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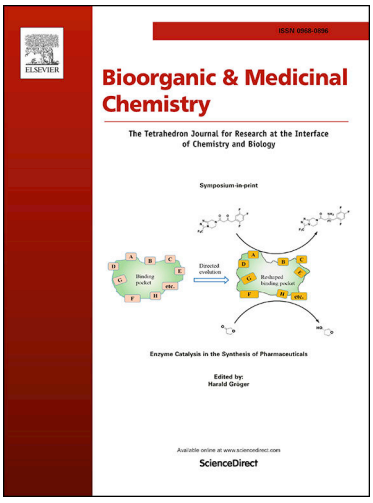

Synthesis and Biological Evaluation of 2-Quinolineacrylamides

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PII: S0968-0896(19)31375-6
DOI: https://doi.org/10.1016/j.bmc.2019.115250
Reference: BMC 115250

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 15 August 2019
Revised Date: 29 November 2019
Accepted Date: 1 December 2019

Please cite this article as: S-W. Wang, M-H. Lin, F-C. Hsu, M-C. Chen, J-P. Liou, Y-T. Liu, S-S. Chen, H-Y. Lee, Synthesis and Biological Evaluation of 2-Quinolineacrylamides, *Bioorganic & Medicinal Chemistry* (2019), doi: https://doi.org/10.1016/j.bmc.2019.115250

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Synthesis and Biological Evaluation of 2-Quinolineacrylamides

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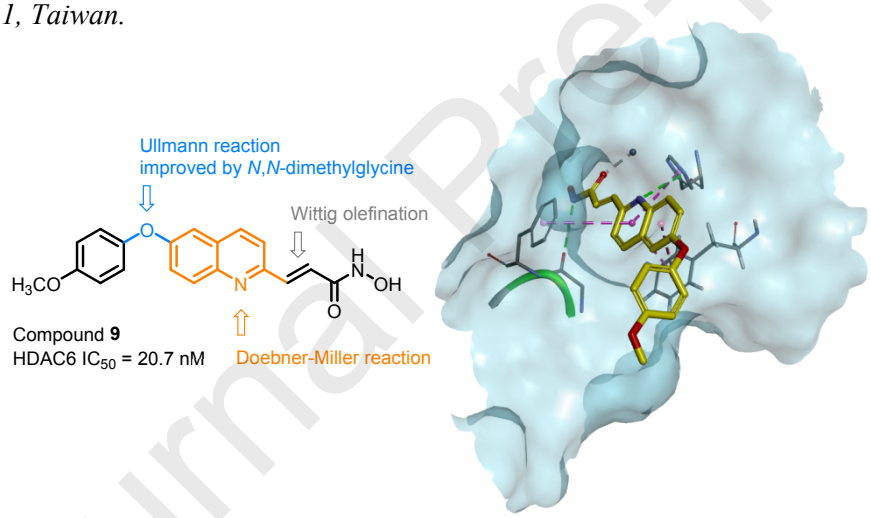

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Histone deacetylase
2-Quinolineacrylamide
Ullmann reaction

ABSTRACT

A series of C6-substituted *N*-hydroxy-2-quinolineacrylamides (**3-15**), with four types of bridging groups have been synthesized. Most of these compounds exhibit antiproliferative activity against A549 and HCT116 cells and Western blot analysis revealed that they are able to inhibit HDAC. Measurement of the HDAC isoform activity of ether-containing compounds showed that compound **9** has distinct HDAC6 selectivity, more than 300-fold over other isoforms. This paper describes the development of 6-aryloxy-*N*-hydroxy-2-quinolineacrylamides as potential HDAC6 inhibitors.

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1. Introduction

In the structure of nucleosomes, histones are wrapped around DNA and covalent binding exists between lysine residues and DNA.[1] The resultant compact structure of the nucleosome helps it fit within the cell nucleus. The acetylation of lysine residues of the histone masks the covalent binding and consequently, the condensed DNA is loosened and the replication process is launched. The acetylation status of the lysines is regulated by two enzymes: histone acetyltansferase (HAT) and histone deacetylase (HDAC).[2,3] This acetylation is clearly correlated with epigenetic modification, which regulates gene expression without changing DNA sequence. Abnormal epigenetic modification is responsible for the development of many diseases including cancer[4], inflammation[5], and neurodegenerative diseases.[6] Consequently HDAC, with its significant role in epigenetic modification is a therapeutic target. To date, several HDAC inhibitors have entered the clinic, including SAHA, FK-228, PXD-101, and LBH589[7-10] (Figure 1). The therapeutic potential of this target has attracted our attention.

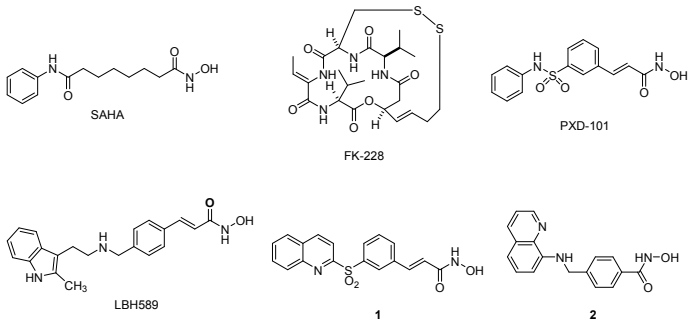

Figure 1. FDA-approved and previously synthesized quinoline-containing HDAC inhibitors.

Bioactive molecules with similar pharmacological mechanisms share common structural features or moieties. The recognition of a specific characteristic often opens an avenue for subsequent relevant research. Because HDAC is a zinc-catalyzed enzyme, several HDAC inhibitors carrying hydroxamic acid and 2-aminobenzamide were designed to interfere with this catalytic interaction.[11] The current study took advantage of hydroxamic acid as the significant moiety in an attempt to develop anti-HDAC activity. In addition to the zinc-binding motif, HDAC inhibitors also possess two additional structural features, a linker

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part of diverse structures. Quinoline-containing derivatives have been found to have promising biological properties such as antimalarial, antibiotic, antituberculosis, antiplasmodial, antitumor and anti-inflammatory activity.[12-15] Quinoline has also been utilized in the development of HDAC inhibitors; for instance, Finn et al. synthesized various carbamic acid derivatives with diverse bicyclic heteroaryl groups including quinoline, quinoxaline, benzoxazole, and benzothiazole.[16] In addition, our previous study in 2-sulfonylquinolines derived from the combination of *N*-hydroxylacrylamide and quinoline found that compound **1** acts as a potent HDAC inhibitor (Figure 1).[17] In other work a combination of the 4-(*N*-hydroxyaminocarbonyl)benzylamino group (−NHCH$_2$PhCONHOH) with quinoline led to compound **2** as a potent HDAC6 inhibitor that is able to ameliorate the symptoms of Alzheimer's disease.[18] These efforts encouraged us to continue exploration of combinations of quinoline and a zinc-binding hydroxamic acid motif. In an attempt to define the structural features of HDAC inhibitors, the quinoline moiety is considered as a linker part in combination with various replacements at C6 position as the surface recognition group, which provides a series of C6-substituted *N*-hydroxy-2-quinolineacrylamides (**3-15**, Figure 2). In addition, there are four bridging groups (sulfonamide, carbonyl, ether, and a simple bond) which link the aryl/heteroaryl motif to the quinoline, which may shed light on their influence on biological activity. In addition, the biological activity and mechanism of action of these compounds are discussed.

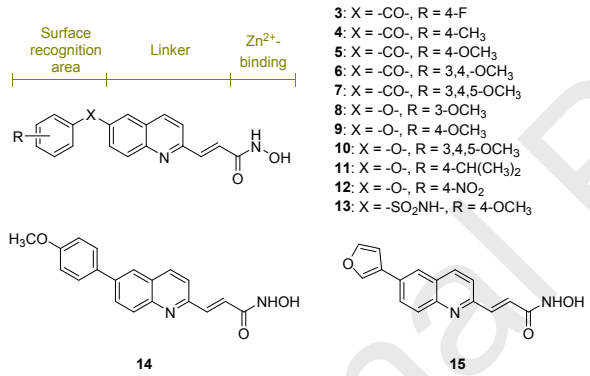
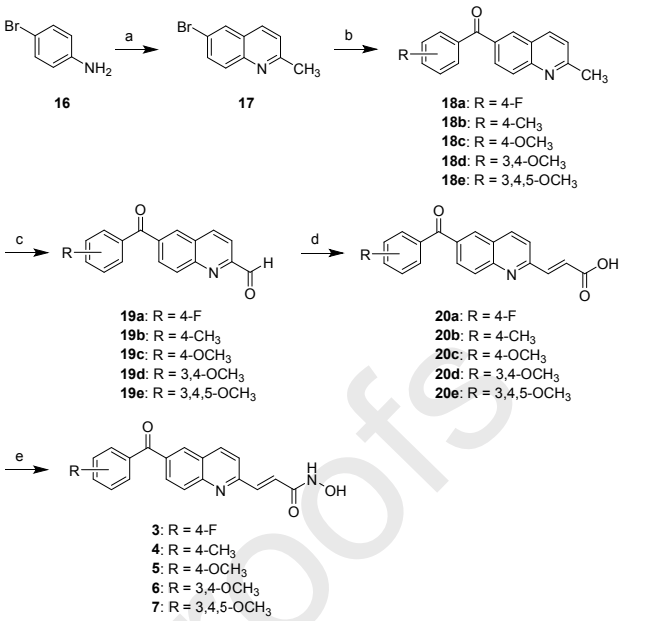


Figure 1. Designed *N*-hydroxy-2-quinolineacrylamides (**3-15**).

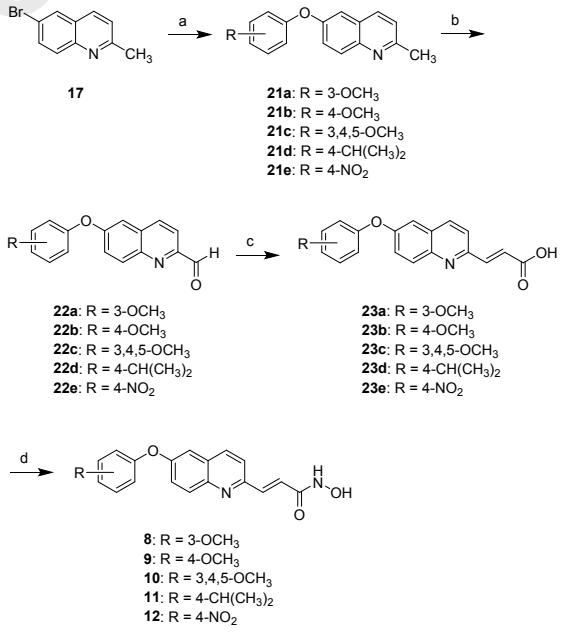
2. Results and discussion

2.1. Chemistry

The synthesis of compounds **3-7** which possess a carbonyl group linking quinoline to a substituted phenyl ring is shown in Scheme 1. 4-Bromoaniline (**16**) underwent a Doebner–Miller reaction with crotonaldehyde under acidic conditions, affording the corresponding 6-bromo-2-methylquinoline (**17**). Treatment of compound **17** with *n*-BuLi followed by addition of substituted benzaldehydes generated the corresponding secondary alcohol which was subjected to oxidation by pyridinium dichromate (PDC) to afford the corresponding 6-aroylquinolines (**18a-18e**). The C2-methyl group of **18a-18e** was oxidized by SeO_2 to afford compounds **19a-19e**. The resulting compounds underwent Wittig olefination with methyl (triphenylphosphoranylidene)acetate to give the acrylates which were subjected to hydrolysis by KOH to obtain the corresponding carboxylic acid **20a-20e**. The amidation of compounds **20a-20e** was carried out using *O*-(tetrahydro-2H-pyran-2-yl)hydroxylamine (NH_2OTHP) in the presence of coupling agents such as EDC·HCl to afford *N*-protected amides the corresponding hydroxamic acids (**3-7**).



Scheme 1. Synthetic approach to the designed 6-aroyl-*N*-hydroxy-2-quinolineacrylamides **3-7**: a. crotonaldehyde, 6 N HCl, toluene, reflux, 15.5%; b. i. *n*-BuLi, substituted benzaldehydes, THF, 0 °C to rt; ii. PDC, molecule sieves, CH_2Cl_2, rt, 42-85%; c. SeO_2, xylene, reflux, 55-95%; d. i. methyl (triphenylphosphor-anylidene)acetate, CH_2Cl_2, rt; ii. KOH, MeOH, reflux, 79-100%; e. i. NH_2OTHP, EDC·HCl, TEA, CH_2Cl_2, rt; ii. 10% $TFA_{(aq)}$, MeOH, rt, 9-20%.



Scheme 2. Synthetic approach to ether-containing *N*-hydroxy-2-quinolineacrylamides (**8-12**): a. substituted phenols, CuI, Cs_2CO_3, *N*,*N*-dimethylglycine, DMF, reflux, 64-95%; b. SeO_2, xylene, reflux, 65-92%; c. i. methyl (triphenylphosphoranylidene)acetate, CH_2Cl_2, rt; ii. KOH, MeOH, reflux, 70-100%; d. i. NH_2OTHP, EDC·HCl, TEA, CH_2Cl_2, rt; ii. 10% $TFA_{(aq)}$, MeOH, rt, 8-33%.

The preparation of compounds **8-12**, containing an ether linkage is illustrated in Scheme 2. The reaction of compound **17** with 4-methoxyphenol in the presence of CuBr under Ullmann conditions generated **21b** in 28% yield. The low reaction yield was also observed in the synthesis of compounds **21a-21e**, but can be overcome by addition of *N*,*N*-dimethylglycine while

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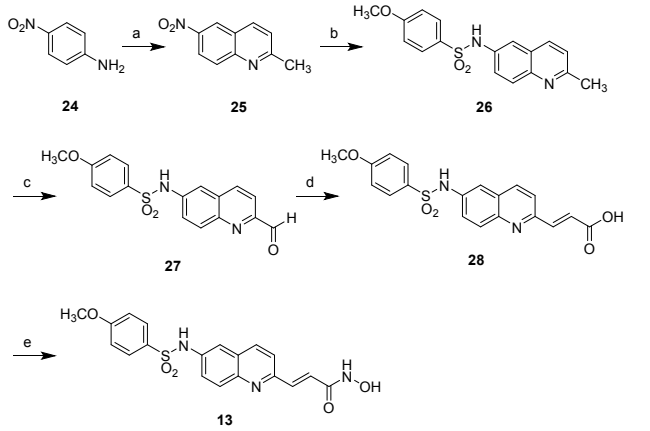
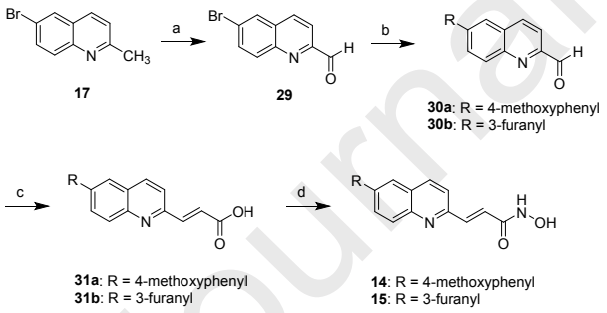
conc... substituted phenols in the presence of CuI and N,N-dimethylglycine to give compounds **21a-21e** with satisfactory yields. The resulting products underwent subsequent reactions such as oxidation by SeO_2, Wittig olefination, hydrolysis, and conversion into hydroxamic acid similar to that shown in Scheme 1 to obtain compounds **8-12**. Scheme 3 depicts the synthesis of compound **13** which has a sulfonamide linkage between quinoline and phenyl ring. 6-Nitro-2-methylquinoline (**25**) was prepared from 4-nitroaniline (**24**) via a Doebner–Miller reaction with crotonaldehyde. The nitro group of **25** was reduced by palladium-catalyzed hydrogenation, and the corresponding amine was subjected to a reaction with 4-methoxybenzenesulfonyl chloride to yield compound **26**. The following synthetic route from compound **26** to the designed *N*-hydroxyacrylamide (**13**) is similar to that used for the conversion of **18a** to **3** shown in Scheme 1.



Scheme 3. Synthetic approach to compound **13**: a. crotonaldehyde, 6 N HCl, toluene, reflux, 55.8%; b. i. Pd/C, H_2, MeOH, rt; ii. 4-methoxybenzenesulfonyl chloride, pyridine, CH_2Cl_2, rt, 55.9%; c. SeO_2, xylene, reflux, 67.1%; d. i. methyl (triphenylphosphoranylidene)acetate, CH_2Cl_2, rt; ii. KOH, MeOH, reflux, 28.3%; e. i. NH_2OTHP, EDC·HCl, TEA, CH_2Cl_2, rt; ii. 10% $TFA_{(aq)}$, MeOH, rt, 20.5%.



Scheme 4. Synthetic approach to the designed 6-aryl-*N*-hydroxy-2-quinolineacrylamides (**14** and **15**): a. SeO_2, xylene, reflux, 60.3%; b. $Pd(PPh_3)_4$, 4-methoxyphenylboronic acid or furan-3-ylboronic acid, TBAB, K_2CO_3, dioxane, H_2O, MW, 120 °C, 66-80%%; c. i. methyl (triphenylphosphoranyl-idene)acetate, CH_2Cl_2, rt; ii. KOH, MeOH, reflux, 29-44%; d. i. NH_2OTHP, EDC·HCl, TEA, CH_2Cl_2, rt; ii. 10% $TFA_{(aq)}$, MeOH, rt, 42-62%.

The preparation of compounds **14** and **15** is shown in Scheme 4. Compound **17** was oxidized by SeO_2 to yield the corresponding aldehyde (**29**). The subsequent Suzuki reaction of **29** with (4-methoxyphenyl)boronic acid and furan-3-ylboronic acid in the presence of $Pd(PPh_3)_4$ with the assistance of microwave radiation yielded compounds **30a** and **30b**. The resulting compounds underwent Wittig olefination with methyl (triphenylphosphoranylidene)acetate to give the acrylates which carboxylic acids (**31a-31b**). Amidation of compounds **31a-31b** was carried out using NH_2OTHP in the presence of coupling agents such as EDC·HCl to afford *N*-protected amides which were subsequently hydrolyzed by TFA to give the corresponding hydroxamic acids **14** and **15**.

Table 1. Antiproliferative activity (GI_{50}) of compounds **3-15** and SAHA.

Compd	$GI_{50} \pm SD^a$ (μM)	
	A549	HCT116
3	1.26 ± 0.22	1.84 ± 0.06
4	2.58 ± 0.2	2.51 ± 0.1
5	1.89 ± 0.2	2.3 ± 0.1
6	3.31 ± 0.31	1.78 ± 0.19
7	3.35 ± 0.5	2.62 ± 0.2
8	4.35 ± 0.07	2.74 ± 0.26
9	3.2 ± 0.56	1.82 ± 0.07
10	2.43 ± 0.77	0.74 ± 0.17
11	3.28 ± 0.18	4.08 ± 0.46
12	1.63 ± 0.23	1.00 ± 0.05
13	4.31 ± 0.13	6.68 ± 0.52
14	2.35 ± 1.12	1.47 ± 0.29
15	1.92 ± 0.49	1.56 ± 0.18
SAHA[b]	2.62 ± 1.37	0.44 ± 0.03
Tubastatin A[c]	> 5	> 5

[a]SD: standard deviation. All experiments were independently performed at least three times. [b]data from reference 20. [c]data from reference 21.

2.2. Biological evaluation

The synthesized compounds (**3-15**) were tested for their antiproliferative activity in two cell lines, A549 and HCT116 (Table 1). The results showed that most of this series of compounds have similar cellular activity with GI_{50} values in single digit μM range. Among them, compound **10** with an ether bridge linking 3,4,5-trimethoxyphenyl group to quinoline had the most potent antiproliferative activity against the growth of HCT116 cells with an GI_{50} value of 0.74 μM. The 3,4,5-trimethoxyphenyl moiety of **10** contributed to slight increase of antiproliferative activity as compared with **9** which has a 4-methoxyphenyl group. The effect of substitution on cellular activity is ambiguous. The result from compounds **5**, **9**, **13**, and **14**, which all possess 4-methoxyphenyl group at C6 position of quinoline revealed that the sulfonamide linkage of **13** led to a slight loss of activity. The discovery of ACY1215[22] and tubastatin A[23] as HDAC6 inhibitors, specifically ACY1215 is undergoing clinical trials, has drawn numerous scientific efforts to seek HDAC isoform inhibitors. Considering cellular activity and the structural features, compounds **9**, **10**, **12**, and **14** were subject to an examination of HDAC selectivity using HDAC1, 2, 6, and 8 (Table 2). In the classification of HDAC isoforms, HDAC1, 2, and 8 belong to class I HDAC, while HDAC6 is a class IIb HDAC.[24] The results showed that **9**, **10**, **12**, and **14** possess distinct inhibitory activity against HDAC6 over the other

thre... selectivity, and is more than 483-fold and 374-fold selective over HDAC1 or HDAC8, respectively. Compound **10**, with a 3,4,5-trimethoxyphenoxy moiety also showed marked HDAC2 inhibitory activity with an IC_{50} value of 18.7 nM, but it lacks selectivity toward specific HDAC isoforms. Comparison of **9** and **14** revealed that the removal of the ether linkage led to a decrease of selectivity. H3 and tubulin have been identified as substrates of HDAC[25], for instance, class I HDACs and HDAC6 are respresponsible for deacetylation of Ac-H3 and Ac-tubulin in cells, respectively. Therefore, compounds **9**, **10**, **12**, and **14** were tested for their influence on the expression of acetylated H3 and acetylated tubulin, in an effort to understand their HDAC inhibitory activity (Figure 3). As shown in Figure 3, treatment with **9**, **10**, **12**, and **14** led to the increase of acetylation status of H3 and tubulin in a dose-dependent manner, which indicates that **9**, **10**, **12**, and **14** are able to inhibit HDAC. Upregulated acetylated tubulin was also observed after treatment with compounds **9**, **10**, **12**, and **14**. The extent of the compound **9** is most pronounced, and this is consistent with the data shown in Table 2. In addition, despite the HDAC6 selectivity of **9** is weaker than that of tubastatin A, **9** exhibited distinct cellular activity (Table 1).

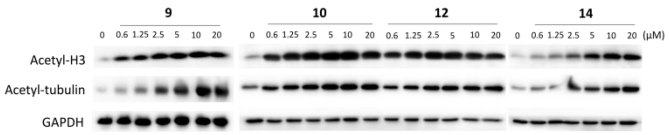


Figure 3. Effect of α-tubulin acetylation and histone H3 acetylation in cultured human colorectal cancer HCT116 cells by compounds **9**, **10**, **12**, and **14** using Western blot analysis.

Table 2. Inhibitory activity (IC_{50}, nM[a]) of compounds **9**, **10**, **12**, and **14** against HDAC1, 2, 6, and 8 (selectivity ratio[b] is shown in brackets).

Compound	HDAC isoform			
	HDAC1	HDAC2	HDAC6	HDAC8
9	> 10000 (> 438)	NC[c]	20.7	7750 (374)
10	1770 (67)	18.7 (0.7)	26.5	2820 (106)
12	6050 (118)	NC	51.4	2320 (45)
14	NC	1310 (27)	49.0	4770 (97)
Tubastatin A[d]	> 10000 (> 729)	> 10000 (> 729)	13.7	NT[e]
Trichostatin A	17.9 (5)	18.7 (5)	3600	650 (181)

[a]IC_{50} values displayed the result of a single experiment. [b]Selectivity ratio: selectivity ratio of HDAC subtypes over HDAC6. [c]NC: no curve, which indicates no inhibition or compound activity that could not be fit to an IC_{50} curve. [d]data from reference 21. [e]NT: not tested.

To understand the interaction of compounds **9** and **10** with HDAC6, we docked **9** and **10** into the available crystal structures of HDAC6 (PDB ID: 6CGP, Figure 4), using *Discovery Studio2017 R2*. The result shows that the *N*-hydroxycinnamate moiety of **9** and **10** is able to insert into a narrow cavity of HDAC6. In addition to interaction with the zinc ion, the and Gly582 (green dashed lines). The quinoline moiety has three π-π interactions (magenta dashed lines) with adjacent amino acids (phe583, His 614, and Phe643). Notably, the hydroxamic acid has no interaction with the zinc ion of HDAC1 and HDAC2 (see supporting information Figure S1), which explains HDAC6 selectivity of compounds **9** and **10**.

3. Conclusion

This study is a continuation of our previous studies on development of quinoline-containing HDAC inhibitors to design a series of *N*-hydroxy-2-quinolineacrylamides (**3-15**) and to investigate the influence of linkages such as sulfonamide, carbonyl and ether on biological activity. Some copper- and palladium-mediated reactions were utilized to construct the corresponding bridging groups. Notably, the presence of *N*,*N*-dimethylglycine improved the Ullmann reaction, which helps to produce ether-containing compounds **8-12** in satisfactory yields. The results of biological assays revealed that compound **10** exhibited the most potent antiproliferative activity against HCT116 cell lines with a GI_{50} value of 0.74 μM. The mechanism of action was shown to involve inhibition of HDAC. Detailed examination of the enzymatic activity of ether-containing compounds **9**, **10**, **12**, and **14** revealed that compound **9** has remarkable HDAC6 selectivity over other HDAC isoforms. These findings assist the development of 6-aryloxy-*N*-hydroxy-2-quinolineacrylamides as potential HDAC6 inhibitors that may be used for the corresponding indications.

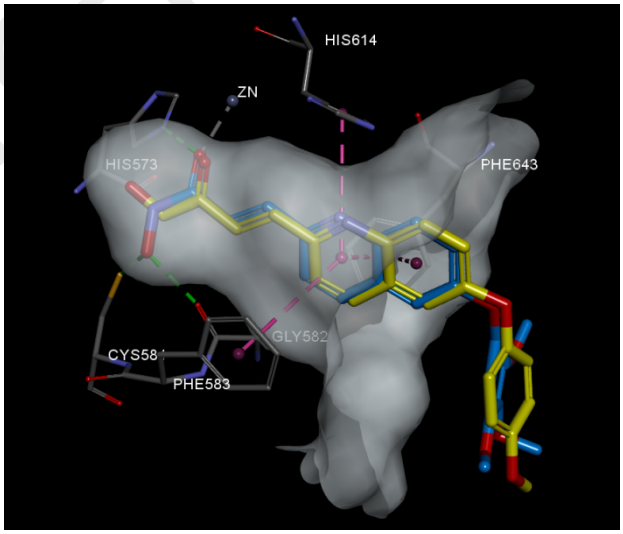


Figure 4. Docking pose of compound **9** (yellow) and **10** (blue) in the binding site of HDAC6 (green, PDB ID: 6CGP).

4. Experimental section

4.1. Chemistry

Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained with a Bruker DRX-300 spectrometer operating at 300 MHz and at 75 MHz, respectively. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS as an internal standard. High-resolution mass spectra (HRMS) were recorded with a JEOL (JMS-700) mass spectrometer. The purities of the final compounds were determined using an Agilent 1100 series HPLC system with a C-18 column (Agilent ZORBAX Eclipse XDB-C18 5 μm, 4.6 mm × 150 mm). Flash column chromatography was conducted using silica gel (Merck Kieselgel 60, No. 9385, 230−400 mesh ASTM). All reactions were conducted under an atmosphere of dry N_2.

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*4.1. hydroxyacrylamide (**3**)*

The title compound was obtained in 9.6% overall yield from compound **20a** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.16 (d, *J* = 15.6 Hz, 1H), 7.40-7.47 (m, 2H), 7.67 (d, *J* = 15.3 Hz, 1H), 7.87-7.96 (m, 3H), 8.00-8.16 (m, 2H), 8.39 (s, 1H), 8.60 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 115.67, 115.96, 122.38, 125.95, 126.76, 129.31, 129.64, 131.36, 132.73, 132.85, 133.57, 133.61, 134.76, 137.35, 139.00, 148.84, 155.61, 161.68, 166.52, 193.91. mp: 186.2-186.6 °C. HRMS (ESI) for $C_{19}H_{12}FN_2O_3$ (M-H) calcd 335.0832, found 335.0830.

*4.1.2. (E)-N-hydroxy-3-(6-(4-methylbenzoyl)quinolin-2-yl)acrylamide (**4**)*

The title compound was obtained in 14.4% overall yield from compound **20b** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.43 (s, 3H), 7.16 (d, *J* = 15.6 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.67 (d, *J* = 15.6 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 8.00-8.15 (m, 2H), 8.36 (d, *J* = 1.2 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.20, 30.68, 122.33, 125.82, 126.73, 129.26, 129.66, 130.01, 131.11, 134.28, 135.13, 137.37, 138.90, 143.38, 148.76, 155.47, 194.88, 206.47. mp: 176.9-177.5 °C. HRMS (ESI) for $C_{20}H_{15}N_2O_3$ (M-H) calcd 331.1083, found 331.1082.

*4.1.3. (E)-N-Hydroxy-3-(6-(4-methoxybenzoyl)quinolin-2-yl)acrylamide (**5**)*

A mixture of compound **20c** (0.1 g, 0.3 mmol), NH_2OTHP (0.04 g, 0.34 mmol), EDC·HCl (0.12 g, 0.63 mmol), triethylamine (0.06 g, 0.59 mmol), and DCM (10 mL) was stirred at rt for 3 h. The reaction was quenched with H_2O and extracted with DCM. The organic layer was collected and dried to afford a crude product. The resulting residue was dissolved in MeOH (5 mL), and then 10% TFA (2 mL) was added. The resulting mixture was stirred at rt for 1 day. The organic solvent was removed under reduced pressure followed by addition of DCM. The precipitate was collected by filtration and washed with DCM to afford compound **5** (0.02 g, 19.1%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.88 (s, 3H), 7.11-7.19 (m, 3H), 7.67 (d, *J* = 15.3 Hz, 1H), 7.83-7.90 (m, 3H), 8.00-8.15 (m, 2H), 8.35 (s, 1H), 8.60 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.66, 114.07, 122.28, 125.86, 126.77, 129.10, 129.36, 129.82, 130.61, 132.39, 135.64, 137.34, 138.90, 148.53, 155.31, 161.70, 163.19, 193.86. mp: 171.8-172.5 °C. HRMS (ESI) for $C_{20}H_{15}N_2O_4$ (M-H) calcd 347.1032, found 347.1033.

*4.1.4. (E)-3-(6-(3,4-dimethoxybenzoyl)quinolin-2-yl)-N-hydroxyacrylamide (**6**)*

The title compound was obtained in 14.9% overall yield from compound **20d** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3H), 3.88 (s, 3H), 7.12-7.19 (m, 2H), 7.40-7.46 (m, 2H), 7.67 (d, *J* = 15.3 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 8.00-8.15 (m, 2H), 8.37 (d, *J* = 1.8 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.57, 55.84, 110.83, 111.98, 122.27, 125.20, 125.74, 126.74, 129.10, 129.26, 129.81, 130.60, 135.64, 138.80, 148.59, 148.76, 153.12, 155.30, 193.85. mp: 141.8-142.4 °C. HRMS (ESI) for $C_{21}H_{17}N_2O_5$ (M-H) calcd 377.1137, found 377.1136.

trimethoxybenzoyl)quinolin-2-yl)acrylamide (7)

The title compound was obtained in 17.5% overall yield from compound **20e** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.79 (s, 3H), 3.81 (s, 6H), 7.12-7.19 (m, 3H), 7.67 (d, *J* = 15.6 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 8.12 (s, 2H), 8.46 (s, 1H), 8.65 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.09, 60.21, 107.57, 122.32, 125.87, 126.82, 129.19, 129.81, 131.35, 131.99, 134.97, 137.38, 139.06, 141.63, 148.77, 152.72, 155.50, 194.12. mp: 140.2-140.7 °C. HRMS (ESI) for $C_{22}H_{19}N_2O_6$ (M-H) calcd 407.1243, found 407.1240.

*4.1.6. (E)-N-hydroxy-3-(6-(3-methoxyphenoxy)quinolin-2-yl)acrylamide (**8**)*

The title compound was obtained in 32.5% overall yield from compound **23a** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3H), 6.67-6.75 (m, 2H), 6.81 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.05 (d, *J* = 15.6 Hz, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 2.7 Hz, 1H), 7.56 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.61 (d, *J* = 15.6 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 9.3 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.36, 105.57, 110.17, 111.44, 112.73, 121.66, 123.98, 124.84, 128.70, 130.40, 130.80, 136.98, 137.14, 143.37, 151.91, 155.48, 156.90, 160.90, 161.80. mp: 159.8-160.5 °C. HRMS (ESI) for $C_{19}H_{15}N_2O_4$ (M-H) calcd 335.1032, found 335.1032.

*4.1.7. (E)-N-hydroxy-3-(6-(4-methoxyphenoxy)quinolin-2-yl)acrylamide (**9**)*

The title compound was obtained in 14.0% overall yield from compound **23b** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.78 (s, 3H), 7.00-7.16 (m, 5H), 7.24 (d, J = 2.7 Hz, 1H), 7.56 (dd, J = 2.7, 9.3 Hz, 1H), 7.61 (d, J = 15.6 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.54, 110.85, 115.42, 121.55, 121.61, 123.49, 128.78, 130.37, 137.06, 148.56, 151.58, 151.60, 156.34, 157.05, 158.19, 158.68, 161.93. mp: 136.1-136.7 °C. HRMS (ESI) for $C_{19}H_{15}N_2O_4$ (M-H) calcd 335.1032, found 335.1031.

*4.1.8. (E)-N-hydroxy-3-(6-(3,4,5-trimethoxyphenoxy)quinolin-2-yl)acryl-amide (**10**)*

The title compound was obtained in 19.2% overall yield from compound **23c** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, CD_3OD): δ = 3.78 (s, 3H), 3.79 (s, 6H), 6.49 (s, 2H), 7.06 (d, *J* = 15.6 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 2.4, 9.3 Hz, 1H), 7.77 (d, *J* = 15.6 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 9.3 Hz, 1H), 8.45 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.14, 60.25, 98.02, 111.70, 121.64, 123.47, 124.41, 128.79, 130.73, 134.51, 136.86, 137.59, 143.71, 151.54, 151.94, 153.93, 156.17, 162.07. HRMS (ESI) for $C_{21}H_{19}N_2O_6$ (M-H) calcd 395.1243, found 395.1240.

*4.1.9. (E)-N-hydroxy-3-(6-(4-isopropylphenoxy)quinolin-2-yl)acrylamide (**11**)*

The title compound was obtained in 8.2% overall yield from compound **23d** in a manner similar to that described for the

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prep .93, = 6.9 Hz, 6H), 2.80-2.97 (m, 1H), 7.00-7.10 (m, 3H), 7.30-7.37 (m, 3H), 7.54 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.60 (d, *J* = 15.6 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 8.01 (d, *J* = 9.6 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.97, 32.81, 112.12, 119.47, 121.69, 123.67, 124.43, 128.02, 128.67, 130.68, 136.73, 144.47, 151.89, 153.62, 155.86, 158.04, 158.54, 161.90. mp: 136.9-138.5 °C. HRMS (ESI) for $C_{21}H_{19}N_2O_3$ (M-H) calcd 347.1396, found 347.1395.

*4.1.10. (E)-N-hydroxy-3-(6-(4-nitrophenoxy)quinolin-2-yl)acrylamide (**12**)*

The title compound was obtained in 28.7% overall yield from compound **23e** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.08 (d, *J* = 15.6 Hz, 1H), 7.29 (d, *J* = 9.3 Hz, 2H), 7.61-7.67 (m, 2H), 7.74 (d, *J* = 2.7 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 8.11(d, *J* = 9.0 Hz, 1H), 8.29 (d, *J* = 9.3 Hz, 2H), 8.39 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 116.21, 118.44, 121.87, 124.69, 125.24, 126.33, 128.71, 131.17, 137.19, 137.38, 142.93, 144.45, 153.00, 153.05, 161.88, 162.20. mp: 139.9-140.4 °C. HRMS (ESI) for $C_{18}H_{12}N_3O_5$ (M-H) calcd 350.0777, found 350.0779.

*4.1.11. (E)-N-Hydroxy-3-(6-((4-methoxyphenyl)sulfonamido)quinolin-2-yl)acrylamide (**13**)*

The title compound was obtained in 20.5% overall yield from compound **28** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.75 (s, 3H), 6.90-7.10 (m, 3H), 7.50-7.64 (m, 3H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.87 (d, *J* = 9.3 Hz, 1H), 8.31 (d, *J* = 8.7 Hz, 1H), 10.65 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.72, 114.60, 121.70, 124.52, 125.09, 128.25, 129.14, 129.39, 130.85, 136.89, 137.51, 143.33, 151.94, 161.87, 162.74. mp: 202.7-203.4 °C. HRMS (ESI) for $C_{19}H_{16}N_3O_5S$ (M-H) calcd 398.0811, found 398.0812.

*4.1.12. (E)-N-Hydroxy-3-(6-(4-methoxyphenyl)quinolin-2-yl)acrylamide (**14**)*

The title compound was obtained in 42.4% overall yield from compound **31a** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.88 (s, 3H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 15.6 Hz, 1H), 7.77-7.88 (m, 3H), 8.20 (d, *J* = 8.4 Hz, 2H), 8.37 (dd, *J* = 1.8, 7.8 Hz, 2H), 8.92 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.31, 114.69, 121.37, 124.29, 126.10, 127.85, 128.21, 128.34, 130.03, 131.10, 138.66, 138.93, 152.44, 158.26, 158.75, 159.59, 161.62. mp: 181.3-182.8 °C. HRMS (ESI) for $C_{19}H_{17}N_2O_3$ ($M+H^+$) calcd 321.1239, found 321.1238.

*4.1.13. (E)-3-(6-(Furan-3-yl)quinolin-2-yl)-N-hydroxyacrylamide (**15**)*

The title compound was obtained in 61.5% overall yield from compound **31b** in a manner similar to that described for the preparation of **5**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.08 (d, *J* = 15.6 Hz, 1H), 7.13 (d, *J* = 0.9 Hz, 1H), 7.64 (d, *J* = 15.3 Hz, 1H), 7.79-7.83 (m, 2H), 8.00 (d, *J* = 9.0 Hz, 1H), 8.09 (dd, *J* = 1.8, 9.0 Hz, 1H), 8.21 (s, 1H), 8.38-8.42 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 108.77, 121.55, 123.48, 125.23, 125.90, 145.09, 152.47, 161.74. mp: 172.0-172.7 °C. HRMS (ESI) for $C_{16}H_{11}N_2O_3$ (M-H) calcd 279.0770, found 279.0769.

*4.1.14. 6-Bromo-2-methylquinoline (**17**)*

A mixture of 4-bromoaniline (3.0 g, 17.5 mmol), crotonaldehyde (1.3 g, 18.6 mmol), 6 N HCl (60 mL, 360 mmol), and toluene (3 mL) was heated to reflux for 2 h. The reaction mixture was cooled and neutralized with aqueous NaOH. The resulting mixture was extracted with EtOAc, and then the organic layer was purified by column chromatography to afford compound **17** (0.6 g, 15.5%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.33 (s, 3H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.76-7.90 (m, 2H), 8.10-8.22 (m, 2H).

*4.1.15. (4-Fluorophenyl)(2-methylquinolin-6-yl)methanone (**18a**)*

The title compound was obtained in 48.6% overall yield from compound **17** in a manner similar to that described for the preparation of **18c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.82 (s, 3H), 7.16-7.23 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.85-7.91 (m, 2H), 7.80-8.20 (m, 4H).

*4.1.16. (2-Methylquinolin-6-yl)(p-tolyl)methanone (**18b**)*

The title compound was obtained in 84.6% overall yield from compound **17** in a manner similar to that described for the preparation of **18c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 2.87 (s, 3H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 8.14 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.20-8.30 (m, 3H).

*4.1.17. (4-Methoxyphenyl)(2-methylquinolin-6-yl)methanone (**18c**)*

n-BuLi (2.5 M in hexane, 3.78 mL) was added dropwise at -78 °C to a solution of compound **17** (2.1 g, 9.5 mmol) in THF (80 mL) then stirred at the same temperature for 1 h. The resulting solution was added slowly to a prepared solution of 4-methoxybenzaldehyde (1.3 g, 9.6 mmol) in THF (80 mL) at 0 °C. The solution was stirred at the same temperature for 1 h and then quenched with H_2O. The resulting mixture was extracted with EtOAc and the organic layer was collected and dried. The resulting residue was dissolved in DCM (50 mL) and then pyridinium dichromate (PDC, 4.69 g, 12.5 mmol) and 4 Å molecular sieves (equal quantity to PDC) were added at rt. After stirring at rt for 6 h, the reaction mixture was filtered through a pad of Celite and the filtrate was purified by flash chromatography to afford **18c** (1.23 g, 46.7%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76 (s, 3H), 3.87 (s, 3H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 8.00-8.16 (m, 4H).

*4.1.18. (3,4-Dimethoxyphenyl)(2-methylquinolin-6-yl)methanone (**18d**)*

The title compound was obtained in 43.4% overall yield from compound **17** in a manner similar to that described for the preparation of **18c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.83 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.38-7.43 (m,

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2H), 8.16-8.21 (m, 3H).

*4.1.19. (2-Methylquinolin-6-yl)(3,4,5-trimethoxyphenyl)methanone (**18e**)*

The title compound was obtained in 42.6% overall yield from compound **17** in a manner similar to that described for the preparation of **18c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 6H), 3.96 (s, 3H), 7.09 (s, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.20-8.28 (m, 3H). ^{13}H NMR (75 MHz, $CDCl_3$): δ = 25.55, 56.30, 60.94, 107.75, 122.99, 125.49, 128.83, 129.52, 130.75, 132.56, 134.84, 137.22, 142.17, 149.37, 152.92, 161.54, 195.10.

*4.1.20. 6-(4-Fluorobenzoyl)quinoline-2-carbaldehyde (**19a**)*

The title compound was obtained in 55.9% overall yield from compound **18a** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19-7.26 (m, 2H), 7.89-7.95 (m, 2H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.21 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.29 (d, *J* = 1.8 Hz, 1H), 8.37-8.45 (m, 2H), 10.28 (s, 1H).

*4.1.21. 6-(4-Methylbenzoyl)quinoline-2-carbaldehyde (**19b**)*

The title compound was obtained in 94.9% overall yield from compound **18b** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 8.11 (d, *J* =8.4 Hz, 1H), 8.23 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.30 (d, *J* = 1.5 Hz, 1H), 8.38-8.45 (m, 2H), 10.30 (s, 1H).

*4.1.22. 6-(4-Methoxybenzoyl)quinoline-2-carbaldehyde (**19c**)*

The title compound was obtained in 77.4% overall yield from compound **18c** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.7 Hz, 2H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.18 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.34 (d, *J* = 9.0 Hz, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 10.25 (s, 1H).

*4.1.23. 6-(3,4-Dimethoxybenzoyl)quinoline-2-carbaldehyde (**19d**)*

The title compound was obtained in 94.3% overall yield from compound **18d** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3H), 3.99 (s, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.20 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.29 (d, *J* = 1.8 Hz, 1H), 8.39-8.47 (m,2H), 10.31 (s, 1H).

*4.1.24. 6-(3,4,5-Trimethoxybenzoyl)quinoline-2-carbaldehyde (**19e**)*

The title compound was obtained in 92.8% overall yield from compound **18e** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 6H), 3.97 (s, 3H), 7.11 (s, 2H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.20 (dd, *J* = 1.8, 8.7 Hz, 1H), 8.31-8.44 (m, 3H), 10.26 (d, *J* = 0.6 Hz, 1H).

*4.1.25. (E)-3-(6-(4-Fluorobenzoyl)quinolin-2-yl)acrylic acid (**20a**)*

The title compound was obtained in 100% overall yield from compound **19a** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.08 (d, *J* = 15.9 Hz, 1H), 7.40-7.50 (m, 2H), 7.74 (d, *J* = 15.9 Hz, 1H), 7.90-7.96 (m, 2H), 8.00-8.19 (m, 3H), 8.39 (d, *J* = 1.5 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H).

*4.1.26. (E)-3-(6-(4-Methylbenzoyl)quinolin-2-yl)acrylic acid (**20b**)*

The title compound was obtained in 97.8% overall yield from compound **19b** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.33 (s, 3H), 7.07 (d, *J* = 15.9 Hz, 1H), 7.40 (d, *J* = 9.3 Hz, 2H), 7.71-7.78 (m, 3H),8.00-8.18 (m, 3H), 8.36 (d, *J* = 1.8 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H).

*4.1.27. (E)-3-(6-(4-Methoxybenzoyl)quinolin-2-yl)acrylic acid (**20c**)*

A mixture of **19c** (0.33 g, 1.1 mmol), methyl (triphenylphosphor-anylidene)acetate (0.38 g, 1.1 mmol), and DCM was heated under reflux for 1 h. The reaction was quenched with H_2O and extracted with DCM. The organic layer was collected and dried under reduced pressure. The resulting residue was dissolved in MeOH (15 mL) and 1 N KOH (2.5 mL) was added. The reaction mixture was heated to reflux for 1 h, then cooled to rt, and neutralized by HCl followed by extraction with EtOAc. The organic layer was collected and dried under reduced pressure to obtain compound **20c** (0.3 g, 79.0%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.88 (s, 3H), 7.07 (d, *J* = 15.9 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 15.9 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 8.00-8.10 (m, 2H), 8.16 (d, *J* = 9.0 Hz, 1H), 8.36 (d, *J* = 1.5 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H).

*4.1.28. (E)-3-(6-(3,4-Dimethoxybenzoyl)quinolin-2-yl)acrylic acid (**20d**)*

The title compound was obtained in 84.9% overall yield from compound **19d** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3H), 3.87 (s, 3H), 7.00-7.15 (m,2H), 7.39-7.45 (m, 2H), 7.76 (d, *J* = 15.9 Hz, 1H), 8.05-8.19 (m, 3H), 8.38 (s, 1H), 8.63 (d, *J* = 8.4 Hz, 1H).

*4.1.29. (E)-3-(6-(3,4,5-Trimethoxybenzoyl)quinolin-2-yl)acrylic acid (**20e**)*

The title compound was obtained in 90.9% overall yield from compound **19e** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.79 (s, 3H), 3.81 (s, 6H), 7.02 (d, *J* = 15.3 Hz, 1H), 7.10-7.13 (m, 2H), 7.75 (d, *J* = 15.9 Hz, 1H), 8.05 (d, *J* = 8.7 Hz, 1H), 8.13-8.16 (m,2H), 8.47 (s, 1H), 8.66 (d, *J* = 8.7 Hz, 1H).

*4.1.30. 6-(3-Methoxyphenoxy)-2-methylquinoline (**21a**)*

The title compound was obtained in 78.0% overall yield from compound **17** in a manner similar to that described for the

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prep ... from 3H), 3.77 (s, 3H), 6.61-6.66 (s, 2H), 6.73-6.78 (m, 1H), 7.26-7.32 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H).

*4.1.31. 6-(4-Methoxyphenoxy)-2-methylquinoline (**21b**)*

A mixture of compound **17** (0.6 g, 2.7 mmol), 4-methoxyphenol (0.36 g, 2.9 mmol), Cs_2CO_3 (2.4 g, 7.4 mmol), CuI (0.06 g, 0.3 mmol), *N*,*N*-dimethylglycine (0.3 g, 1.0 mmol), and DMF (6.0 mL) was heated to 100 °C under microwave radiation for 10 min. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The organic layer was collected and purified by column chromatography to afford compound **21b** (0.65 g, 90.0%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71 (s, 3H), 3.83 (s, 3H), 6.92 (d, *J* = 9.3 Hz, 2H), 7.00-7.10 (m, 3H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.42 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H).

*4.1.32. 2-Methyl-6-(3,4,5-trimethoxyphenoxy)quinoline (**21c**)*

The title compound was obtained in 64.3% overall yield from compound **17** in a manner similar to that described for the preparation of **21b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.85 (s, 3H), 3.80 (s, 6H), 3.86 (s, 3H), 6.33 (s, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.53 (dd, *J* = 2.4, 9.0 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 6.9 Hz, 1H).

*4.1.33. 6-(4-Isopropylphenoxy)-2-methylquinoline (**21d**)*

The title compound was obtained in 95.0% overall yield from compound **17** in a manner similar to that described for the preparation of **21b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.28 (s, 3H), 2.74 (s, 3H), 2.85-3.00 (m, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 2.7 Hz, 1H), 7.20-7.30 (m, 3H), 7.45 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 9.3 Hz, 1H).

*4.1.34. 2-Methyl-6-(4-nitrophenoxy)quinoline (**21e**)*

The title compound was obtained in 64.9% overall yield from compound **17** in a manner similar to that described for the preparation of **21b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.79 (s, 3H), 7.08 (d, *J* = 9.3 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.40-7.49 (m, 2H), 8.02 (d, *J* = 8.7 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 8.23 (d, *J* = 9.3 Hz, 2H).

*4.1.35. 6-(3-Methoxyphenoxy)quinoline-2-carbaldehyde (**22a**)*

The title compound was obtained in 90.0% overall yield from compound **21a** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H), 6.69-6.82 (m, 3H), 7.24 (d, *J* = 2.7 Hz, 1H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.59 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 9.0 Hz, 1H), 10.18 (d, *J* = 0.9 Hz, 1H).

*4.1.36. 6-(4-Methoxyphenoxy)quinoline-2-carbaldehyde (**22b**)*

The title compound was obtained in 83.0% overall yield from compound **21b** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H), 6.97 (d, *J* = 9.3 Hz, 2H), 7.00-7.12 (m, 3H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.57 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 9.3 Hz, 1H), 10.18 (s, 1H).

*4.1.37. 6-(3,4,5-Trimethoxyphenoxy)quinoline-2-carbaldehyde (**22c**)*

The title compound was obtained in 83.0% overall yield from compound **21c** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 6H), 3.86 (s, 3H), 6.37 (s, 2H), 7.19 (d, *J* = 2.7 Hz, 1H), 7.56 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 9.3 Hz, 1H), 10.15 (s, 1H).

*4.1.38. 6-(4-Isopropylphenoxy)quinoline-2-carbaldehyde (**22d**)*

The title compound was obtained in 65.8% overall yield from compound **21d** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3H), 1.30 (s, 3H), 2.89-3.10 (m, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 2.7 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.59 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* =8.7 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 10.20 (s, 1H).

*4.1.39. 6-(4-Nitrophenoxy)quinoline-2-carbaldehyde (**22e**)*

The title compound was obtained in 88.6% overall yield from compound **21e** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 9.0 Hz, 2H), 7.47 (d, *J* = 2.7 Hz, 1H), 7.61 (dd, *J* = 2.7, 9.3 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.7 Hz, 1H), 8.29 (d, *J* = 9.3 Hz, 2H), 8.34 (d, *J* = 9.3 Hz, 1H), 10.24 (s, 1H).

*4.1.40. (E)-3-(6-(3-Methoxyphenoxy)quinolin-2-yl)acrylic acid (**23a**)*

The title compound was obtained in 99.1% overall yield from compound **22a** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 3H), 6.67-6.75 (m, 2H), 6.78-6.83 (m, 1H), 6.95 (d, *J* = 15.9 Hz, 1H), 7.32-7.42 (m, 2H), 7.55 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 8.32 (d, *J* = 8.7 Hz, 1H).

*4.1.41. (E)-3-(6-(4-Methoxyphenoxy)quinolin-2-yl)acrylic acid (**23b**)*

The title compound was obtained in 99.3% overall yield from compound **22b** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.78 (s, 3H), 7.00-7.24 (m, 6H), 7.53 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H).

*4.1.42. (E)-3-(6-(3,4,5-Trimethoxyphenoxy)quinolin-2-yl)acrylic acid (**23c**)*

The title compound was obtained in 99.1% overall yield from compound **22c** in a manner similar to that described for the

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3H), 3.72 (s, 6H), 6.51 (s, 2H), 6.94 (d, *J* = 15.9 Hz, 1H), 7.37 (d, *J* = 3.0 Hz, 1H), 7.54 (dd, *J* = 3.0, 9.0 Hz, 1H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 8.33 (d, *J* = 8.7 Hz, 1H).

*4.1.43. (E)-3-(6-(4-Isopropylphenoxy)quinolin-2-yl)acrylic acid (**23d**)*

The title compound was obtained in 70.9% overall yield from compound **22d** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, MeOD): δ = 1.26 (d, *J* = 6.6 Hz, 6H), 2.85-3.00 (m, 1H), 6.90 (d, *J* = 16.2 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 2.7 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.49 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.72-7.52 (m, 2H), 8.00 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H).

*4.1.44. (E)-3-(6-(4-Nitrophenoxy)quinolin-2-yl)acrylic acid (**23e**)*

The title compound was obtained in 85.0% overall yield from compound **22e** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.99 (d, *J* = 16.2 Hz, 1H), 7.28 (d, *J* = 9.3 Hz, 2H), 7.65 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.68-7.75 (m, 2H), 7.98 (d, *J* = 8.7 Hz, 1H), 8.14 (d, *J* = 9.3 Hz, 1H), 8.28 (d, *J* = 9.3 Hz, 2H), 8.39 (d, *J* = 8.4 Hz, 1H).

*4.1.45. 2-Methyl-6-nitroquinoline (**25**)*

The title compound was obtained in 55.8% overall yield from compound **24** in a manner similar to that described for the preparation of **17**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (s, 3H), 7.44 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 9.3 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.43 (dd, *J* = 2.7, 9.3 Hz, 1H), 8.73 (d, *J* = 2.4 Hz, 1H).

*4.1.46. 4-Methoxy-N-(2-methylquinolin-6-yl)benzenesulfonamide (**26**)*

A mixture of compound **25** (0.4 g, 2.1 mmol), a catalytic amount of Pd/C, and MeOH (10 mL) was stirred under hydrogen at rt for 2 h. The reaction was filtered to remove the Pd/C, and then the resulting filtrate was dried under reduced pressure to afford a gray solid. The resulting solid was dissolved in DCM (10 mL), and then 4-methoxybenzenesulfonyl chloride (0.48 g, 2.3 mmol) and pyridine (0.18 mL, 2.2 mmol) were added and the mixture was stirred for 1 h. The reaction mixture was filtered and the filtrate was purified by column chromatography to afford compound **26** (0.39 g, 55.9%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71 (s,3H), 3.75 (s, 3H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 2.4, 9.0 Hz, 1H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 2H), 7.88-7.96 (m, 2H).

*4.1.47. N-(2-Formylquinolin-6-yl)-4-methoxybenzenesulfonamide (**27**)*

The title compound was obtained in 67.1% overall yield from compound **26** in a manner similar to that described for the preparation of **29**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.56 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.08-8.18 (m, 2H), 10.14 (s, 1H).

*4.1.48. (E)-3-(6-(4-Methoxyphenylsulfonamido)quinolin-2-yl)acrylic acid (**28**)*

The title compound was obtained in 28.3% overall yield from compound **27** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.75 (s, 3H), 6.92 (d, *J* = 15.9 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.53 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.60-7.70 (m, 2H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.80-7.93 (m, 2H), 8.30 (d, *J* = 8.7 Hz, 1H).

*4.1.49. 6-Bromoquinoline-2-carbaldehyde (**29**)*

A mixture of compound **17** (1.28 g, 5.8 mmol), SeO_2 (0.96 g, 8.7 mmol), and xylene (13 mL) was heated to reflux for 4 h. The reaction mixture was filtered to remove SeO_2 and the resulting filtrate was purified by column chromatography to afford compound **29** (0.82 g, 60.3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 2.1, 9.0 Hz, 1H), 8.00-8.13 (m, 3H), 8.22 (d, *J* = 8.4 Hz, 1H), 10. 20 (s, 1H).

*4.1.50. 6-(4-Methoxyphenyl)quinoline-2-carbaldehyde (**30a**)*

The title compound was obtained in 79.3% overall yield from compound **29** in a manner similar to that described for the preparation of **30b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 3H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 8.01-8.10 (m, 3H), 8.26-8.35 (m, 2H), 10.23 (d, *J* = 0.9 Hz, 1H).

*4.1.51. 6-(Furan-3-yl)quinoline-2-carbaldehyde (**30b**)*

A mixture of **29** (0.7 g, mmol), furan-3-ylboronic acid (0.35 g, mmol), $Pd(PPh_3)_4$ (0.21 g, mmol), TBAB (0.13 g, mmol), K_2CO_3 (1.2 g, mmol), H_2O (5.25 mL), and dioxane (10.5 mL) was placed in a sealed tube and irradiated by microwaves at 120 °C for 20 min. The reaction mixture was filtered and the filtrate was purified by column chromatography to obtain compound **30b** (0.44 g, 66.0%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (dd, *J* = 0.9, 2.1 Hz, 1H), 7.56 (t, *J* = 1.5 Hz, 1H), 7.93-8.00 (m, 3H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 10.23 (s, 1H).

*4.1.52. (E)-3-(6-(4-Methoxyphenyl)quinolin-2-yl)acrylic acid (**31a**)*

The title compound was obtained in 43.1% overall yield from compound **30a** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.81 (s, 3H), 7.00-7.12 (m, 3H), 7.64 (d, *J* = 15.6 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 8.7 Hz, 1H), 8.00-8.15 (m, 2H), 8.25 (d, *J* = 1.8 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H).

*4.1.53. (E)-3-(6-(Furan-3-yl)quinolin-2-yl)acrylic acid (**31b**)*

The title compound was obtained in 29.5% overall yield from compound **30b** in a manner similar to that described for the preparation of **20c**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.04 (d, *J* = 15.9 Hz, 1H), 7.13 (dd, *J* = 0.9, 1.8 Hz, 1H), 7.75 (d, *J* = 16.2 Hz, 1H), 7.82 (t, *J* = 1.8 Hz, 1H), 8.00-8.16 (m, 3H), 8.24 (d, *J* = 1.8 Hz, 1H), 8.40-8.46 (m, 2H).

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4.2.1. Cell culture

The colon cancer cell line HCT116 and non-small cell lung cancer cell line A549 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 the 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% AcOH. Unbound SRB was washed out by 1% AcOH and SRB-containing cells were solubilized with 10 mM Trizma base. The absorbance was measured 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 (T_x), the percentage of growth was calculated at each of the compound concentration levels. Growth inhibition of 50% (GI_{50}) was calculated from the equation $[(T_i-T_z)/(C-T_z)] \times 100 = 50$, 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. Western blot analysis

HCT116 cells were treated with 0.1% DMSO or indicated test compound at 0.6, 1.25, 2.5, 5, 10, 20 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 rt in 5% nonfat milk in PBS, transblotted membrane was washed twice with tris-buffered saline containing 0.1% Tween 20 (TBST). The 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 rt. 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).

In order to get clear Western blot results, we had different exposure times for Ac-histone H3, Ac-tubulin, and GAPDH shown in Figure 3. For example, the exposure time of Ac-histone H3 was longer than Ac-tubulin in DMSO/compound **9**-treated both Ac-histone H3 and Ac-tubulin and easily to underestimate the selectivity toward HDAC6 of compound **9**. A similar effect can be observed in the increased-levels of Ac-histone H3 and Ac-tubulin between compound **9** and compound **10**. The different exposure times of compound **9** and **10** caused more significant expression level of Ac-tubulin in compound **10** (0.6 μM)-treated group than compound **9** (0.6 μM)-treated one. However, the relative fold increase of compound **10** (0.6 μM)/control was not higher than compound **9** (0.6 μM)/control. The level of Ac-tubulin was much higher in control/compound **10** than control/compound **9** since the exposure time is shorter in DMSO/compound **9**-treated cells.

4.2.4. HDAC enzyme inhibition assays

Enzyme inhibition assays were conducted by the Reaction Biology Corporation, Malvern, PA. Compounds were dissolved in DMSO and tested in at least 10-dose IC_{50} mode with 3-fold serial dilution starting at 10 μM. HDAC Control Compound trichostatin A was tested in a 10-dose IC_{50} with 3-fold serial dilution starting at 10 μM.

Acknowledgments

This research were supported by the Ministry of Science and Technology, Taiwan (grant no. MOST 105-2320-B-038-010) and Taipei Medical University grant (TMU104-AE1-B17)

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Journal Pre-proofs

Conflicts of interest

There are no conflicts to declare.

Journal Pre-proofs