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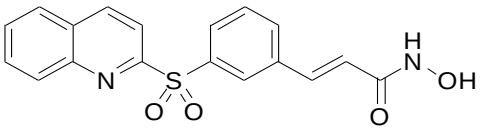
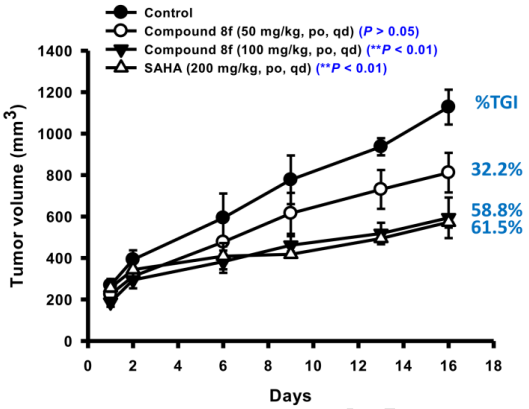


8f

GI_{50} = 0.08 μM (HCT116 cells)



The 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamide derivative **8f** showed potent antiproliferative activity with anti-HDAC activity.

European Journal of Medicinal Chemistry

2-(Phenylsulfonyl)quinoline *N*-Hydroxyacrylamides as Potent Anticancer Agents Inhibiting Histone Deacetylase

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Abstract. This study reports the design and synthesis of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides (**8a-k**). Structure-activity relationship studies focusing on regio-effect of *N*-hydroxyacrylamide moiety and influence of the sulfonyl linker revealed that *N*-hydroxy-3-[3-(quinoline-2-sulfonyl)-phenyl]-acrylamide (**8f**) showed remarkable enzymatic and cellular activity. The GI_{50} values of **8f** for HL-60, HCT116, PC-3, and A549 cells were found to be 0.29, 0.08, 0.15, and 0.27 μM, respectively. The compounds are therefore more potent than FDA approved PXD-101 and SAHA. They also have an effect on the acetylation degree of histone H3 and α-tubulin. In *in vivo* studies, **8f** showed marked inhibition of the growth of HCT116 xenografts.

KEYWORDS. Anticancer agents, Histone Deacetylase Inhibitors, 2-(Phenylsulfonyl)quinoline

1. Introduction

Histone deacetylases (HDACs) which are involved with the degree of acetylation of histone, have been identified as a crucial target for cancer therapy. Acetylation of histone, a covalent modification,

also named an epigenetic process, is regulated by two classes of enzymes, histone acetyltransferase (HAT) and histone deacetylase (HDAC) [1,2]. The balance between these controls is highly correlated with development of cancer. The use of HDAC inhibitors helps restore the aberrant epigenetic process and consequently, HDAC has become a significant target for cancer therapy. To date, the U.S Food and Drug Administration has approved several HDAC inhibitors for various indications. These include SAHA (vorinostat) and FK-228 (romidepsin) for the treatment of refractory cutaneous T-cell lymphoma [3,4], PXD101 (belinostat) for treatment of refractory peripheral T-cell lymphoma [5], and LBH589 (panobinostat) for the treatment of multiple myeloma [6].

All of these compounds possess a distinct moiety such as hydroxamic acid or 2-aminophenylamide, and such moieties are felt to be characteristic of HDAC inhibitors [7]. Hydroxamic acid has been widely used in the development of HDAC inhibitors and the structures of PXD-101 and LBH589, both possess a *N*-hydroxyacrylamide moiety (C=C-CO-NH-OH, bold in Figure 2). Our previous work on 1-arylsulfonyl-5-(*N*-hydroxyacrylamide)indoles (**5a**) [8], 1-arylsulfonyl- 5-(*N*-hydroxyacrylamide)indolines (**5b**) [9,10], azaindolylsulfonamides (**6**) [11], and 1-arylsulfonyl-5-(N-hydroxyacrylamide)tetrahydroquinolines (**7**) [12], suggests that the *N*-hydroxyacrylamide moiety is associated with significant HDAC inhibitory activity. Compounds (**5-7**) that we reported previously have three components (Figure 2): a heterocycle (blue), a benzenesulfonyl group (purplish red), and an *N*-hydroxyacrylamide moiety (bold). In these cases, the heterocycles are linked to a benzenesulfonyl group forming a sulfonamide group. In the current study our plan was to assemble these two components providing an alternative link between the heterocycle and the benzenesulfonyl group, forming non-sulfonamide molecules. In this way, we synthesized a series of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides (**8a-k**) and studied their structure-activity relationships. The influence of the sulfonyl linker and the regio-effect of *N*-hydroxyacrylamide on antiproliferative activity were also investigated.

2. Results and Discussion

2.1. *Chemistry*

The general route used for the synthesis of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides (**8a-k**) is described in Scheme 1. Different 2-chloroquinolines (**9a-j**) were reacted with substituted thiophenols under basic conditions and this was followed by oxidation with *m*-CPBA, yielding the 2-(phenylsulfonyl)quinolines (**10a-k**). The resulting products underwent Heck olefination with *tert*-butyl acrylate to afford compounds **11a-k**, which were subjected to hydrolysis by TFA to yield the corresponding carboxylic acids (**12a-k**). Compounds **12a-k** were then reacted with NH_2OTHP in the presence of EDC·HCl followed by hydrolysis with 10% TFA to produce the target compounds (**8a-k**). Compounds **18a-b**, in which the sulfonyl has been replaced by a carbonyl group, were synthesized according to the method shown in Scheme 2. Quinoline-2-carbaldehyde (**13**) underwent nucleophilic addition with (3-(diethoxymethyl)phenyl)magnesium bromide or (4-(dimethoxymethyl)phenyl)- magnesium bromide followed by oxidation with pyridinium dichromate (PDC) to obtain the 2-benzoylquinolines (**14a-b**). Subsequently, the dialkoxymethyl groups in **14a** and **14b** were hydrolyzed under acidic condition to provide the corresponding benzaldehydes (**15a-b**). The subsequent Wittig olefination of **15a-b** with methyl (triphenylphosphoranyl)acetate yielded compounds **16a-b**, which underwent the hydrolysis, amidation, and deprotection reactions shown in Scheme 1 to give compounds **18a-b**. The synthetic approach to compound **23** is shown in Scheme 3. The starting material, 2-chloropyridine, underwent substitution, oxidation, Heck reaction, hydrolysis, amidation, and deprotection reactions similar to those described in Scheme 1 to afford compound **23**.

2.2. Biological evaluation

2.2.1. In vitro cell growth inhibitory activity

All synthesized compounds (**8a-k**, **18a-b**, and **23**) together with the reference compounds, PXD101 and SAHA, were tested for their antiproliferative activity in four cancer cell lines, human promyelocytic leukemia HL-60, colon carcinoma HCT116, human prostate cancer PC-3, and human lung cancer A549 (Table 1).

The results obtained from compounds **8a-k**, shown in Table 1, revealed the regio-effect of the *N*-hydroxyacrylamide moiety. Compounds **8f** with *N*-hydroxyacrylamide groups at C3' position showed the most potent antiproliferative activity against HL-60, HCT116, PC-3, and A549 cells with GI_{50} values of 0.29, 0.08, 0.15, and 0.27 μM, respectively. This cellular activity is better than that obtained with PXD101 and SAHA. The shift of the *N*-hydroxyacrylamide moiety from C3' (**8f**) to C4' (**8g**) led to a slight decrease of cellular activity, but the potency was still essentially sustained. Compound **8g** exhibited antiproliferative activity against tested cells with a mean GI_{50} value of 0.62 μM, which is comparable to that of PXD101 and SAHA. The potencies of compounds **8c-e** with a C6-, C7-, and C8-*N*-hydroxyacrylamide moiety respectively, are somewhat less than those of PXD101 and SAHA. Compounds **8a** and **8b**, which possess C3- and C5-*N*-hydroxyacrylamide moiety, have negligible antiproliferative activity. These results indicate that *N*-hydroxyacrylamide is most effective in the C3'- or C4'-position. The following discussion focuses on the substitution effect of the quinoline ring on the cytotoxicity in compounds in which the *N*-hydroxyacrylamide group is at the C3' position. Test data from compounds **8h-k** showed that the presence of replacements such as $-OCH_3$, -Cl, and -F led to decrease of activity. This phenomena is also observed in the comparison of compounds **18a** and **18b** with **8f** and **8g**. The replacement of $-SO_2-$ with -CO- also led to slight decrease of antiproliferative activity. The change of the quinoline in **8f** to a pyridine (**23**) led to a dramatic decrease of cellular activity.

2.2.2. Upregulation Effect of Histone and α-Tubulin.

To evaluate the inhibitory activity of this series of molecules, compounds **8f** and **8j** were tested for their effects on the levels of α-tubulin in HCT116 and PC-3 cells (Figure 3), using PXD101 and

SAHA as reference compounds. The results show that compounds **8f** and **8j** can increase the amount of acetylated histone H3 and α-tubulin in a dose-dependent manner, which is similar to the behavior of PXD101 and SAHA. Notably, the effect of **8f** and **8j** on the acetylation degree of histone H3 was observed at a concentration of 0.3 μM, which is lower than the concentration of the reference compounds that achieved the same effect.

2.2.3. HDAC Isoform Inhibition.

To understand the detailed effect of this series of compounds on isozymes of HDAC, the inhibitory activity of **8f**, **8j**, PXD101, and SAHA on HDAC1, 2, 6, and 8 was assessed (Table 2). The IC_{50} values of **8f** and **8j** for the inhibition of HDAC1, 2, and 6 are smaller than that of PXD101, and SAHA. However, compounds **8f** and **8j** failed to display selectivity toward any HDAC isozymes, and these molecules therefore behave as pan-HDAC inhibitors.

2.2.4. Growth Inhibition of Human Colon Cancer Xenografts in Vivo.

Compound **8f** was tested for its ability to suppress growth of HCT-116 xenografts in nude mice, using SAHA as a reference compound. As shown in Figure 4, compound **8f** inhibited tumor growth in a dose-dependent manner. Oral administration of 100 mg/kg of compound **8f** suppressed tumor growth by a factor of 58.8%, which is similar to the result from treatment with 200 mg/kg of SAHA. There was no change of body weight of tested animals after treatment with compound **8f** or SAHA (Figure 4).

3. Conclusion

A series of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides (**8a-k**) have been synthesized. Structure-activity relationship studies revealed that the *N*-hydroxyacrylamide group is favored in the C3' position and the sulfone linker, when compared to the carbonyl bridge plays a significant role in the biological activity. The study found that compound **8f** inhibits cancer proliferation with a mean

GI_{50} value of 0.19 μM, and is thus more potent than SAHA or PXD101. It also proved able to inhibit HDAC in the study on the degree of acetylation of histone H3 and α-tubulin. In *in vivo* studies, compound **8f** inhibited tumor growth of HCT116 xenografts by a factor of 58.8% with no effect on body weight.

In summary, this study has produced a series of novel 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides with potential as anticancer agents.

4. Experimental section

4.1. Chemistry

Nuclear magnetic resonance (^{1}H NMR) spectra were obtained with Bruker Fourier 300 and DRX-500 spectrometers, with chemical shift in parts per million (ppm, δ) downfield from TMS as an internal standard. High-resolution mass spectra (HRMS) were recorded with a FINNIGAN MAT 95S Mass Spectrometer. The purity of the final compounds was determined using a Hitachi 2000 series HPLC system using C-18 column (Agilent ZORBAX Eclipse XDB-C18 5 μm, 4.6 mm × 150 mm) with the solvent system (mobile phase A consisting of MeCN; mobile phase B consisting of H_2O containing 0.1% formic acid + 10 mmol NH_4OAc) and was found in all cases to be ≥ 95%. Flash column chromatography was done using silica gel (Merck Kieselgel 60, no. 9385, 230−400 mesh ASTM). All reactions were carried out under an atmosphere of dry nitrogen.

*4.1.1. General procedure for synthesis of 2-phenylsulfonylquinoline (**10a-k**) and 2-phenylsulfonylpyridine (**20**)*

A mixture of the 2-chloroquinoline or the 2-chloropyridine (1 equiv), substituted thiophenol (1.2 equiv), K_2CO_3 (1.5 equiv), and DMF (0.5 M) was heated to 110 ^{o}C under N_2 for 12 h. The resulting mixture was diluted with EtOAc and filtered. The filtrate was washed with H_2O three times, and then the organic layer was purified through column chromatography. The resulting product (1 equiv) was

dissolved in DCM (0.1 M), and then *meta*-chloroperoxybenzoic acid (2.1 equiv, 70%) was added at 0 ^{o}C under N_2 and the mixture was stirred at room temperature for additional 12 h. The reaction mixture was washed with cold 2N NaOH solution three times, and then the organic layer was collected and evaporated to provide the product.

*4.1.1.1. 3-Bromo-2-(4-methoxyphenylsulfonyl)quinoline (**10a**)*

Light yellow solid; yield: 62%; mp: 164-165 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H), 7.16-7.22 (m, 2H), 7.74-7.80 (m, 1H), 7.81-8.86 (m, 2H), 7.90-7.96 (m, 2H), 8.00-8.04 (m, 1H), 9.00 (s, 1H).

*4.1.1.2. 5-Bromo-2-(4-methoxyphenylsulfonyl)quinoline (**10b**)*

Colorless oily liquid; yield: 54%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H), 7.13-7.19 (m, 2H), 7.75-7.82 (m, 1H), 7.95-8.00 (m, 2H), 8.06-8.12 (m, 2H), 8.33 (d, 1H, J = 8.7 Hz), 8.80 (dd, 1H, J = 0.6, 9.0 Hz).

*4.1.1.3. 6-Bromo-2-((4-methoxyphenyl)sulfonyl)quinoline (**10c**)*

Colorless oily liquid; yield: 59%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H), 7.13-7.19 (m, 2H), 7.94-8.00 (m, 4H), 8.26 (d, 1H, J = 8.7 Hz), 8.42-8.44 (m, 1H), 8.68 (d, 1H, J = 8.7 Hz).

*4.1.1.4. 7-Bromo-2-((4-methoxyphenyl)sulfonyl)quinoline (**10d**)*

Yellow solid; yield: 72%; mp: 160-162 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, $3H_3$), 7.01 (d, 2H, J = 9.0 Hz), 7.72-7.74 (m, 2H), 8.04-8.07 (m, 2H), 8.21 (d, 1H, J = 8.5 Hz), 8.34 (d, 2H, J = 8.0 Hz).

*4.1.1.5. 8-Bromo-2-((4-methoxyphenyl)sulfonyl)quinoline (**10e**)*

Light yellow solid; yield: 65%; mp: 112-114 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H),

7.16-7.20 (m, 2H), 7.60-7.66 (m, 1H), 8.02-8.07 (m, 2H), 8.12 (d, 1H, *J* = 8.1 Hz), 8.21-8.30 (m, 2H), 8.77 (d, 1H, *J* = 8.4 Hz).

*4.1.1.6. 2-((3-Bromophenyl)sulfonyl)quinoline (**10f**)*

Light yellow solid; yield: 63%; mp: 114-116 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75-7.82 (m, 1H), 7.84-7.93 (m, 3H), 7.95-8.00 (m, 2H), 8.04-8.08 (m, 1H), 8.26 (d, 1H, *J* = 8.4 Hz), 8.76 (d, 1H, *J* = 8.4 Hz).

*4.1.1.7. 2-(4-Bromophenylsulfonyl)quinoline (**10g**)*

Light yellow solid; yield: 80%; mp: 146-148 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74-7.81 (m, 1H), 7.83-7.92 (m, 3H), 7.95-8.00 (m, 2H), 8.05 (d, 1H, *J* = 8.1 Hz), 8.11-8.15 (m, 1H), 8.26 (d, 1H, *J* = 8.7 Hz), 8.76 (d, 1H, *J* = 8.7 Hz).

*4.1.1.8. 2-(3-Bromophenylsulfonyl)-6-methoxyquinoline (**10h**)*

Light yellow solid; yield: 67%; mp: 194-196 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.92 (s, 3H), 7.50-7.55 (m, 2H), 7.57-7.63 (m, 1H), 7.92-8.05 (m, 3H), 8.13-8.15 (m, 1H), 8.23 (d, 1H, *J* = 8.7 Hz), 8.60 (d, 1H, *J* = 8.7 Hz).

*4.1.1.9. 2-((3-Bromophenyl)sulfonyl)-6-chloroquinoline (**10i**)*

White solid; yield: 45%; mp: 116-118 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 1H, *J* = 8.7 Hz), 7.18-7.22 (m, 1H), 7.27-7.33 (m, 1H), 7.36-7.41 (m, 1H), 7.44 (t, 1H, *J* = 2.1 Hz), 7.56 (d, 1H, *J* = 2.4, 9.0 Hz), 7.70-7.76 (m, 2H). 8.06 (d, 1H, *J* = 9.0 Hz).

*4.1.1.10. 2-((3-Bromophenyl)sulfonyl)-8-fluoroquinoline (**10j**)*

White solid; yield: 72%; mp: 122-124 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29-7.34 (m, 1H), 7.36

(d, 1H, *J* = 9.0 Hz), 7.40-7.56 (m, 4H), 7.58 (t, 1H, *J* = 1.8 Hz), 7.77-7.81 (m, 1H), 8.47-8.52 (m, 1H).

*4.1.1.11. 2-((3-Bromophenyl)sulfonyl)-8-chloroquinoline (**10k**)*

White solid; yield: 76%; mp: 104-106 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34-7.51 (m, 5H), 7.71-7.73 (m, 1H), 7.86 (dd, 1H, *J* = 1.2, 7.5 Hz), 7.95 (dd, 1H, *J* = 1.2, 7.5 Hz), 8.50 (d, 1H, *J* = 4.5 Hz).

*4.1.1.12. 2-((3-Bromophenyl)sulfonyl)pyridine (**20**)*

White solid; yield: 66%; mp: 103-105 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.57-7.63 (m, 1H), 7.68-7.73 (m, 1H), 7.93-7.99 (m, 2H), 8.09 (t, 1H, *J* = 1.8 Hz), 8.13-8.19 (m, 1H), 8.23-8.26 (m, 1H), 8.70-8.73 (m, 1H).

*4.1.2. General procedure for synthesis of (E)-tert-butyl acrylates (**11a-k** and **21**)*

A mixture of aryl bromide (1 equiv), *tert*-butyl acrylate (1.2 equiv), $Pd_2(dba)_3$ (0.06 equiv), [(*n*-Bu)$_3$PH]BF_4 (0.12 equiv), Cy_2NMe (1.1 equiv), and DMF (0.5 M) was heated to 100 ^{o}C under N_2 for 12 h. The resulting mixture was diluted with EtOAc and filtered. The filtrate was washed with H_2O three times and the organic layer was collected and purified by chromatography (ethyl acetate/hexane) to provide the corresponding acrylate.

*4.1.2.1. (E)-tert-Butyl 3-(2-(4-methoxyphenylsulfonyl)quinolin-3-yl)acrylate (**11a**)*

Yellow solid; yield: 85%; mp: 123 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52(s, 9H), 3.87(s, 3H), 6.70 (d, 1H, *J* = 15.9 Hz), 7.16-7.22 (m, 2H), 7.75-7.82 (m, 1H), 7.84-7.92 (m, 4H), 8.08 (d, 1H, *J* = 8.1 Hz), 8.50 (d, 1H, *J* = 15.6 Hz), 9.12 (s, 1H).

*4.1.2.2. (E)-tert-Butyl 3-(2-((4-methoxyphenyl)sulfonyl)quinolin-5-yl)acrylate (**11b**)*

Light yellow solid; yield: 86%; mp: 174-176 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51(s, 9H), 3.83(s, 3H), 6.66 (d, 1H, J = 15.6 Hz), 7.15-7.19 (m, 2H), 7.86-7.93 (m, 1H), 7.96-8.01 (m, 2H), 8.10 (d, 1H, J = 8.4 Hz), 8.18-8.32 (m, 3H), 8.99-9.03 (m, 1H).

*4.1.2.3. (E)-tert-Butyl 3-(2-((4-methoxyphenyl)sulfonyl)quinolin-6-yl)acrylate (**11c**)*

Colorless oily liquid; yield: 89%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.49 (s, 9H), 3.83 (s, 3H), 6.76 (d, 1H, J = 16.2 Hz), 7.13-7.19 (m, 2H), 7.72 (d, 1H, J = 15.9 Hz), 7.94-8.00 (m, 2H), 8.02 (d, 1H, J = 9.0 Hz), 8.21-8.27 (m, 2H), 8.40 (d, 1H, J = 1.8 Hz), 8.68 (d, 1H, J = 8.4 Hz).

*4.1.2.4. (E)-tert-Butyl 3-(2-((4-methoxyphenyl)sulfonyl)quinolin-7-yl)acrylate (**11d**)*

Colorless oily liquid; yield: 61%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 9H), 3.86 (s, 3H), 6.54 (d, 1H, J = 16.0 Hz), 7.01 (d, 2H, J = 9.0 Hz), 7.72 (d, 1H, J = 16.0 Hz), 7.79 (d, 1H, J = 8.5 Hz), 7.85 (d, 1H, J = 8.5 Hz), 8.07 (d, 2H, J = 9.0 Hz), 8.19 (d, 1H, J = 8.5 Hz), 8.22 (s, 1H), 8.33 (d, 1H, J = 8.5 Hz).

*4.1.2.5. (E)-tert-Butyl 3-(2-((4-methoxyphenyl)sulfonyl)quinolin-8-yl)acrylate (**11e**)*

Yield: 89%; colorless oily liquid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 9H), 3.84 (s, 3H), 6.88 (d, 1H, J = 16.2 Hz), 7.15-7.20 (m, 2H), 7.78 (t, 1H, J = 7.8 Hz), 7.98-8.03 (m, 2H), 8.17 (d, 1H, J = 8.1 Hz), 8.27 (d, 1H, J = 8.7 Hz), 8.33-8.43 (m, 2H), 8.77 (d, 1H, J = 8.4 Hz).

*4.1.2.6. (E)-tert-Butyl 3-(3-(quinolin-2-ylsulfonyl)phenyl)acrylate (**11f**)*

Light yellow solid; yield: 88%; mp: 194-196 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.46 (s, 9H), 6.67 (d, 1H, J = 15.9 Hz), 7.59 (d, 1H, J = 15.9 Hz), 7.76-7.82 (m, 1H), 7.87-7.97 (m, 3H), 8.02-8.09 (m, 3H), 8.14 (d, 1H, J = 8.1 Hz), 8.28 (d, 1H, J = 8.7 Hz), 8.76 (d, 1H, J = 8.7 Hz).

*4.1.2.7. (E)-tert-Butyl 3-(4-(quinolin-2-ylsulfonyl)phenyl)acrylate (**11g**)*

Light yellow solid; yield: 77%; mp: 199-200 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.46 (s, 9H), 6.67 (d, 1H, J = 15.9 Hz), 7.59 (d, 1H, J = 16.2 Hz), 7.76-7.82 (m, 1H), 7.87-7.97 (m, 3H), 8.02-8.09 (m, 3H), 8.12-8.16 (m, 1H), 8.28 (d, 1H, J = 8.7 Hz) , 8.76 (d, 1H, J = 8.4 Hz).

*4.1.2.8. (E)-tert-Butyl 3-(3-((6-methoxyquinolin-2-yl)sulfonyl)phenyl)acrylate (**11h**)*

Light yellow solid; yield: 45%; mp: 71-73 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53 (s, 9H), 3.94 (s, 3H), 6.45 (d, 1H, J = 16.0 Hz), 7.09 (d, 1H, J = 3.0 Hz), 7.42 (dd, 1H, J = 2.5, 9.5 Hz), 7.51-7.59 (m, 2H), 7.68 (d, 1H, J = 7.5 Hz), 8.04 (d, 1H, J = 9.5 Hz), 8.09 (d, 1H, J = 8.0 Hz), 8.16 (d, 1H, J = 8.5 Hz), 8.23 (d, 2H, J = 8.0 Hz).

*4.1.2.9. (E)-tert-Butyl 3-(3-((6-chloroquinolin-2-yl)sulfonyl)phenyl)acrylate (**11i**)*

Brown oily liquid; yield: 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 9H), 6.38 (d, 1H, J = 16.2 Hz), 7.13 (d, 1H, J = 8.7 Hz), 7.24-7.29 (m, 1H), 7.36-7.46 (m, 3H), 7.52-7.56 (m, 1H), 7.61 (d, 1H, J = 15.9 Hz), 7.68-7.74 (m, 2H), 8.04 (d, 1H, J = 8.7 Hz).

*4.1.2.10. (E)-tert-Butyl 3-(3-((8-fluoroquinolin-2-yl)sulfonyl)phenyl)acrylate (**11j**)*

Yellow solid; yield: 86%; mp: 69-71 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H), 6.37 (d, 1H, J = 15.9 Hz), 7.14 (d, 1H, J = 9.0 Hz), 7.31-7.38 (m, 4H), 7.40-7.48 (m, 2H), 7.53-7.62 (m, 2H), 8.13-8.17 (m, 1H).

*4.1.2.11. (E)-tert-Butyl 3-(3-((8-chloroquinolin-2-yl)sulfonyl)phenyl)acrylate (**11k**)*

Yellow oily liquid; yield: 90%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H), 6.37 (d, 1H, J = 16.2 Hz), 7.14 (d, 1H, J = 9.0 Hz), 7.31-7.47 (m, 6H), 7.53-7.62 (m, 2H), 8.15 (dd, 1H, J = 1.8, 9.0 Hz).

*4.1.2.12. (E)-tert-Butyl 3-(3-(pyridin-2-ylsulfonyl)phenyl)acrylate (**21**)*

Colorless oily liquid; yield: 90%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.46 (s, 9H), 6.64 (d, 1H, J = 16.2 Hz), 7.61-7.71 (m, 3H), 7.96-8.00 (m, 1H), 8.06-8.09 (m, 1H), 8.12-8.18 (m, 1H), 8.20-8.22 (m, 1H), 8.23-8.27 (m, 1H), 8.67-8.70 (m, 1H).

*4.1.3. General procedure for synthesis of (E)-acrylic acids (**12a-k** and **22**)*

To a stirred solution of (*E*)-*tert*-butyl acrylate in DCM (10 mL), trifluoroacetic acid (3-5 mL) was added at room temperature and the mixture was stirred for 12 h. The solution was evaporated and H_2O was added. The pH value of the reaction mixture was adjusted to pH 4 by the addition of 2N NaOH and the precipitate was collected by filtration to afford the product.

*4.1.3.1. (E)-3-(2-((4-Methoxyphenyl)sulfonyl)quinolin-3-yl)acrylic acid (**12a**)*

Brown solid; yield: 91%; mp: 142 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.87(s, 3H), 6.71 (d, 1H, J = 15.9 Hz), 7.17-7.23 (m, 2H), 7.74-7.88 (m, 3H), 7.87-7.93 (m, 2H), 8.09 (d, 1H, J = 8.1 Hz), 8.56 (d, 1H, J = 15.3 Hz), 9.10 (s, 1H).

*4.1.3.2. (E)-3-(2-((4-Methoxyphenyl)sulfonyl)quinolin-5-yl)acrylic acid (**12b**)*

Light yellow solid; yield: 90%; mp: 141 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83(s, 3H), 6.68 (d, 1H, J = 15.6 Hz), 7.14-7.20 (m, 2H), 7.88-7.94 (m, 1H), 7.95-8.01 (m, 2H), 8.11 (d, 1H, J = 8.4 Hz), 8.19 (d, 1H, J = 7.2 Hz), 8.24 (d, 1H, J = 9.0 Hz), 8.32 (d, 1H, J = 15.9 Hz), 9.02 (d, 1H, J = 8.7 Hz).

*4.1.3.3. (E)-3-(2-(4-Methoxyphenylsulfonyl)quinolin-6-yl)acrylic acid (**12c**)*

Brown solid; yield: 96%; mp: 168 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83(s, 3H), 6.76 (d, 1H, J = 16.2 Hz), 7.14-7.20 (m, 2H), 7.76 (d, 1H, J = 15.9 Hz), 7.94-8.00 (m, 2H), 8.04 (d, 1H, J = 9.0 Hz),

8.21-8.26 (m, 2H), 8.39 (d, 1H, *J* = 1.5 Hz), 8.69 (d, 1H, *J* = 8.7 Hz).

*4.1.3.4. (E)-3-(2-((4-Methoxyphenyl)sulfonyl)quinolin-7-yl)acrylic acid (**12d**)*

Light brown solid; yield: 94%; mp: 169 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H), 6.79 (d, 1H, *J* = 16.2 Hz), 7.16 (d, 2H, *J* = 8.7 Hz), 7.79 (d, 1H, *J* = 16.2 Hz), 7.97 (d, 2H, *J* = 9.0 Hz), 8.08-8.15 (m, 2H), 8.21 (d, 1H, *J* = 8.7 Hz), 8.29 (s, 1H), 8.70 (d, 1H, *J* = 8.7 Hz).

*4.1.3.5. (E)-3-(2-((4-Methoxyphenyl)sulfonyl)quinolin-8-yl)acrylic acid (**12e**)*

Light brown solid; yield: 76%; mp: 185 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H), 6.88 (d, 1H, *J* = 16.5 Hz), 7.17 (d, 1H, *J* = 9.0 Hz), 7.62-7.82 (m, 1H), 7.98-8.02 (m, 1H), 8.16 (d, 1H, *J* = 8.1 Hz), 8.25 (d, 1H, *J* = 8.7 Hz), 8.33 (d, 1H, *J* = 7.2 Hz), 8.42 (d, 1H, *J* = 8.1 Hz), 8.77 (d, 1H, *J* = 8.7 Hz).

*4.1.3.6. (E)-3-(3-(Quinolin-2-ylsulfonyl)phenyl)acrylic acid (**12f**)*

Light yellow solid; yield: 90%; mp: 182 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.67 (d, 1H, *J* = 16.2 Hz), 7.65-7.72 (m, 2H), 7.75-7.81 (m, 1H), 7.86-7.92 (m, 1H), 8.05-8.15 (m, 4H), 8.29-8.32 (m, 2H), 8.76 (d, 1H, *J* = 8.7 Hz).

*4.1.3.7. (E)-3-(4-(Quinolin-2-ylsulfonyl)phenyl)acrylic acid (**12g**)*

White solid; yield: 95%; mp: 240 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.67 (d, 1H, *J* = 15.9 Hz), 7.62 (d, 1H, *J* = 16.2 Hz), 7.76-7.82 (m, 1H), 7.87-7.96 (m, 3H), 8.03-8.09 (m, 3H), 8.12-8.16 (m, 1H), 8.27 (d, 1H, *J* = 8.4 Hz), 8.76 (d, 1H, *J* = 8.7 Hz).

*4.1.3.8. (E)-3-(3-((6-Methoxyquinolin-2-yl)sulfonyl)phenyl)acrylic acid (**12h**)*

White solid; yield: 97%; mp: 216 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.91 (s, 3H), 6.66 (d, 1H, *J* =

15.9 Hz), 7.49-7.54 (m, 2H), 7.64-7.71 (m, 2H), 7.95-7.99 (m, 1H), 8.02-8.08 (m, 2H), 8.22-8.27 (m, 2H), 8.59 (d, 1H, *J* = 8.4 Hz).

*4.1.3.9. (E)-3-(3-((6-Chloroquinolin-2-yl)sulfonyl)phenyl)acrylic acid (**12i**)*

Colorless oily liquid; yield: 92%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.67 (d, 1H, *J* = 16.2 Hz), 7.65-7.77 (m, 3H), 8.05-8.14 (m, 4H), 8.35-8.39 (m, 2H), 8.85 (d, 1H, *J* = 8.7 Hz), 12.58 (brs, 1H).

*4.1.3.10. (E)-3-(3-((8-Fluoroquinolin-2-yl)sulfonyl)phenyl)acrylic acid (**12j**)*

Light yellow solid; yield: 95%; mp: 212 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.57 (d, 1H, *J* = 16.2 Hz), 7.31-7.38 (m, 2H), 7.42-7.54 (m, 3H), 7.58-7.67 (m, 3H), 7.77-7.81 (m, 1H) 8.49 (dd, 1H, *J* = 1.8, 9.0 Hz), 12.44 (brs, 1H).

*4.1.3.11. (E)-3-(3-((8-Chloroquinolin-2-yl)sulfonyl)phenyl)acrylic acid (**12k**)*

White solid; yield: 92%; mp: 220 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.58 (d, 1H, *J* = 16.2 Hz), 7.32-7.41 (m, 2H), 7.43-7.52 (m, 2H), 7.55-7.62 (m, 1H), 7.74-7.76 (m, 1H), 7.82-7.86 (m, 1H), 7.94 (dd, 1H, *J* = 8.1, 1.2 Hz), 8.49 (d, 1H, *J* = 4.5 Hz).

*4.1.3.12. (E)-3-(3-(Pyridin-2-ylsulfonyl)phenyl)acrylic acid (**22**)*

White solid; yield: 81%; mp: 203 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.65 (d, 1H, *J* = 16.2 Hz), 7.64-7.71 (m, 3H), 7.96-8.00 (m, 1H), 8.05-8.09 (m, 1H), 8.12-8.20 (m, 2H), 8.23-8.27 (m, 1H), 8.68-8.70 (m, 1H).

*4.1.4. General procedure for synthesis of (E)-N-hydroxyacrylamide (**8a-k**, **18a-b**, and **23**)*

A mixture of (*E*)-acrylic acid (1 equiv), NH_2OTHP (1.2 equiv), EDC·HCl (2 equiv), DMAP (0.5 equiv), and DCM (0.1 M) was stirred at room temperature under N_2 for 12 h. The reaction mixture

was washed with H_2O three times. The organic layer was collected and purified through column chromatography. The resulting product was dissolved in MeOH and then 1N HCl solution (10-20 mL) was added slowly at 0 ^oC and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O and the solid was collected to provide the desired product.

*4.1.4.1. (E)-N-Hydroxy-3-(2-((4-methoxyphenyl)sulfonyl)quinolin-3-yl)acrylamide (**8a**)*

White solid; yield: 57%; mp: 106-107 ^oC. IR (KBr, cm^{-1}): 3232, 1686. ^1H NMR (500 MHz, DMSO-d_6) δ 3.87(s, 3H), 6.55 (d, 1H, J = 15.6 Hz), 7.19 (d, 2H, J = 8.7 Hz), 7.74-7.91 (m, 5H), 8.13 (d, 1H, J = 8.1 Hz), 8.40 (d, 1H, J = 15.6 Hz), 8.86 (s, 1H), 9.21 (s, 1H), 10.94 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.79, 115.46, 125.40, 127.07, 129.34, 129.40, 130.01, 130.15, 130.70, 132.36, 132.87, 133.30, 138.43, 145.73, 156.70, 162.71, 164.68. HRMS-ESI calcd. for $C_{19}H_{17}N_2O_5S$ $[M + H]^+$ 385.0858, found 385.0853.

*4.1.4.2. (E)-N-Hydroxy-3-(2-((4-methoxyphenyl)sulfonyl)quinolin-5-yl)acrylamide (**8b**)*

Light yellow solid; yield: 81%; mp: 74-75 ^oC. IR (KBr, cm^{-1}): 3196, 1662. ^1H NMR (500 MHz, DMSO-d_6) δ 3.83 (s, 3H), 6.59 (d, 1H, J = 15.5 Hz), 7.17 (d, 1H, J = 8.0 Hz), 7.90-7.94 (m, 1H), 7.97-8.01 (m, 3H), 8.07 (d, 1H, J = 8.0 Hz), 8.16 (d, 1H, J = 15.5 Hz), 8.24 (d, 1H, J = 9.5 Hz), 8.99 (d, 1H, J = 8.5 Hz), 9.14 (s, 1H), 10.91 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.77, 115.88, 118.67, 125.11, 127.48, 128.04, 130.60, 131.40, 131.93, 132.31, 133.97, 134.08, 137.04, 147.74, 159.29, 163.19, 164.70. HRMS-ESI calcd. for $C_{19}H_{17}N_2O_5S$ $[M + H]^+$ 385.0858, found 385.0852.

*4.1.4.3. (E)-N-Hydroxy-3-(2-((4-methoxyphenyl)sulfonyl)quinolin-6-yl)acrylamide (**8c**)*

White solid; yield: 67%. mp: 119 ^oC. IR (KBr, cm^{-1}): 3208, 1653. ^1H NMR (500 MHz, DMSO-d_6) δ 3.83 (s, 3H), 6.67 (d, 1H, J = 15.5 Hz), 7.17 (d, 2H, J = 9.0 Hz), 7.63 (d, 1H, J = 15.5 Hz), 7.97 (d, 2H, J = 8.5 Hz), 8.05-8.07 (m, 2H), 8.22 (d, 1H, J = 8.5 Hz), 8.27 (s, 1H), 8.70 (d, 1H, J = 8.5 Hz).

^{13}C NMR (75 MHz, DMSO-d_6) δ 56.79, 115.90, 119.06, 123.07, 129.26, 129.72, 130.31, 130.68, 130.86, 131.91, 136.55, 137.90, 141.06, 147.78, 159.45, 164.70. HRMS-ESI calcd. for $C_{19}H_{17}N_2O_5S$ $[M + H]^+$ 385.0858, found 385.0848.

*4.1.4.4. (E)-N-Hydroxy-3-(2-((4-methoxyphenyl)sulfonyl)quinolin-7-yl)acrylamide (**8d**)*

Light yellow solid; yield: 72%; mp: 125-126 ^{o}C. IR (KBr, cm^{-1}): 3196, 1659. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.83 (s, 3H), 6.71 (d, 1H, J = 16.0 Hz), 7.17 (d, 2H, J = 9.0 Hz), 7.66 (d, 1H, J = 16.0 Hz), 7.95-7.99 (m, 3H), 8.13 (d, 1H, J = 8.5 Hz), 8.17-8.21 (m, 2H), 8.70 (d, 1H, J = 8.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.77, 115.88, 118.78, 123.36, 128.08, 129.80, 129.88, 130.67, 131.88, 137.88, 139.02, 140.58, 147.76, 159.81, 164.66. HRMS-ESI calcd. for $C_{19}H_{17}N_2O_5S$ $[M + H]^+$ 385.0858, found 385.0848.

*4.1.4.5. (E)-N-Hydroxy-3-(2-((4-methoxyphenyl)sulfonyl)quinolin-8-yl)acrylamide (**8e**)*

White solid; yield: 73%; mp: 198 ^{o}C. IR (KBr, cm^{-1}): 3322, 3112, 1671. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H), 6.76 (d, 1H, J = 15.9 Hz), 7.14-7.20 (m, 2H), 7.77 (t, 1H, J = 7.8 Hz), 8.00-8.06 (m, 2H), 8.09-8.17 (m, 2H), 8.23 (d, 1H, J = 8.4 Hz), 8.40 (d, 1H, J = 16.2 Hz), 8.73 (d, 1H, J = 8.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.75, 115.78, 118.16, 123.02, 129.60, 129.73, 130.19, 130.39, 132.13, 133.86, 134.10, 141.23, 141.38, 144.88, 158.84, 163.60, 164.72. HRMS-ESI calcd. for $C_{19}H_{17}N_2O_5S$ $[M + H]^+$ 385.0858, found 385.0850.

*4.1.4.6. (E)-N-Hydroxy-3-(3-(quinolin-2-ylsulfonyl)phenyl)acrylamide (**8f**)*

Light brown solid; yield: 78%; mp: 132-33 ^{o}C. IR (KBr, cm^{-1}): 3226, 1665. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.62 (d, 1H, J = 15.6 Hz), 7.54 (d, 1H, J = 15.9 Hz), 7.69 (t, 1H, J = 7.5 Hz), 7.76-7.82 (m, 1H), 7.87-7.93 (m, 2H), 8.00-8.30 (m, 5H), 8.77 (d, 1H, J = 8.4 Hz), 9.15 (s, 1H), 10.79 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 118.62, 122.79, 127.50, 129.28, 129.97, 130.23, 130.51, 131.32,

132.68, 134.20, 137.31, 140.34, 140.97, 147.45, 158.30, 163.08. HRMS-ESI calcd. for $C_{18}H_{15}N_2O_4S$ $[M + H]^+$ 355.0753, found 355.0749.

*4.1.4.7. (E)-N-Hydroxy-3-(4-(quinolin-2-ylsulfonyl)phenyl)acrylamide (**8g**)*

Light yellow solid; yield: 68%; mp: 133-34 ^oC. IR (KBr, cm^{-1}): 3316, 3172, 1668. ^1H NMR (300 MHz, DMSO-d_6) δ 6.59 (d, 1H, J = 15.9 Hz), 7.49 (d, 1H, J = 15.9 Hz), 7.76-7.88 (m, 3H), 7.88-7.93 (m, 1H), 8.04-8.08 (m, 3H), 8.12-8.16 (m, 1H), 8.26 (d, 1H, J = 8.4 Hz), 8.76 (d, 1H, J = 8.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 118.56, 124.00, 129.26, 129.34, 129.56, 130.13, 130.21, 130.47, 132.66, 137.34, 139.55, 140.95, 141.38, 147.47, 158.42, 162.93. HRMS-ESI calcd. for $C_{18}H_{15}N_2O_4S$ $[M + H]^+$ 355.0753, found 355.0745.

*4.1.4.8. (E)-N-Hydroxy-3-(3-(6-methoxyquinolin-2-ylsulfonyl)phenyl)acrylamide (**8h**)*

White solid; yield: 65%; mp: 80-81 ^oC. IR (KBr, cm^{-1}): 3202, 1668. ^1H NMR (300 MHz, DMSO-d_6) δ 3.91 (s, 3H), 6.61 (d, 1H, J = 15.9 Hz), 7.49-7.56 (m, 3H), 7.67 (t, 1H, J = 7.8 Hz), 7.89 (d, 1H, J = 7.8 Hz), 7.95-8.01 (m, 2H), 8.22 (d, 2H, J = 8.7 Hz), 8.59 (d, 1H, J = 8.4 Hz), 10.80 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.79, 106.58, 119.14, 122.76, 125.60, 127.35, 129.82, 131.30, 131.38, 131.79, 134.04, 137.30, 138.98, 140.78, 143.62, 155.58, 160.42, 163.12. HRMS-ESI calcd. for $C_{19}H_{17}N_2O_5S$ $[M + H]^+$ 385.0858, found 385.0855.

*4.1.4.9. (E)-3-(3-((6-Chloroquinolin-2-yl)sulfonyl)phenyl)-N-hydroxyacrylamide (**8i**)*

Light yellow solid; yield: 72%; mp: 167 ^oC. IR (KBr, cm^{-1}): 3274, 1659. ^1H NMR (300 MHz, DMSO-d_6) δ 6.48 (d, 1H, J = 15.9 Hz), 7.24-7.28 (m, 1H), 7.36 (d, 1H, J = 8.7 Hz), 7.44-7.53 (m, 4H), 7.65 (d, 2H, J = 1.5 Hz), 8.09 (t, 1H, J = 1.5 Hz), 8.41 (d, 1H, J = 9.0 Hz), 9.05 (s, 1H), 10.72 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 119.65, 122.79, 127.53, 128.00, 129.96, 130.35, 131.34, 132.31, 133.31, 133.21, 134.27, 134.99, 137.20, 137.33, 140.08, 140.40, 145.89, 158.68, 163.00.

HRMS-ESI calcd. for $C_{18}H_{14}ClN_2O_4S$ $[M + H]^+$ 389.0363, found 389.0360.

*4.1.4.10. (E)-3-(3-((8-Fluoroquinolin-2-yl)sulfonyl)phenyl)-N-hydroxyacrylamide (**8j**)*

Light red solid; yield: 79%; mp: 130-131 ^oC. IR (KBr, cm^{-1}): 3190, 1662. ^1H NMR (300 MHz, DMSO-d_6) δ 6.48 (d, 1H, J = 15.9 Hz), 7.27-7.31 (m, 1H), 7.36 (d, 1H, J = 8.7 Hz), 7.45-7.54 (m, 6H), 7.77-7.81 (m, 1H), 8.47-8.51 (m, 1H), 9.05 (s, 1H), 10.73 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 116.51, 116.75, 119.71, 122.81, 125.26, 125.32, 127.64, 130.07, 130.78, 130.88, 131.13, 131.38, 134.33, 137.17, 137.36, 140.00, 141.11, 141.15, 156.13, 158.56, 159.55, 162.98. HRMS-ESI calcd. for $C_{18}H_{14}FN_2O_4S$ $[M + H]^+$ 373.0658, found 373.0653.

*4.1.4.11. (E)-3-(3-((8-Chloroquinolin-2-yl)sulfonyl)phenyl)-N-hydroxyacrylamide (**8k**)*

White solid; yield: 73%; mp: 110 ^oC. IR (KBr, cm^{-1}): 3196, 1665. ^1H NMR (300 MHz, DMSO-d_6) δ 6.49 (d, 1H, J = 15.9 Hz), 7.34-7.38 (m, 2H), 7.44-7.59 (m, 5H), 7.83-7.87 (m, 1H), 7.95 (dd, 1H, J = 1.2, 8.1 Hz), 8.50 (d, 1H, J = 9.0 Hz), 10.74 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 122.63, 128.02, 128.64, 130.21, 130.63, 131.04, 131.16, 132.50, 133.51, 134.54, 137.16, 137.33, 139.75, 141.84, 143.48, 158.96, 163.11. HRMS-ESI calcd. for $C_{18}H_{14}ClN_2O_4S$ $[M + H]^+$ 389.0363, found 389.0355.

*4.1.4.12. N-Hydroxy-3-[3-(quinoline-2-carbonyl)-phenyl]-acrylamide (**18a**)*

White solid; yield: 73%; mp: 128-129 ^oC. IR (KBr, cm^{-1}): 3304, 1677. ^1H NMR (300 MHz, DMSO-d_6) δ 6.54 (d, 1H, J = 15.6 Hz), 7.51-7.64 (m, 2H), 7.74-7.80 (m, 1H), 7.85-7.90 (m, 2H), 8.04-8.14 (m, 4H), 8.27-8.31 (m, 1H), 8.64 (d, 1H, J = 8.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 121.21, 121.39, 128.99, 129.60, 129.72, 129.92, 130.07, 130.82, 131.59, 132.61, 133.09, 135.86, 137.51, 138.70, 146.95, 155.05, 194.03. HRMS-ESI calcd. for $C_{19}H_{15}N_2O_3$ $[M + H]^+$ 319.1083, found 319.1069.

*4.1.4.13. N-Hydroxy-3-[4-(quinoline-2-carbonyl)-phenyl]-acrylamide (**18b**)*

Light yellow solid; yield: 70%; mp: 132-133 ^{o}C. IR (KBr, cm^{-1}): 3346, 1650. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.62 (d, 1H, J = 15.9 Hz), 7.56 (d, 1H, J = 15.9 Hz), 7.73-7.80 (m, 3H), 7.84-7.90 (m, 1H), 8.05-8.14 (m, 5H), 8.63 (d, 1H, J = 8.1 Hz), 9.13 (s, 1H), 10.88 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 121.37, 122.83, 128.22, 129.01, 129.56, 129.66, 130.74, 131.55, 132.45, 137.18, 138.22, 138.68, 140.22, 145.93, 155.24, 163.27, 193.66. HRMS-ESI calcd. for $C_{19}H_{15}N_2O_3$ $[M + H]^+$ 319.1083, found 319.1065.

*4.1.4.14. (E)-N-Hydroxy-3-(3-(pyridin-2-ylsulfonyl)phenyl)acrylamide (**23**)*

White solid; yield: 63%; mp: 156-157 ^{o}C. IR (KBr, cm^{-1}): 3196, 1662. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.59 (d, 1H, J = 15.9 Hz), 7.53 (d, 1H, J = 15.9 Hz), 7.64-7.72 (m, 2H), 7.89-7.95 (m, 2H), 8.12-8.19 (m, 2H), 8.22-8.26 (m, 1H), 8.68-8.71 (m, 1H), 9.13 (s, 1H), 10.79 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 122.71, 123.10, 127.27, 128.93, 129.89, 131.30, 134.20, 137.22, 140.20, 140.26, 151.63, 158.52. HRMS-ESI calcd. for $C_{14}H_{13}N_2O_4S$ $[M + H]^+$305.0596, found 305.0578.

*4.1.5. General procedure for synthesis of acetals (**14a-b**)*

Grignard reagent (1.2 equiv 3.82 mL, 1 M in dry THF) was added slowly to a solution of quinoline-2-carbaldehyde (0.5 g, 3.18 mmol) in dry THF (20 mL) at 0 ^{o}C. The resulting solution was stirred at room temperature for 12 h. The reaction was quenched with NH_4Cl solution and extracted with EtOAc. The organic layer was collected and purified through column chromatography to afford the benzhydrol compound. Pyridinium dichromate (1.5 equiv 1.8 g, 4.77 mmol) and 4 Å molecular sieves was added to a solution of the benzhydrol compound in DCM (0.2 M) and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a pad of Celite and the filtrate was purified by column chromatography to yield the desired product.

*4.1.5.1. (3-Diethoxymethyl-phenyl)-quinolin-2-yl-methanone (**14a**)*

Colorless oily liquid; yield: 23.4%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10-1.16 (m, 6H), 3.44-3.63 (m, 4H), 5.57 (s, 1H), 7.53-7.59 (m, 1H), 7.69-7.78 (m, 2H), 7.83-7.89 (m, 1H), 8.03-8.15 (m, 6H), 8.59-8.65 (m, 1H).

*4.1.5.2. (4-Dimethoxymethyl-phenyl)-quinolin-2-yl-methanone (**14b**)*

Colorless oily liquid; yield: 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 6H), 5.48 (s, 1H), 7.59-7.68 (m, 3H), 7.74-7.81 (m, 1H), 7.87-7.91 (m, 1H), 8.10 (d, 1H, J = 8.4 Hz), 8.18 (d, 1H, J = 8.7 Hz), 8.23-8.27 (m, 2H), 8.33 (d, 1H, J = 8.4 Hz).

*4.1.6. General procedure for hydrolysis of acetal groups to afford the corresponding benzaldehyde derivatives (**15a-b**)*

1N HCl was added to a stirring solution of the acetal compound in THF at room temperature and stirred for 12 h. The solvent was evaporated *in vacuo* and the pH value of the mixture was adjusted to pH 7 by addition of 1N NaOH. The precipitate was collected by filtration to afford the anticipated product.

*4.1.6.1. 3-(Quinoline-2-carbonyl)-benzaldehyde (**15a**)*

White solid; yield: 92%; mp: 140-141 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75-7.91 (m, 3H), 8.09-8.17 (m, 3H), 8.19-8.23 (m, 1H), 8.42 (dt, 1H, J = 1.5, 7.8 Hz), 8.61-8.63 (m, 1H), 8.66 (d, 1H, J = 8.4 Hz), 10.12 (s, 1H).

*4.1.6.2. 4-(Quinoline-2-carbonyl)-benzaldehyde (**15b**)*

White solid; yield: 88%; mp: 171-173 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74-7.80 (m, 1H),

7.84-7.90 (m, 1H), 8.06-8.16 (m, 5H), 8.22-8.25 (m, 2H), 8.65 (d, 1H, *J* = 8.4 Hz), 10.15 (s, 1H).

*4.1.7. General procedure for Wittig reaction to afford the corresponding methyl acrylates (**16a-b**)*

A mixture of benzaldehyde (1.0 equiv), methyl (triphenylphosphoranylidene)acetate (1.0 equiv), and DCM was stirred at room temperature for 4 h. The resulting solution was washed with H_2O three times. The organic layer was collected and purified by column chromatography to provide the desired product.

*4.1.7.1. 3-[3-(Quinoline-2-carbonyl)-phenyl]-acrylic acid methyl ester (**16a**)*

Yello solid; yield: 90%; mp: 100-101 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.51 (d, 1H, *J* = 15.9 Hz), 7.55 (t, 1H, *J* = 7.8 Hz), 7.66-7.72 (m, 1H), 7.74-7.84 (m, 3H), 7.93 (dd, 1H, *J* = 1.2, 8.1 Hz), 8.14-8.21 (m, 2H), 8.24-8.28 (m, 1H), 8.38 (d, 1H, *J* = 8.4 Hz), 8.43 (t, 1H, *J* = 1.5 Hz).

*4.1.7.2. 3-[4-(Quinoline-2-carbonyl)-phenyl]-acrylic acid methyl ester (**16b**)*

White solid; yield: 89%; mp: 118-120 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.57 (d, 1H, *J* = 15.9 Hz), 7.64-7.83 (m, 5H), 7.92 (d, 1H, *J* = 8.4 Hz), 8.14 (d, 1H, *J* = 8.4 Hz), 8.20 (d, 1H, *J* = 8.4 Hz), 8.28 (d, 2H, *J* = 8.4 Hz), 8.36 (d, 1H, *J* = 8.4 Hz).

*4.1.8. General procedure for hydrolysis of methyl acrylates to afford the corresponding acrylic acids (**17a-b**)*

1N LiOH (1.0 equiv) was added to a solution of methyl acrylate (1.0 equiv) in THF (0.1 M), at room temperature and the mixture was stirred for 12 h. The solvent was evaporated *in vacuo*. The pH value of the resulting mixture was adjusted to pH 4 by addition of 1N HCl and the precipitate was collected to afford the product.

*4.1.8.1. 3-[3-(Quinoline-2-carbonyl)-phenyl]-acrylic acid (**17a**)*

White solid; yield: 89%; mp: 168 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.59 (d, 1H, J = 16.2 Hz), 7.58-7.71 (m, 2H), 7.73-7.79 (m, 1H), 7.83-7.90 (m, 1H), 8.01-8.14 (m, 5H), 8.32 (s, 1H), 8.63 (d, 1H, J = 8.4 Hz).

*4.1.8.2. 3-[4-(Quinoline-2-carbonyl)-phenyl]-acrylic acid (**17b**)*

Light yellow solid; yield: 88%; mp: 180 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.70 (d, 1H, J = 15.9 Hz), 7.68 (d, 1H, J = 15.9 Hz), 7.73-7.79 (m, 1H), 7.83-7.89 (m, 3H), 8.06-8.12 (m, 5H), 8.63 (d, 1H, J = 8.4 Hz).

4.2. Biology

4.2.1 Cell Culture

The human leukaemia cell line HL-60, colon cancer cell line HCT116, prostate cancer cell line PC-3 and non-small cell lung cancer cell line were maintained in RPMI 1640 medium containing 10% fetal bovine serum, 100 units/mL penicillin, 100 μg/mL streptomycin and 2.5 μg/mL amphotericin B. Cells were cultured in tissue culture flasks in a humidified incubator at 37 °C, in an atmosphere of 5% CO_2 and 95% air.

4.2.2 Sulforhodamine B (SRB) Assays

Counted cells were seeded in 96-well plates in medium with 5% FBS. After 24 h, cells were fixed with 10% trichloroacetic acid (TCA) to represent cell population at the time of compound addition (T_0). After additional incubation of DMSO or test compound for 48 h, cells were fixed with 10% TCA and then stained with SRB at 0.4 % (w/v) in 1% acetic acid. Unbound SRB was washed out by 1% acetic acid and SRB-containing cells were solubilized with 10 mM Trizma base. The absorbance was read at a wavelength of 515 nm. Using the following absorbance measurements, such as time

zero (T_0), control growth (C), and cell growth in the presence of the compound (Tx), the percentage of growth was calculated at each of the compound concentration levels. Growth inhibition of 50% (GI_{50}) was calculated from the equation [(Ti-Tz)/(C-Tz)] x 100 = 50, which provides the compound concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the incubation with the compound.

4.2.3 HDAC Biochemical Assays

The *in vitro* HDACs activities of recombinant human HDAC 1, 2, 6, and 8 (BPS Biosciences) were detected by fluorogenic release of 7-amino-4-methylcoumarin from substrate upon deacetylase enzymatic activity. The half maximum inhibitory concentration (IC_{50}) is determined at the drug concentration resulting in 50% reduction of enzyme activity.

4.2.4 Western Blot Analysis

HCT116 and PC3 cells were treated with 0.1% DMSO or indicated test compound at 0.03, 0.1, 0.3, 1, and 3 µM in RPMI 1640 supplemented with 10% FBS for 48 h. The cells were then collected in ice-cold lysis buffer [10 mmol/L Tris-HCl (pH 7.4), 150 mmol/L NaCl, 1 mmol/L EGTA, 1 mmol/L phenylmethylsulfonyl fluoride, 10 mg/mL aprotinin, 10 mg/mL leupeptin, 1 mM sodium orthovanadate, 1 mM NaF, and 1% Triton X-100] and sonicated. Protein concentrations in the resultant lysates were determined by a Bradford protein assay kit (Bio-Rad, Hercules, CA). The protein lysates, containing the same amount of proteins, were subjected to 10% SDS-polyacrylamide gel electrophoresis. The proteins were then transferred to a polyvinylidene difluoride (PVDF) membrane (Millipore, Bellerica, MA). After 1 h incubation at room temperature in 5% nonfat milk in PBS, transblotted membrane was washed twice with tris-buffered saline containing 0.1% Tween 20 (TBST). Membrane was then incubated with a primary antibody specific to Acetyl-H3 (Millipore, Billerica, M), H3 (Cell signalling, Beverly, MA), Acetyl-α-tubulin (Cell signalling, Beverly, MA), α-tubulin (Cell signalling, Beverly, MA) and GAPDH (Novus Biologicals, Littleton, CO) in

TBST/1% nonfat milk at 4 °C overnight. The membrane was washed three times with TBST for a total of 15 min and then incubated with a goat anti-rabbit (Santa Cruz Biotechnology, Santa Cruz, CA) or anti-mouse (Santa Cruz Biotechnology, Santa Cruz, CA) IgG antibody conjugated with horseradish (diluted 1:3000) for 1 h at room temperature. After washing the membrane at least three times with TBST, the signal intensity for each protein band was determined using an enhanced chemiluminescence detection kit (Amersham, Buckinghamshire, UK).

4.2.5 Antitumor Activity in vivo

8 week old male nude mice (TMU Animal Facility) were fed ad libitum H_2O (reverse osmosis, 1 ppm Cl) and PicoLab Rodent Diet 20 Modified and Irradiated Lab Diet® consisting of 20.0% crude protein, 9.9% crude fat, and 4.7% crude fiber. The mice were housed at the Taipei Medical University Laboratory Animal Center, on a 12-hour light cycle at 21–23 °C and 60–85% humidity. Nude mice were maintained in accordance with the Institutional Animal Care and Use Committee procedures and guidelines. The human HCT116 colorectal adenocarcinoma cells used for implantation were harvested during log phase growth and resuspended in phosphate-buffered saline at 5 x 10^7 cells/mL. Each mouse was injected s.c. in the right flank with 1 x 10^7 cells (0.2 mL cell suspension). Mice arranged in four groups of 7 mice were examined frequently for overt signs of any adverse, drug-related side effects. All doses were administered at a volume of 10 mL/kg (0.2 mL/20 g mouse), scaled to the body weight of each animal. Control group mice received vehicle daily p.o. to endpoint. Group 2 received reference **8f** daily p.o. at 50 mg/kg to endpoint. Group 3 received compound **8f** daily p.o. at 100 mg/kg to end schedule. Group 4 received SAHA daily p.o. at 200 mg/kg to end schedule. Tumor size, in mm^3, was calculated from: Tumor Volume = $(w^2 \times l)/2$, where w = width and l = length in mm of the tumor. Tumor weight can be estimated with the assumption that 1 mm^3 of tumor volume is equivalent to 1 mg.

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Table 1
Antiproliferative Activity (GI_{50}) of Compounds **8a-k**, **18a-b**, and **23**.

	GI_{50} ± SD[a] (μM)			
Compd	HL-60	HCT116	PC-3	A549
8a	>10	>10	>10	>10
8b	>10	>10	>10	>10
8c	1.14±0.20	1.39±0.06	1.35±0.17	4.75±0.25
8d	0.83±0.21	0.24±0.02	1.01±0.12	1.51±0.16
8e	1.17±0.15	0.31±0.02	0.79±0.22	1.32±0.02
8f	0.29±0.06	0.08±0.001	0.15±0.01	0.27±0.02
8g	0.80±0.10	0.31±0.02	0.49±0.05	0.88±0.02
8h	0.72±0.10	0.24±0.01	0.28±0.02	0.35±0.03
8i	1.33±0.07	0.92±0.15	0.76±0.05	1.01±0.05
8j	0.72±0.10	0.44±0.11	0.32±0.04	0.64±0.04
8k	2.64±0.95	1.31±0.31	1.35±0.29	1.42±0.13
18a	1.23±0.03	0.35±0.03	0.47±0.08	0.84±0.02
18b	1.15±0.25	0.36±0.04	0.56±0.04	1.13±0.05
23	1.98±0.64	1.48±0.26	2.65±0.52	1.71±0.10
SAHA	1.74±0.21	0.15±0.03	0.73±0.05	1.02±0.15
PXD101	1.09±0.20	0.13±0.01	0.39±0.07	0.78±0.07

[a]SD: standard deviation, all experiments were independently performed at least three times.

Table 2
Activities of **8f**, **8j**, PXD101, and SAHA against HDAC Isoforms 1,2, 6, and 8

	IC_{50} ± SD (nM))			
Compd	HDAC1	HDAC2	HDAC6	HDAC8
8f	14	11.48	15	130
8j	5.74	15	5.89	200
PXD101	48	49	50	200
SAHA	110	120	110	>300

Caption

Figure 1. FDA-approved HDAC inhibitors.

Figure 2. Design of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides.

Figure 3. Effect of α-tubulin acetylation and histone H3 acetylation in cultured human colorectal HCT-116 cancer and prostate PC-3 cancer cells using Western blot analysis. Quantitative analysis of Western blot was done with ImageQuant (Molecular Dynamics, U.S.).

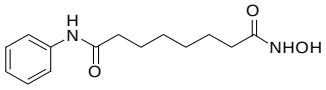
Figure 4. Inhibition of human HCT-116 cancer xenograft growth in nude mice (n = 4-5).

Scheme 1. Reagents and conditions: (a) i. 4-methoxybenzenethiol or 3-bromobenzenethiol, K_2CO_3, DMF, 100 ^oC; ii. mCPBA, DCM, 0 ^oC to rt; (b) *tert*-butyl acrylate, $Pd_2(dba)_3$, $[P(t\text{-}Bu)_3]HBF_4$,Cy_2NMe, DMF, 100 ^oC; (c) TFA, DCM, rt; (d) i. NH_2OTHP, EDC·HCl, DMAP, DCM, rt; ii. 1 N $HCl_{(aq)}$, MeOH, 0 ^oC to rt.

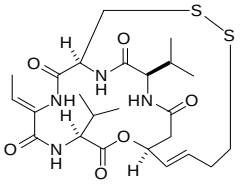
Scheme 2. Reagents and conditions: (a) i. (3-(diethoxymethyl)phenyl)magnesium bromide or (4-(dimethoxymethyl)phenyl)magnesium bromide, THF, 0 ^oC to rt; ii. PDC, MS, DCM, rt; (b) 2 N HCl, THF, 0 ^oC to rt; (c) methyl (triphenylphosphoranyl)acetate, DCM, rt; (d) 1 N LiOH, THF, rt; (e) i. NH_2OTHP, EDC·HCl, DMAP, DCM, rt; ii. 1 N HCl, MeOH, rt.

Scheme 3. Reagents and conditions: (a) i. 3-bromobenzenethiol, K_2CO_3, DMF, 100 ^oC; ii. mCPBA, DCM, 0 ^oC to rt; (b) *tert*-butyl acrylate, $Pd_2(dba)_3$, $[P(t\text{-}Bu)_3]HBF_4$,Cy_2NMe, DMF, 100 ^oC; (c) TFA, DCM, rt; (d) i. NH_2OTHP, EDC·HCl, DMAP, DCM, rt; ii. 1 N $HCl_{(aq.)}$, MeOH, 0 ^oC to rt.

Figure 1.



1, **SAHA**



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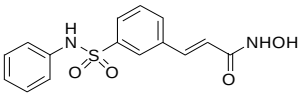
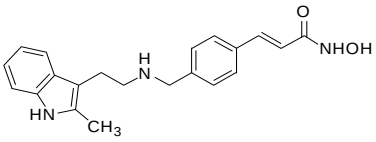


3, **PXD-101**



4, **LBH-589**

Figure 2.

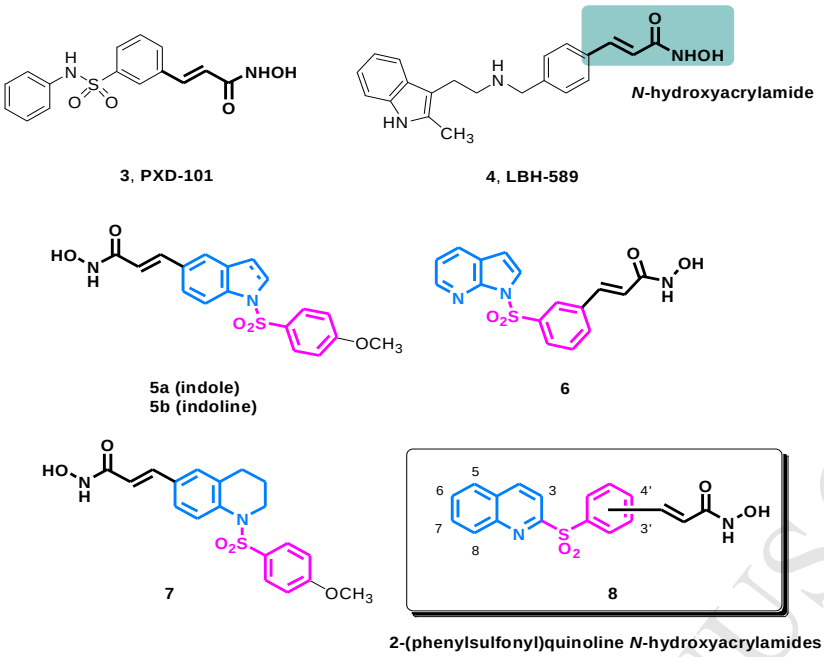


Figure 3.

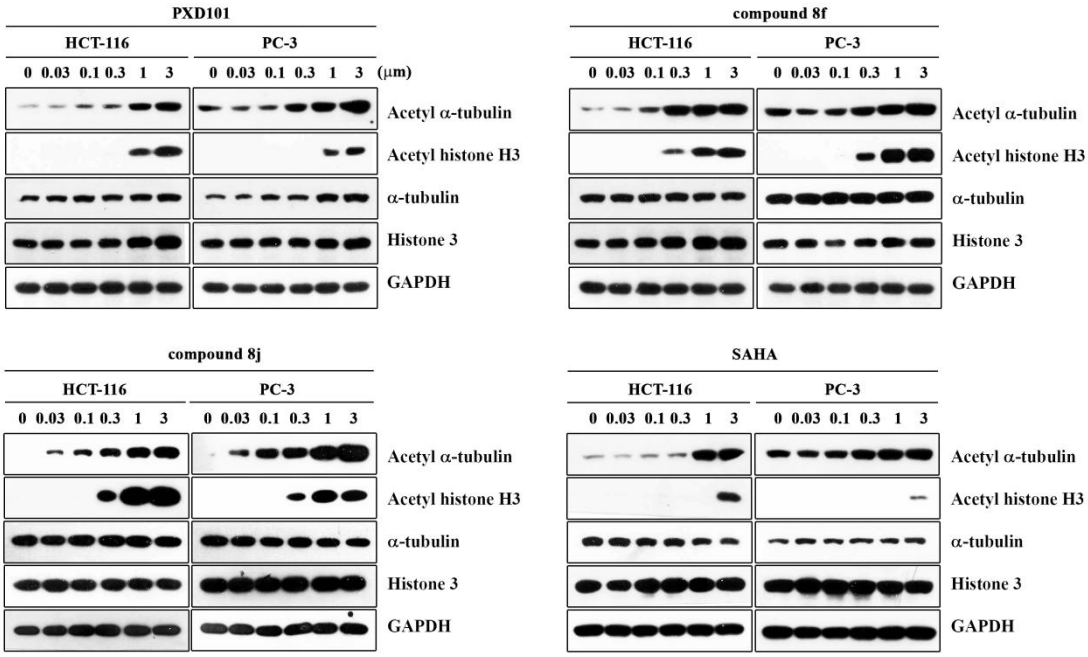
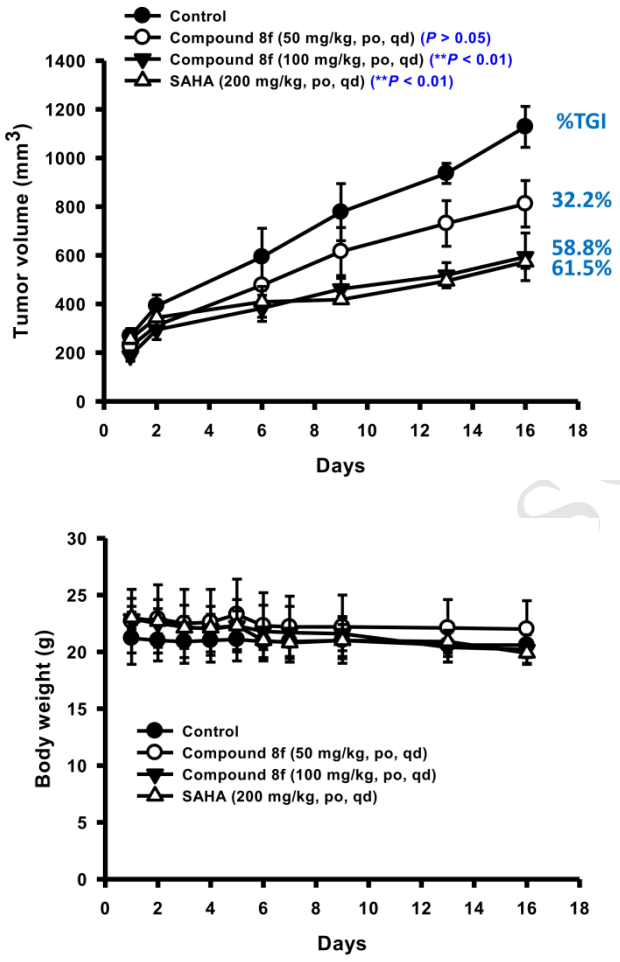
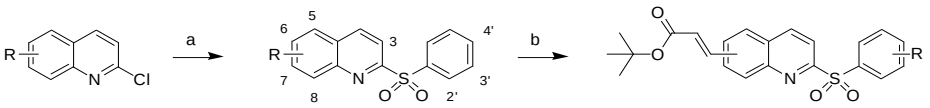


Figure 4.



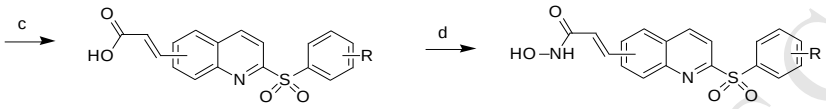
Scheme 1.



9a: R = 3-Br
9b: R = 5-Br
9c: R = 6-Br
9d: R = 7-Br
9e: R = 8-Br
9f: R = H
9g: R = 6-OCH_3
9h: R = 6-Cl
9i: R = 8-F
9j: R = 8-Cl

10a: R = 3-Br, 4'-OCH_3
10b: R = 5-Br, 4'-OCH_3
10c: R = 6-Br, 4'-OCH_3
10d: R = 7-Br, 4'-OCH_3
10e: R = 8-Br, 4'-OCH_3
10f: R = 3'-Br
10g: R = 4'-Br
10h: R = 6-OCH_3, 3'-Br
10i: R = 6-Cl, 3'-Br
10j: R = 8-F, 3'-Br
10k: R = 8-Cl, 3'-Br

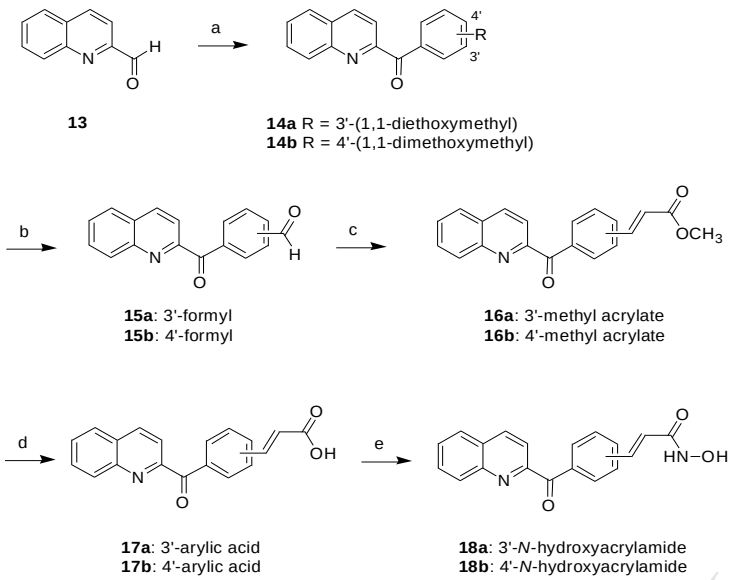
11a: 3-*t*-butyl acrylate, R = 4'-OCH_3
11b: 5-*t*-butyl acrylate, R = 4'-OCH_3
11c: 6-*t*-butyl acrylate, R = 4'-OCH_3
11d: 7-*t*-butyl acrylate, R = 4'-OCH_3
11e: 8-*t*-butyl acrylate, R = 4'-OCH_3
11f: 3'-*t*-butyl acrylate, R = H
11g: 4'-*t*-butyl acrylate, R = H
11h: 3'-*t*-butyl acrylate, R = 6-OCH_3
11i: 3'-*t*-butyl acrylate, R = 6-Cl
11j: 3'-*t*-butyl acrylate, R = 8-F
11k: 3'-*t*-butyl acrylate, R = 8-Cl



12a: 3-acrylic acid, R = 4'-OCH_3
12b: 5-acrylic acid, R = 4'-OCH_3
12c: 6-acrylic acid, R = 4'-OCH_3
12d: 7-acrylic acid, R = 4'-OCH_3
12e: 8-acrylic acid, R = 4'-OCH_3
12f: 3'-acrylic acid, R = H
12g: 4'-acrylic acid, R = H
12h: 3'-acrylic acid, R = 6-OCH_3
12i: 3'-acrylic acid, R = 6-Cl
12j: 3'-acrylic acid, R = 8-F
12k: 3'-acrylic acid, R = 8-Cl

8a: 3-*N*-hydroxyacrylamide, R = 4'-OCH_3
8b: 5-*N*-hydroxyacrylamide, R = 4'-OCH_3
8c: 6-*N*-hydroxyacrylamide, R = 4'-OCH_3
8d: 7-*N*-hydroxyacrylamide, R = 4'-OCH_3
8e: 8-*N*-hydroxyacrylamide, R = 4'-OCH_3
8f: 3'-*N*-hydroxyacrylamide, R = H
8g: 4'-*N*-hydroxyacrylamide, R = H
8h: 3'-*N*-hydroxyacrylamide, R = 6-OCH_3
8i: 3'-*N*-hydroxyacrylamide, R = 6-Cl
8j: 3'-*N*-hydroxyacrylamide, R = 8-F
8k: 3'-*N*-hydroxyacrylamide, R = 8-Cl

Scheme 2.



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14a R = 3'-(1,1-diethoxymethyl)
14b R = 4'-(1,1-dimethoxymethyl)

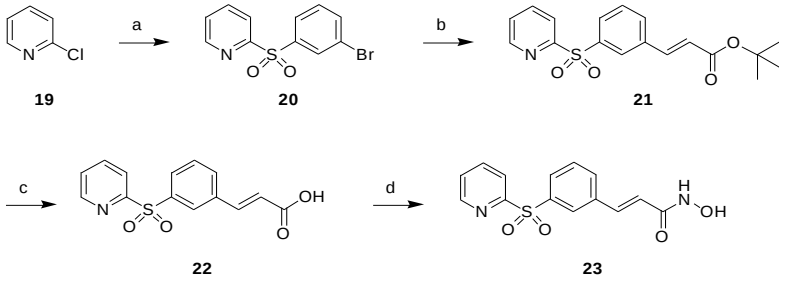
15a: 3'-formyl
15b: 4'-formyl

16a: 3'-methyl acrylate
16b: 4'-methyl acrylate

17a: 3'-arylic acid
17b: 4'-arylic acid

18a: 3'-*N*-hydroxyacrylamide
18b: 4'-*N*-hydroxyacrylamide

Scheme 3.



Research highlights

> A series of 2-(phenylsulfonyl)quinoline N-hydroxyacrylamides were designed and synthesized.
> Two compounds (**8f** and **8j**) with potent antiproliferative activity were identified.
> Compounds **8f** was potent to inhibit HDAC function.