger than that of Compound 2 (Fig. 1). Thus, the
ability of these compounds to induce histone acetylation in cancer
cells largely correlated with their ability to inhibit HDAC1 in vitro.
Although Compound 3 was more potent than Compounds 1–2 on
inhibition of HDAC1 enzyme activity in vitro, Compound 3 was less
effective on induction of histone acetylation in whole cells, possibly
because of its relatively high cLogP value (cLogP = 4.8) compared
with that of Compound 1 or Compound 2 (cLogP = 3.2 or 3.6,
respectively). Induction of histone acetylation by this class of
compounds was independent of p53 and was not cell line specific. Similar
induction of histone acetylation by these compounds was also ob-
erved in other human cancer cell lines that express p53 (A549 and
HCT116, data not shown).

Antiproliferative Activity in Human Cancer Cells but not in
Normal Human Cells. Antiproliferative activities of Compounds 1–3 against human cancer cells correlated well with their abilities to
induce histone acetylation in intact cells (Fig. 1). Among these com-
ounds, Compounds 1 and 2 exhibited significant antiproliferative activity against a broad panel of human cancer cells as shown in Table
2. Antiproliferative activities of Compounds 1 and 2 were not limited
to a specific tumor type and were p53 independent. In contrast,
Compound 3 was less potent in inhibiting growth of human cancer
cell lines, whereas Compound 4 could not inhibit the growth of any of
the human cancer cell lines.

Compounds 1 and 2 selectively inhibited growth of human cancer
cells but not normal human diploid fibroblasts (MRHF) or normal
human epithelial cells (HMEC) as shown in Table 2. This effect is
consistent with a report that HDAC inhibitors do not cause growth
inhibition in human normal dermal fibroblasts (31).

RESULTS

Inhibition of Human HDAC Activities. We designed and syn-
thesized a family of sulfonamide anilides (28). In Table 1, four of

Table 1 Structure and in vitro HDAC-inhibitory activity of Compounds 1–4 and MS-275

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>HDAC1 IC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>6.0±/1.3</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>3.6±/1.0</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>1.3±/0.2</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>&gt;100</td>
</tr>
<tr>
<td>MS-275</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>1.2±/0.3</td>
</tr>
</tbody>
</table>

* Results are shown as means ± SD based on five independent experiments on each
compound.
To determine whether sulfonamide anilides blocked growth of human cancer cells in vitro in a reversible or irreversible manner, we performed a growth curve analysis of HCT116 cancer cells treated with Compound 2 (5 \( \mu \)M). As shown in Fig. 2A, although the continuous presence of Compound 2 in cell culture media significantly blocked growth of HCT116 cells and induced histone acetylation, the wash-out of Compound 2 from cells after 24-h initial treatment allowed the growth of the cells to recover and histone acetylation decreased to basal level (Fig. 2B). Induction of histone acetylation by Compound 2 in HCT116 cells directly correlated with its ability to block proliferation of these cancer cells (Fig. 2B).

**Selective Induction of Cell Cycle Arrest in Human Cancer Cells.** Compounds 1 and 2 induced a dose-dependent G0-G1 arrest in the human cancer cell lines HCT116 (Fig. 3, A and B), T24, A549, DU145, and MCF-7 (data not shown) but not in normal HMEC cells (Fig. 3, C and D). However, unlike in a previous report where MS-275 (1 \( \mu \)M) can induce G2-M arrest in human cancer A2780 cells (21), we found that MS-275 (at 1–10 \( \mu \)M) similarly induced G2-M arrest as Compound 2 in those human cancer cell lines we have tested (data not shown).

**In Vivo Antitumor Activity.** We used a human colon cancer xenograft model (HCT116) to assay in vivo antitumor activity of Compounds 1 and 2. Compound 1 exhibited weak antitumor activity in vivo. From two independent experiments, the growth of tumors in mice treated with Compound 1 at 40 mg/kg body weight (MPK) for 18 days by daily i.p. injection was inhibited by 33 and 26% compared with that of control mice treated with only the vehicle (DMSO).

For Compound 2, three independent experiments were performed. In the first two experiments, Compound 2 was administered by i.p. injection into animals at 40 MPK daily for 18 days. Growth of tumors in treated mice was inhibited by 46 and 51% compared with that of control mice treated with only the vehicle (DMSO). In the third experiment, Compound 2 or MS-275 were given to mice at 20 MPK/day for 20 days by i.p. injection. We found that the growth of tumors in mice treated with Compound 2 was inhibited by 48%, whereas the growth of tumors in mice treated with MS-275 was inhibited by 54% (Fig. 4A) compared with that of tumors of vehicle-treated animals. Thus, Compound 2 has significant antitumor activity in this human colon cancer xenograft model in vivo. This antitumor activity is comparable with that of MS-275 under the same experimental condition.

**Compound 2 Exhibited Less Toxicity than MS-275 in Mice.** All mice treated with Compound 2 or MS-275 (both at 20 MPK) in Fig. 4A did not show gross body weight loss. However, MS-275 reduced the number of peripheral RBCs by 12% compared with that of control mice treated with only the vehicle (DMSO). In the third experiment, Compound 2 or MS-275 were given to mice at 20 MPK/day for 20 days by i.p. injection. We found that the growth of tumors in mice treated with Compound 2 was inhibited by 48%, whereas the growth of tumors in mice treated with MS-275 was inhibited by 54% (Fig. 4A) compared with that of tumors of vehicle-treated animals. Thus, Compound 2 has significant antitumor activity in this human colon cancer xenograft model in vivo. This antitumor activity is comparable with that of MS-275 under the same experimental condition.

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Spleen weights from animals treated with MS-275 or Compound 2 (both at 20 MPK for 20 days by daily i.p. injection) in two independent experiments were pooled and analyzed. As shown in Fig. 5, spleen weights of animals treated with MS-275 were reduced to 77% of those treated with Compound 2. HCT116 cells were plated 1 day before treatment with Cpd 2 (5 \( \mu \)M) in 1% DMSO or 1% DMSO alone (\( \Delta \)) at 0 h. At 24 h, Cpd 2 was either continuously present (\( \Delta \)) or washed out from media (\( \square \)). Cells were counted at 24, 48, 72, and 96 h by trypan blue exclusion. B, immunoblot of core histone acetylation of HCT116 cells. Cells from various points of the growth curve analysis in A were harvested. Extracted histones were analyzed by Western blotting using antibodies against acetylated H4 or acetylated H3 histones. + Cpd 2 indicates the continuous presence of Cpd 2 at 5 \( \mu \)M (see points in \( \Delta \) in A). – Cpd 2 indicates the wash-out of Compound 2 after an initial treatment of 24 h (see points in \( \square \) in A). Cpd 2, Compound 2.
with vehicle alone (P/h11022) affect spleen weights of animals compared with those of mice treated of vehicle-treated animals (P/h11005). Our results suggest that Compound 2 has significantly less gross toxicity than MS-275 in vivo (O/O).

In Fig. 2A, growth inhibitory effect of Compound 2 on cancer cells was reversible. Does the gene expression profile of HCT116 cells treated with Compound 2 correlate with the phenotype response? We found that after 48 h of treatment, Compound 2 altered expression of more genes (67 genes) in HCT116 cells compared with that after 24 h of treatment (30 genes). Expression of 46 of 67 genes was dependent on the continuous presence of Compound 2. For example, Compound 2 significantly induced gene expression of p21WAF1/Cip1 by 2- or 3-fold after 24 or 48 h of treatment, respectively (Table 3). Transcription of p21WAF1/Cip1 returned to basal level if Compound 2 was depleted from the media for the last 24 h after the initial 24-h treatment. Similarly, expression of cyclins A or B1 was down-regulated significantly by Compound 2 after 24- to 48-h treatment, but the depletion of Compound 2 reversed the down-regulation of expression of these two cyclins (Table 3). Thus, gene expression changes correlated with the phenotypic responses of cells treated with Compound 2 (Fig. 2).

Time Course of Protein Expression of p21WAF1/Cip1 and Cyclins A and B1 Affected by Compound 2. At the protein level, Compound 2 significantly induced the expression of p21WAF1/Cip1 while down-regulating the expression of cyclins A and cyclin B1 in HCT116 cells (Fig. 6). Induction of p21WAF1/Cip1 expression by Compound 2 was already dramatic at 24 h and peaked at 48 h posttreatment in HCT116 cells (Fig. 6). Down-regulation of the expression of cyclins A and B1 by Compound 2 in HCT116 cells peaked at ~48 h posttreatment (Fig. 6). Alteration of expression of these three genes was largely maintained even at 72 h posttreatment. The ability of Compound 2 to alter the expression of these cell cycle regulators was consistent with its ability to induce cell cycle arrest and block cell proliferation of HCT116 cells (Fig. 2, Fig. 3, and Table 2).

Induction of p21WAF1/Cip1 and down-regulation of cyclins A and cyclin B1 expression at the protein level by Compound 2 in cancer cells was independent of p53 status and was not cell line specific; similar observations were obtained in all human cancer cell lines we tested (T24, A549, and Du145 cells; data not shown). These observations are consistent with other reports that HDAC inhibitors can induce p21WAF1/Cip1 expression and down-regulate cyclin protein expression (21–25).

Table 3  Fold alteration of gene expression a by Compound 2 (Cpd 2) and MS-275 in human HCT116 cells b by cDNA expression array analysis

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Cpd 2 24 h</th>
<th>Cpd 2 48 h</th>
<th>Cpd 2 24/48 h</th>
<th>MS-275 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>p21</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cyclin A</td>
<td>-3</td>
<td>-10</td>
<td>1</td>
<td>-5</td>
</tr>
<tr>
<td>Cyclin B1</td>
<td>-3</td>
<td>-10</td>
<td>1</td>
<td>-5</td>
</tr>
<tr>
<td>Keratin 19</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Keratin 8</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

 a Fold change of gene expression compared with that of DMSO-treated cells. +/- indicates fold change indicates down-regulation of gene expression.

 b HCT116 cells were treated with Cpd 2 (5 µM) or MS-275 (1 µM) continuously for either 24 h (+24 h) or 48 h (+48 h). Alternatively, cells were treated with Cpd 2 initially for 24 h and then maintained in media free of Cpd 2 for another 24 h (+24/-24 h).
Compound 2 induces morphological change in human cancer cells (i.e., HCT116) at concentrations > 5 μM (data not shown). The expression of several keratins (i.e., keratins 8 and 19) was significantly induced in HCT116 cells at the RNA level (Table 3) by Compound 2 in a reversible manner. At the protein level, we found that Compound 2 induced the expression of keratin 19 and gelsolin (Fig. 6). We found that other HDAC inhibitors such as MS-275 and TSA could also induce expression of keratin genes not only in HCT116 cells but also in other cancer cell lines tested (data not shown). It is possible that keratins, similarly to gelsolin, are mediators of HDAC inhibitor-induced morphological changes in human cancer cells. In the literature, other HDAC inhibitors can similarly induce expression of gelsolin and keratins in various human cancer cells (21, 24, 34).

Compound 2 induced apoptosis at higher concentrations (e.g., 25 μM) in HCT116 cells (data not shown). Consistent with its ability to induce apoptosis, expression of an antiapoptotic protein, survivin (35), was significantly down-regulated at both the RNA and protein level in these cells (data not shown). Expression of BAD (36), a proapoptotic protein, was elevated by Compound 2 at the RNA level in HCT116 cells. It is not clear whether the induction of apoptosis by Compound 2 contributes to its antitumor activity in human cancer cells.

Compound 2 appears to have comparable antitumor activity in vivo to MS-275 (Fig. 4A), a compound currently in Phase I clinical trial. However, Compound 2 appears to have an improved safety profile compared with MS-275 (Figs. 4, B and C, and 5), although Compound 2 and MS-275 are both aniline-based HDAC inhibitors. The basis for the improved therapeutic window in vivo for Compound 2 needs to be investigated further to develop potent and safe cancer therapeutic agents of this class.

In summary, we demonstrated that sulfonamide anilides, especially Compound 2, are novel HDAC inhibitors with significant antitumor activity in vitro and in vivo. The antitumor activity of Compound 2 correlates well with its ability to arrest cell cycles and to alter expression of cell cycle regulators, i.e., p21/WAF1/Cip1, cyclin A, and cyclin B1. We conclude that sulfonamide anilides may be useful as antiproliferative agents in future human cancer therapy.

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