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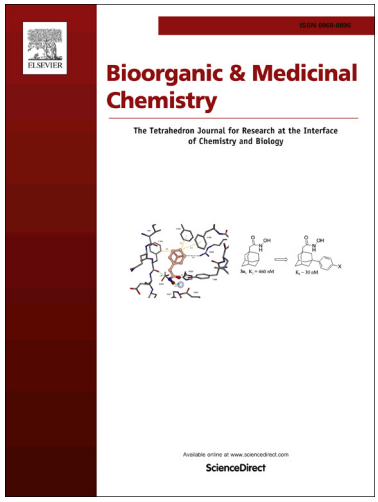

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Design, synthesis and preliminary bioactivity evaluations of substituted quinoline hydroxamic acid derivatives as novel histone deacetylase (HDAC) inhibitors

Lei Wang [a], Xuben Hou [a], Huansheng Fu[a], Xiaole Pan [a], Wenfang Xu [a], Weiping Tang [b], Hao Fang [a*]

[a] *Department of Medicinal Chemistry, Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmacy, Shandong University, Ji'nan, Shandong, 250012, P.R. China*

[b] *School of Pharmacy, University of Wisconsin, 777 Highland Avenue, Madison 53705, USA*

Abstract:

Inhibition of HDACs activity has become a promising therapeutic strategy in clinical practice to reverse the abnormal epigenetic states of cancer and other diseases. Therefore, HDAC inhibitors become a relatively new class of anti-cancer agent. In the present study, we reported the design and synthesis of a series of novel HDAC inhibitors using various substituted quinoline rings as the cap group. In *vitro* studies showed that some compounds have good inhibitory activities against HDACs and potent antiproliferative activities in some tumor cell lines. Especially, compound **9w** (IC_{50} = 85 nM), exhibited better inhibitory effect compared with SAHA (IC_{50} = 161 nM).

Keywords: quinoline; hydroxamic acid; HDAC; inhibitor; anti-proliferative

1. Introduction

The histone acetylation status plays an essential role in initiation and progression of tumor among the complex epigenetic regulations.[1, 2] The imbalance between histone acetylation and deacetylation in cells will lead to changes in cell cycle and metabolism profile, which in turn trigger the formation of tumors.[3] Histone deacetylases (HDACs) are important enzymes regulating the balance of acetylation and deacetylation of histones and non-histone proteins, by catalyzing hydrolysis of ε-amide bond of lysine residues. The overexpression of HDACs suppresses gene transcription and leads to silencing of tumor suppressor genes.[4] Thus, HDAC inhibitors (HDACi) have been recognized as a new class of anticancer agents. HDAC inhibitors have exhibited outstanding anti-tumor activity by enhancing the level of histone acetylation and inducing cell cycle arrest, differentiation and apoptosis.[5]

To date, three HDAC inhibitors (Vorinostat, Romidepsin and Belinostat) have approved for the clinical therapy of cutaneous T-cell lymphoma (CTCL) or peripheral T-cell lymphoma (PTCL) by FDA. Meanwhile, more than 20 promising HDAC inhibitors are in clinical or pre-clinical studies for the treatment of various cancers.[6] Generally, the HDAC inhibitors have a common pharmacophore model including a zinc ion binding group (ZBG), linker and a cap group (**Figure 1**). The ZBG chelates zinc ion at the bottom of HDACs active site. The cap group enhances the affinity with the surface of HDACs and linker connects the ZBG and the cap group.

* Corresponding author. Phone: +86-531-88382731. Fax: +86-531-88382548. E-mail: haofangcn@sdu.edu.cn.

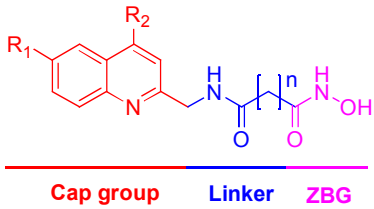


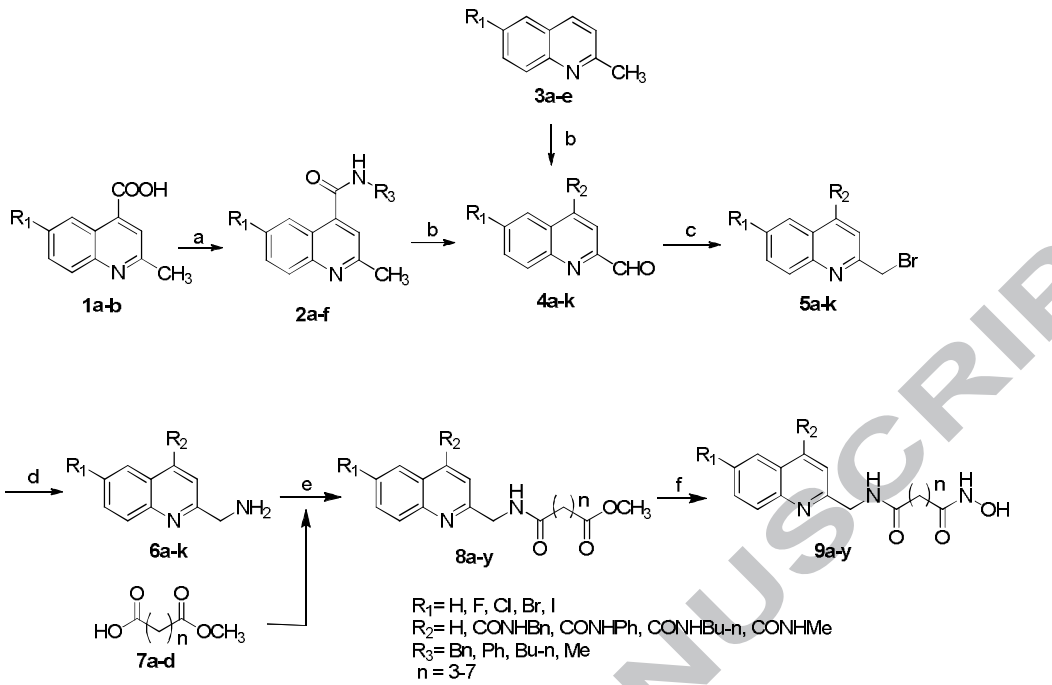
Figure 1 HDAC inhibitor pharmacophore model and the quinoline-based hydroxamic acid derivative in current study.

Previously, we have used different heterocycles as the surface recognition cap group in the design of novel HDAC inhibitors, such as tetrahydroisoquinoline[7, 8], 1,3,4-thiadiazole[9, 10], 2-dihydrobenzo[*d*]isothiazol-3-one-1,1-dioxide[11], indole[12, 13] and purine[14]. In particular, the tetrahydroisoquinoline-bearing hydroxamic acid analogues showed potent HDAC inhibitory activity in *in-vitro* biological evaluations and intriguing growth inhibition in multiple tumor cell lines. Structurally similar to tetrahydroisoquinoline, heterocycle quinolone could be used as surface recognition cap and recently Moffat[15] reported one compound containing 6-fluoro quinolone (CHR-3996) possessed potent HDAC inhibitory activity and antiproliferative activities. In order to study the further structure-activity relationship, we designed a series of novel HDAC inhibitors bearing various substituents in the quinoline ring (**Figure 1**), and evaluated their inhibitory activities against HDACs.

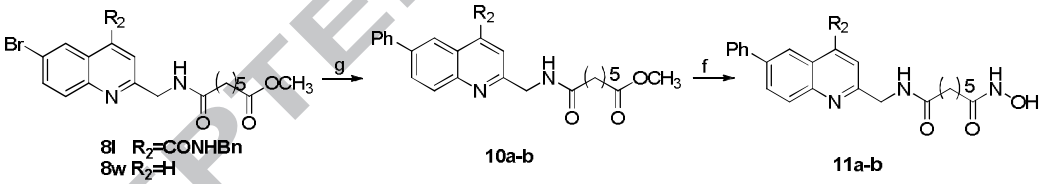
2. Chemical synthesis

The synthetic route of our novel HDACi is described in **Schemes 1-2**. Carboxylic acids **1a-b** were coupled with various amines to obtain intermediates **2a-f**. The methyl group of intermediates **2a-f** and **3a-e** were oxidized to afford 2-formylquinoline analogs **4a-k**. Reduction of **4a-k** yielded substituted 2-hydroxymethylquinolines, which were then reacted with PBr_3 to form alkyl bromides **5a-k**. Sequential treatment of **5a-k** with NaN_3 in DMF and Staudinger reaction gave **6a-k**. Compounds **6a-k** were coupled with various acids to obtain intermediates **8a-y**, which were converted to hydroxamic acids **9a-y** by treating with hydroxylamine.

To gain more structure diversity, compounds **10a-b** were prepared by Suzuki cross-coupling reaction. Compounds **10a-b** were then converted to hydroxamic acids **11a-b** by the same method described above.



Scheme 1. Reagents and conditions: (a) EDCI, HOBT, Et_3N, CH_2Cl_2, substituted aniline, 0 °C to rt, overnight; (b) SeO_2, 1,4-dixoane, reflux, 1 h; (c) (i) $NaBH_4$, MeOH, rt, 15 min; (ii) PBr_3, CH_2Cl_2, rt, overnight; (d) (i) NaN_3, DMF, rt, overnight; (ii) PPh_3, THF, rt, 5 h; (e) EDCI, HOBT, Et_3N, CH_2Cl_2, 0 °C to RT, overnight; or $SOCl_2$, Et_3N, THF, 0 °C to RT, overnight; (f) $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 1 h.



Scheme 2. Reagents and conditions: (g) $Pd(OAc)_2$, PPh_3, phenylboronic acid, Na_2CO_3, toluene, reflux, overnight; (f) $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 1 h.

3. Results and discussion

HDAC enzymatic inhibitory activities of these quinoline hydroxamic acid derivatives were evaluated using the Color de Lys™ assay (BML-AK501, Enzo® Life Sciences) including HDAC 1 & 2. The results were calculated and tabulated as IC_{50} values in **Table 1**.

According to the data in **Table 1**, we found that both the linker and the substituents in quinoline ring played a significant role in the inhibitory activities against HDACs. For example, the compounds with shorter linker (n = 3-4, e.g. **9a-9b**, **9q-9r**) or longer linker (n = 6-7, e.g. **9d-9e**, **9m-9n**) showed poor inhibition on HDACs. Compounds with the five methylene units linker showed similar or better enzyme inhibitory activity compared with SAHA, such as, **9c, 9f, 9v, 9w** *etc*. This

results may be explained by the fact that suitable length of the linker (n = 5) is helpful for the ZBG to chelate with the Zn^{2+} ion located at the bottom of active site of HDACs.

In addition, the substituents on the C4 and C6-position of quinoline ring also significantly impact the inhibitory activity. According to the data in **Table 1**, substituents on the C4-position of quinoline ring decreased the enzyme inhibitory activity. For example, compounds **9c**, **9f**, **9h** and **9j** (IC_{50} = 399, 301, 444, 642 nM, respectively) showed poorer inhibitory activity against HDAC than compound **9s** (IC_{50} = 266 nM) without C4-substituent. Moreover, the inhibitory activities of compounds **9l, 9o** and **9w** also confirmed this conclusion. Interestingly, introducing different substituent groups to the C6-position of quinoline ring enhanced the enzymatic inhibitory activity. For instance, compounds **9l** and **9o** (IC_{50} = 343 and 196 nM, respectively) showed better inhibitory activities compared with the corresponding compounds **9c** and **9f** (IC_{50} = 399 and 301 nM, respectively) without C6-substituent. The inhibitory activities of compounds **9s** and **9w** also proved this conclusion. This result demonstrated that the C6-substituent was also crucial to binding affinities. On the other hand, replacement of halogen substituents with a phenyl group (such as **9w** and **11b**) resulted in the decrease of enzymatic inhibitory activity, suggesting a preference for small group on the C6-position as a surface recognition cap group.

Notably, we could find the fact that only suitable length of the linker (n = 5) is favor, which is helpful for the ZBG to chelate with the Zn^{2+} ion located at the bottom of active site of HDACs. Substituents on the C4-position of quinoline ring decreased the enzyme inhibitory activity obviously. Interestingly, introducing different substituent groups to the C6-position of quinoline ring enhanced the enzymatic inhibitory activity, except the bulky substituents. Therefore, we got a potent target compound **9w** (IC_{50} = 85 nM) which showed better activity than FDA approved drug SAHA (IC_{50} = 161 nM) (Figure 2).

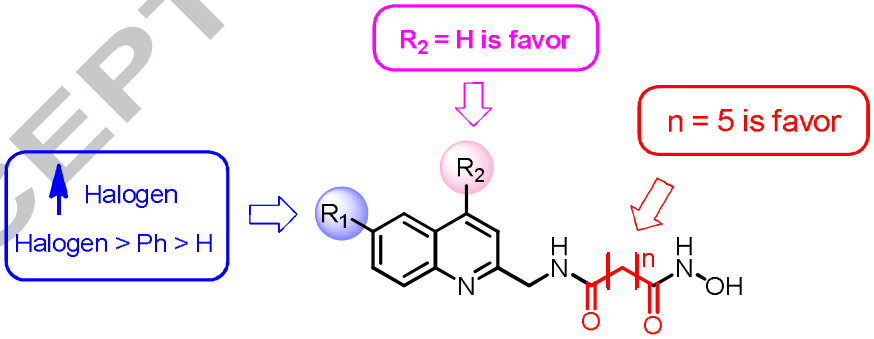
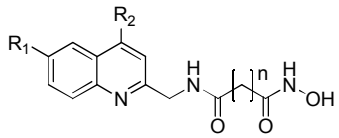


Figure 2 Compounds SARs analysis

Table1 The chemical structures and HDACs inhibitory activities of quinoline hydroxamate derivatives



Compd	R_1	R_2	n	IC_{50}[a] of HDACs (nM)
9a	H	-CONHBn	3	> 1000
9b	H	-CONHBn	4	> 1000
9c	H	-CONHBn	5	399 ± 26
9d	H	-CONHBn	6	780 ± 285
9e	H	-CONHBn	7	> 1000
9f	H	-CONHPh	5	301 ± 166
9g	H	-CONHPh	6	562 ± 177
9h	H	-CONHBu-n	5	444 ± 40
9i	H	-CONHBu-n	6	> 1000
9j	H	-CONHMe	5	642 ± 237
9k	H	-CONHMe	6	> 1000
9l	Br	-CONHBn	5	343 ± 86
9m	Br	-CONHBn	6	> 1000
9n	Br	-CONHBn	7	> 1000
9o	Br	-CONHPh	5	196 ± 43
9p	Br	-CONHPh	6	> 1000
9q	H	H	3	> 1000
9r	H	H	4	> 1000
9s	H	H	5	266 ± 110
9t	H	H	6	678 ± 332
9u	F	H	5	155 ± 58
9v	Cl	H	5	120 ± 15
9w	Br	H	5	85 ± 32
9x	Br	H	6	146 ± 31
9y	I	H	5	132 ± 29
11a	Ph	-CONHBn	5	341 ± 46
11b	Ph	H	5	152 ± 43
SAHA				161 ± 51

[a] Values are the mean of three independent determinations and expressed with standard deviations.

For a better understanding of the interaction between these quinoline based derivatives and HDAC, the most active compound **9w** was docked to the active site of HDAC2 (PDB code: 4LXZ) using Surflex-dock[16, 17]. The result in **Figure 3** suggested that compound **9w** could bind to the active site of HDAC2 and there was a similar binding mode for compound **9w** compared with co-crystallized SAHA, which all chelated Zn^{2+} ion by hydroxamic acid group. In addition, the amide bond of compound **9w** and SAHA could form hydrogen bond with ASP104 in the active site of HDAC2.

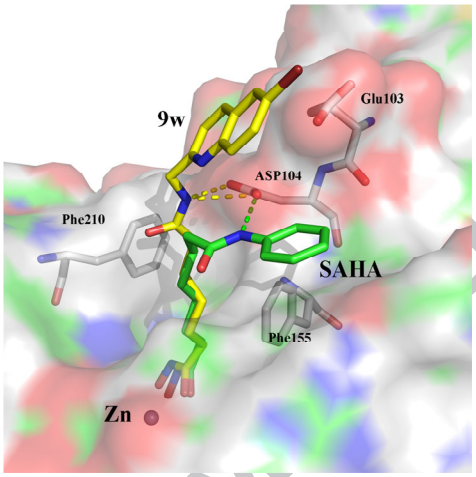


Figure 3 The molecular binding mode of compound **9w** (yellow) and SAHA (green) in the active site of HDAC2 using Surflex-dock[16, 17].

Structurally speaking, suitable length linker (n = 5) is vital for compound **9w** to chelate the Zn^{2+} at the active site and the cap group of the compound **9w** chould interact with catalytic pocket comfortably. It is reported that the active site is highly conserved, the rim of the catalytic pocket differ greatly among different HDAC isozymes. Significantly, variation of amino acid residues region produces a significantly narrower catalytic pocket in the homology model of HDAC1. Compounds with a large and rigid cap group could not occupy catalytic region of HDAC1. [18, 19]Hence, compound **9w** exhibited the most potent inhibitory effect.

To further ascertain the activities of these quinoline-based HDAC inhibitors at the cellular level, three compounds **9v**, **9w** and **9y** were selected to evaluate their antiproliferative activities *in vitro* using cancer cell lines of MDA-MB-231 (breast cancer cell), PC3 (prostatic cancer cell), K562 (chronic myelogenous leukemia cell) and A549 (lung cancer cell) by MTT assay. The IC_{50} values were summarized in **Table 2.** According to the inhibition data, all tested compounds showed obvious anti-proliferative activities compared with SAHA. Moreover, MDA-MB-231 was the most sensitive cell line to our quinoline-based HDAC inhibitors and **9w** showed the better anti-proliferative activity than SAHA. In addition, **9y** exhibited most potent anti-proliferative activities in PC-3, K562 and A549 cell lines.

Table 2 Anti-proliferative activities against MDA-MB231, PC3, K562 and A549 cell lines.

Compd.	$IC_{50}(\mu M)^a$			
	MDA-MB-231	PC-3	K562	A549
9v	1.84 ± 0.11	9.13 ± 1.91	3.39 ± 0.38	2.71 ± 0.34
9w	0.90 ± 0.25	9.26 ± 0.50	4.86 ± 1.38	3.89 ± 0.72
9y	1.41 ± 0.37	8.48 ± 1.29	2.45 ± 0.59	2.58 ± 0.31
SAHA	2.02 ± 0.30	7.30 ± 0.20	3.94 ± 0.39	5.32 ± 1.64

[a] Values are the mean of three independent determinations and expressed with standard deviations.

4. Conclusions

In summary, we designed and synthesized a series of novel HDAC inhibitors with different length linkers and substituents in quinoline ring as the cap group. Among them, **9v, 9w** and **9y** exhibited similar or higher inhibitory activities in both enzymatic inhibitory activity and cellular anti-proliferative activity assay compared with SAHA. These results suggest that compound **9w** could be used as new lead compound to develop more potent HDAC inhibitors in the future.

5. Experimental section

5.1. Chemistry: general procedures

Unless mentioned, all start materials, reagents and solvents are analytical reagents without further purification. All reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (60GF-254) and visualized with UV light, chloride ferric or iodine vapor. Melting points were determined by the RY-1 electrothermal melting point apparatus without correction. ESI-MS was determined on an Aglient-1100 series LC/MSD trap spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Brucker DRX spectrometer (300 MHz, 400 MHz). The chemical shifts are defined as δ values (parts per million) relative to TMS as internal standard. Significant ^{1}H-NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) number of protons. HRMS spectrums were conducted on an Agilent 6510 Quadrupole Time-of-Flight LC/MS deliver.

5.1.1. *N*-benzyl-2-methylquinoline-4-carboxamide (2a)

To a solution of **1a** (0.94 g, 5 mmol) and Et_3N (1.3 mL, 10 mmol) in the anhydrous THF (150 mL) was added isobutyl chloroformate (0.76 mL, 6 mmol) slowly under the ice baths. After 1 h, benzylamine (0.82 mL, 7.5 mmol) was added. The mixture was stirred vigorously overnight at room temperature. The resultant solution was filtered. The filtrate was concentrated, dissolved in dichloromethane (150 mL), and washed with 10% citric acid (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL) and brine (3 × 50 mL), dried over with $MgSO_4$, and the solution was evaporated under vacuum. The crude product was purified by column chromatography to afford compound **2a** (0.86 g, 62%) as a white solid. Mp: 184-186 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.30 (t, J = 5.85 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.1 Hz,

1H), 7.75 (t, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 8.25 Hz, 1H), 7.50 (s, 1H), 7.42-7.35 (m, 4H), 7.31-7.27 (m, 1H), 4.56 (d, *J* = 6 Hz, 2H), 2.69 (s, 3H). ESI-MS m/z: 277.3 $[M+H]^+$.

Compounds **2b-2d** were synthesized by the same method described above.

5.1.2. *N*-phenyl-2-methylquinoline-4-carboxamide (2b)

Yield: 57%, mp: 177-179 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.80-7.75 (m, 3H), 7.63-7.58 (m, 2H), 7.40 (t, *J* = 7.95 Hz, 2H), 7.16 (t, *J* = 7.35 Hz, 1H), 2.73 (s, 3H). ESI-MS m/z: 263.3 $[M+H]^+$.

5.1.3. *N*-butyl-2-methylquinoline-4-carboxamide (2c)

Yield: 71%, mp: 106-108 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.69 (t, *J* = 5.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 8.3 Hz, 1H), 7.57 (t, *J* = 8.2 Hz, 1H), 7.42 (s, 1H), 3.36-3.33 (m, 2H), 2.68 (s, 3H), 1.58-1.52 (m, 2H), 1.43-1.36 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ESI-MS m/z: 243.5 $[M+H]^+$.

5.1.4. *N*,2-dimethylquinoline-4-carboxamide (2d)

Yield: 66%, mp: 140-142 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.65-8.61 (m, 1H), 8.10 (dd, J_1 = 8.1 Hz, J_2 = 0.9 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.74 (t, *J* = 9 Hz, 1H), 7.56 (t, *J* = 8.3 Hz, 1H), 7.44 (s, 1H), 2.87 (d, *J* = 4.5 Hz, 3H), 2.68 (s, 3H). ESI-MS m/z: 201.4 $[M+H]^+$.

5.1.5. *N*-benzyl-6-bromo-2-methylquinoline-4-carboxamide (2e)

To a solution of **1b** (2.66 g, 10 mmol) and Et_3N (2.6 mL, 20 mmol) in the anhydrous CH_2Cl_2 (150 mL) under the ice baths was added slowly HOBT (1.62 g, 12 mmol), followed by EDCI (2.30 g, 12 mmol). After 1 h, benzylamine (2.18 mL, 20 mmol) was added. After the night, the solution of CH_2Cl_2 was washed with 10% citric acid (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL) and brine (3 × 50 mL), dried over with $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was purified by column chromatography to afford compound **2e** (2.1 g, 59%) as a white solid. Mp: 198-200 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.37 (t, *J* = 6 Hz, 1H), 8.29 (d, *J* = 2.1 Hz, 1H), 7.95-7.86 (m, 2H), 7.59 (s, 1H), 7.45-7.36 (m, 4H), 7.32-7.26 (m, 1H), 4.56 (d, *J* = 6 Hz, 2H), 2.68 (s, 3H). ESI-MS m/z: 356.4 $[M+H]^+$.

Compound **2f** was synthesized by the same method described above.

5.1.6. *N*-phenyl-6-bromo-2-methylquinoline-4-carboxamide (2f)

Yield: 60%, mp: 210-212 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.30 (d, *J* = 4 Hz, 1H), 7.99 (d, *J* = 9 Hz, 1H), 7.93 (m, 1H), 7.80 (d, *J* = 8 Hz, 2H), 7.74 (s, 1H), 7.41 (t, *J* = 8 Hz, 2H), 7.17 (t, *J* = 8 Hz, 1H), 2.73 (s, 3H). ESI-MS m/z: 341.4 $[M+H]^+$.

5.1.7. *N*-benzyl-2-formylquinoline-4-carboxamide (4a)

The compound **2a** (0.55 g, 2 mmol) was dissolved in 1,4-dioxane (50 mL), then

SeO_2 (0.27 g, 2.4 mmol) was added. The mixed solution was refluxed for 1 h. Solvent was concentrated and dissolved in the CH_2Cl_2 (150 mL). The organic layer was washed with saturated Na_2CO_3 and brine, dried over anhydrous $MgSO_4$, and the solution was evaporated under vacuum. The residue was purified by chromatography on silica gel to give **4a** (0.44 g, 76%) as a white solid. Mp: 169-171 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.50 (t, J = 6 Hz, 1H), 8.29 (t, J = 8.85 Hz, 2H), 8.00-7.95 (m, 2H), 7.86 (t, J = 8.4 Hz, 1H), 7.44-7.37 (m, 4H), 7.35-7.27 (m, 1H), 4.60 (d, J = 6 Hz, 2H). ESI-MS m/z: 291.3 $[M+H]^+$.
Compounds **4b-4k** were synthesized by the same method described above.

5.1.8. *N*-phenyl-2-formylquinoline-4-carboxamide (4b)
Yield: 72%, mp: 216-218 ºC, ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.88 (s, 1H), 10.20 (s, 1H), 8.35 (d, J = 7.8 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H), 8.00 (t, J = 8.4 Hz, 1H), 7.89 (t, J = 8.25 Hz, 1H), 7.81 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.95 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H). ESI-MS m/z: 277.3 $[M+H]^+$.

5.1.9. *N*-butyl-2-formylquinoline-4-carboxamide (4c)
Yield: 49%, mp: 146-147 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.89 (t, J = 5.2 Hz, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.95 (t, J = 7.6 Hz, 1H), 7.93 (s, 1H), 7.85 (t, J = 7.6 Hz, 1H), 3.37 (m, 2H), 1.62-1.54 (m, 2H), 1.44-1.35 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ESI-MS m/z: 257.4 $[M+H]^+$.

5.1.10. *N*-methyl-2-formylquinoline-4-carboxamide (4d)
Yield: 69%, mp: 170-172 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.87 (d, J = 4.5 Hz, 1H), 8.30 (d, J = 7.8 Hz, 2H), 8.00-7.94 (m, 2H), 7.85 (t, J = 8.3 Hz, 1H), 2.90 (d, J = 4.5 Hz, 3H). ESI-MS m/z: 215.5 $[M+H]^+$.

5.1.11. *N*-benzyl-6-bromo-2-formylquinoline-4-carboxamide (4e)
Yield: 76%, mp: 188-190 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.14 (s, 1H), 9.56 (s, 1H), 8.50 (d, J = 1.8 Hz, 1H), 8.26 (d, J = 9 Hz, 1H), 8.12-8.07 (m, 2H), 7.42-7.30 (m, 5H), 4.59 (d, J = 6 Hz, 2H). ESI-MS m/z: 370.3 $[M+H]^+$.

5.1.12. *N*-phenyl-6-bromo-2-formylquinoline-4-carboxamide (4f)
Yield: 53%, mp: > 250 ºC, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.19 (s, 1H), 8.50 (d, J = 2 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 8.21 (s, 1H), 8.15 (dd, J_1 = 8.8 Hz, J_2 = 2.2 Hz, 1H), 7.81 (d, J = 8 Hz, 2H), 7.42 (t, J = 8 Hz, 2H), 7.19 (t, J = 8 Hz, 1H). ESI-MS m/z: 356.3 $[M+H]^+$.

5.1.13. Quinoline-2-carbaldehyde (4g)
Yield: 72%, mp: 72-74 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.64 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.93 (t, J = 7.6 Hz, 1H), 7.81 (t, J = 7.5 Hz, 1H). ESI-MS m/z: 158.1 $[M+H]^+$.

5.1.14. 6-fluoroquinoline-2-carbaldehyde (4h)

Yield: 64%, mp: 122-124 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.61 (d, J = 8.8 Hz, 1H), 8.34-8.30 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.99 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 7.88 (td, J_1 = 10.4 Hz, J_2 = 2.8 Hz, 1H). ESI-MS m/z: 176.2 $[M+H]^+$.

5.1.15. 6-chloroquinoline-2-carbaldehyde (4i)

Yield: 77%, mp: 146-148 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.60 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 9.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.95 (dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, 1H). ESI-MS m/z: 192.6 $[M+H]^+$.

5.1.16. 6-bromoquinoline-2-carbaldehyde (4j)

Yield: 80%, mp: 162-164 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.61 (d, J = 8.4 Hz, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.19 (d, J = 9 Hz, 1H), 8.06-8.02 (m, 2H). ESI-MS m/z: 237.1 $[M+H]^+$.

5.1.17. 6-iodoquinoline-2-carbaldehyde (4k)

Yield: 75%, mp: 180-182 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.32 (s, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.05 (t, J = 9.1 Hz, 2H), 7.96 (d, J = 8.9 Hz, 1H); ESI-MS m/z: 284.1 $[M+H]^+$.

5.1.18. *N*-benzyl-2-(bromomethyl)quinoline-4-carboxamide (5a)

$NaBH_4$ (0.1 g, 2.5 mmol) was added partially to a solution of **4a** (1.45 g, 5 mmol) in MeOH (25 mL) at 0 ºC. Then the mixture was stirred at room temperature for 15 min. Then MeOH was evaporated under vacuum to give the crude product *N*-benzyl-2-(hydroxymethyl)quinoline-4-carboxamide.

PBr_3 (0.24 mL, 2.5 mmol) was added slowly dropwise to a solution of *N*-benzyl-2-(hydroxymethyl)quinoline-4-carboxamide (0.73 g, 2.5 mmol) and Et_3N (0.3 mL, 2.5 mmol) in CH_2Cl_2 (150 mL) under ice-bath. Then the resulting mixture was stirred overnight at room temperature. The resulting reaction was washed with brine (50 mL), dried over anhydrous $MgSO_4$, and the solution was evaporated under vacuum to afford **5a** as a white solid. Yield: 40%, mp: 196-198 ºC, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.38 (t, J = 5.9 Hz, 1H), 8.09-8.05 (m, 2H), 7.83 (t, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.43-7.32 (m, 4H), 7.31-7.29 (m, 1H), 4.89 (s, 2H), 4.57 (d, J = 6 Hz, 2H). ESI-MS m/z: 356.2 $[M+H]^+$.

Compounds **5b-5k** were synthesized by the same method described above.

5.1.19. *N*-phenyl-2-(bromomethyl)quinoline-4-carboxamide (5b)

Yield: 51%, mp: 212-214 ºC, ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.89-7.84 (m, 2H), 7.80 (d, J = 7.5 Hz, 2H), 7.74-7.68 (m, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 4.92 (s, 2H). ESI-MS m/z: 342.2 $[M+H]^+$.

5.1.20. *N*-butyl-2-(bromomethyl)quinoline-4-carboxamide (5c)

Yield: 25%, mp: 139-141 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.80 (t, J = 4.7 Hz, 1H), 8.09-8.04 (m, 2H), 7.86-7.80 (m, 1H), 7.71-7.67 (m, 1H), 7.66 (s, 1H), 4.98 (s,

2H), 3.38-3.32 (m, 2H), 1.62-1.52 (m, 2H), 1.47-1.34 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H). ESI-MS m/z: 322.2 $[M+H]^+$.

5.1.21. *N*-methyl-2-(bromomethyl)quinoline-4-carboxamide (5d)
Yield: 60%, mp: 182-184 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.76 (q, J = 4.2 Hz, 1H), 8.11-8.04 (m, 2H), 7.83 (t, J = 8.4 Hz, 1H), 7.70-7.64 (m, 2H), 4.88 (s, 2H), 2.88 (d, J = 4.8 Hz, 3H). ESI-MS m/z: 280.2 $[M+H]^+$.

5.1.22. *N*-benzyl-6-bromo-2-(bromomethyl)quinoline-4-carboxamide (5e)
Yield: 67%, mp: 197-199 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.46 (t, J = 5.7 Hz, 1H), 8.29 (d, J = 2.1 Hz, 1H), 8.04-7.94 (m, 2H), 7.81 (s, 1H), 7.44-7.28 (m, 5H), 4.88 (s, 2H), 4.57 (d, J = 6 Hz, 2H). ESI-MS m/z: 435.1 $[M+H]^+$.

5.1.23. *N*-phenyl-6-bromo-2-(bromomethyl)quinoline-4-carboxamide (5f)
Yield: 70%, mp: 196-198 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.32 (d, J = 2 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.02 (dd, J_1 = 8.8 Hz, J_2 = 2.2 Hz, 1H), 7.96 (s, 1H), 7.80 (d, J = 8 Hz, 2H), 7.42 (t, J = 8 Hz, 2H), 7.18 (t, J = 8 Hz, 1H), 5.02 (s, 2H). ESI-MS m/z: 421.1 $[M+H]^+$.

5.1.24. 2-(bromomethyl)quinoline (5g)
Yield: 45%, mp: 56-58 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.80 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.74-7.70 (m, 1H), 7.57-7.52 (m, 2H), 4.71 (s, 2H); ESI-MS m/z: 223.1 $[M+H]^+$.

5.1.25. 2-(bromomethyl)-6-fluoroquinoline (5h)
Yield: 43%, mp: 75-77 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 8.8 Hz, 1H), 8.04 (dd, J_1 = 9.2 Hz, J_2 = 5.6 Hz, 1H), 7.80 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 7.74-7.68 (m, 1H), 7.66 (d, J = 2.8 Hz, 1H), 4.74 (s, 2H); ESI-MS m/z: 241.1 $[M+H]^+$.

5.1.26. 2-(bromomethyl)-6-chloroquinoline (5i)
Yield: 60%, mp: 110-112 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.77-7.72 (m, 1H), 4.87 (s, 2H). ESI-MS m/z: 257.5 $[M+H]^+$.

5.1.27. 6-bromo-2-(bromomethyl)quinoline (5j)
Yield: 48%, mp: 144-146 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.42 (d, J = 8.7 Hz, 1H), 8.31 (d, J = 1.8 Hz, 1H), 7.96-7.91 (m, 2H), 7.75 (d, J = 8.7 Hz, 1H), 4.85 (s, 2H). ESI-MS m/z: 302.0 $[M+H]^+$.

5.1.28. 2-(bromomethyl)-6-iodoquinoline (5k)
Yield: 50%, mp: 156-158 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.42 (d, J = 8.7 Hz, 1H), 8.31 (d, J = 1.8 Hz, 1H), 7.96-7.91 (m, 2H), 7.75 (d, J = 8.7 Hz, 1H), 4.85 (s, 2H). ESI-MS m/z: 349.0 $[M+H]^+$.

5.1.29. 2-(aminomethyl)-*N*-benzylquinoline-4-carboxamide (6a)

NaN_3 (0.65 g, 10 mmol) was added carefully to a solution of **5a** (1.78 g, 5 mmol) in DMF (10 mL). The reaction was stirred overnight at room temperature. The reaction mixture was extracted with EtOAc/H_2O. Then the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solution was evaporated under vacuum to give the crude product 2-(azidomethyl)-*N*-benzylquinoline-4-carboxamide.

PPh_3 (1.57 g, 6 mmol) was added to a solution of 2-(azidomethyl)-*N*-benzylquinoline-4-carboxamide in TFH/H_2O (20 mL, 9:1). Five hours later, the solution was concentrated under vacuum and the residue was added to 1MHCl (20 mL). The mixture was stirred for 30 min, then the mixture was filtered to get aqueous phase. The aqueous phase was basified to pH 10 by the $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the solution was evaporated under vacuum to give target compound **6a** without purification for next procedure.

Compounds **6b-6k** were synthesized by the same method described above.

The general synthesis method for **8a-8y**:

Method A:

To a solution of **7a** (0.73 g, 5 mmol) and Et_3N (1.3 mL, 10 mmol) in the anhydrous CH_2Cl_2 (150 mL) was added HOBT (0.81 g, 6 mmol), followed by EDCI (1.15 g, 6 mmol) at 0 ℃. After 1 h, compound **6a** (2.19 g, 7.5 mmol) was added, and the mixture was stirred vigorously overnight at room temperature. The mixture was washed with 10% citric acid (3 × 80 mL), saturated $NaHCO_3$ (3 × 80 mL) and brine (3 × 80 mL), dried over with $MgSO_4$, and the solution was evaporated under vacuum to give the crude product. The crude product was depurated by column chromatography to afford compound **8a** as a white solid.

Method B:

A solution of **7a** (0.73 g, 5 mmol) in $SOCl_2$ (4 mL) was refluxed for 1.5 h. The removal of $SOCl_2$ under reduced pressure yielded orange oil, which was dissolved in THF (15 mL). The resulting solution was added dropwise to a solution of **6a** (2.19 g, 7.5 mmol) and Et_3N (1.3 mL, 10 mmol) in THF (100 mL) at 0 °C. The resulting reaction mixture was stirred overnight at room temperature. The resultant solution was filtered. The filtrate was concentrated, dissolved in CH_2Cl_2 (150 mL), and washed with 10% citric acid (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL) and brine (3 × 50 mL), dried over with $MgSO_4$, and the solution was evaporated under vacuum. The crude product was purified by column chromatography to afford compound **8a** as a white solid.

5.1.30. Methyl 5-(((4-(benzylcarbamoyl)quinolin-2-yl)methyl)amino)-5-oxo pentanoate (8a)

Yield: 62%, mp: 152-154 ℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.31 (t, J = 6 Hz, 1H),

8.55 (t, *J* = 6 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 8.03 (d, *J* = 8 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.48 (s, 1H), 7.42-7.29 (m, 5H), 4.57-4.55 (m, 4H), 3.59 (s, 3H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 1.83-1.80 (m, 2H). ESI-MS m/z: 420.5 $[M+H]^+$.

5.1.31. Methyl 6-(((4-(benzylcarbamoyl)quinolin-2-yl)methyl)amino)-6-oxo hexanoate (8b)

Yield: 49%, mp: 122-124 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.31 (t, *J* = 6 Hz, 1H), 8.54 (t, *J* = 6 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 8.02 (d, *J* = 8 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.47 (s, 1H), 7.39-7.36 (m, 4H), 7.31-7.27 (m, 1H), 4.56 (d, *J* = 6 Hz, 4H), 3.58 (s, 3H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.58-1.52 (m, 4H). ESI-MS m/z: 434.6 $[M+H]^+$.

5.1.32. Methyl 7-(((4-(benzylcarbamoyl)quinolin-2-yl)methyl)amino)-7-oxo heptanoate (8c)

Yield: 37%, mp: 119-120 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.32 (t, *J* = 6 Hz, 1H), 8.53 (t, *J* = 6 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 8.02 (d, *J* = 8 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.47 (s, 1H), 7.41-7.36 (m, 4H), 7.31-7.27 (m, 1H), 4.56 (d, *J* = 6 Hz, 4H), 3.58 (s, 3H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.58-1.49 (m, 4H), 1.32-1.30 (m, 2H). ESI-MS m/z: 448.5 $[M+H]^+$.

5.1.33. Methyl 8-(((4-(benzylcarbamoyl)quinolin-2-yl)methyl)amino)-8-oxo octanoate (8d)

Yield: 63%, mp: 150-152 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.34 (t, *J* = 6 Hz, 1H), 8.54 (t, *J* = 6 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.47 (s, 1H), 7.41-7.32 (m, 4H), 7.30-7.26 (m, 1H), 4.55 (d, *J* = 6 Hz, 4H), 3.57 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.57-1.46 (m, 4H), 1.28-1.26 (m, 4H). ESI-MS m/z: 462.5 $[M+H]^+$.

5.1.34. Methyl 9-(((4-(benzylcarbamoyl)quinolin-2-yl)methyl)amino)-9-oxo nonanoate (8e)

Yield: 56%, mp: 136-137 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.34 (t, *J* = 6 Hz, 1H), 8.55 (t, *J* = 6 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8 Hz, 1H), 7.79 (t, *J* = 8.4 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.48 (s, 1H), 7.42-7.29 (m, 5H), 4.57-4.55 (m, 4H), 3.57 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 1.56-1.48 (m, 4H), 1.26 (m, 6H). ESI-MS m/z: 476.6 $[M+H]^+$.

5.1.35. Methyl 7-oxo-7-(((4-(phenylcarbamoyl)quinolin-2-yl)methyl)amino) heptanoate (8f)

Yield: 83%, mp: 120-122 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.57 (t, *J* = 6 Hz, 1H), 8.08-8.04 (m, 2H), 7.85-7.76 (m, 3H), 7.65 (t, *J* = 8.3 Hz, 1H), 7.58 (s, 1H), 7.39 (t, *J* = 8 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 4.61 (d, *J* = 6 Hz, 2H), 3.55 (s, 3H), 2.28-2.19 (m, 4H), 1.60-1.47 (m, 4H), 1.33-1.24 (m, 2H). ESI-MS m/z: 434.6 $[M+H]^+$.

5.1.36. Methyl 8-oxo-8-(((4-(phenylcarbamoyl)quinolin-2-yl)methyl)amino) octanoate (8g)

Yield: 35%, mp: 128-130 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.57 (t, J = 6 Hz, 1H), 8.08-8.04 (m, 2H), 7.85-7.76 (m, 3H), 7.65 (t, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.39 (t, J = 7.1 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 4.61 (d, J = 6 Hz, 2H), 3.57 (s, 3H), 2.31-2.16 (m, 4H), 1.57-1.43 (m, 4H), 1.27-1.25 (m, 4H). ESI-MS m/z: 448.5 $[M+H]^+$.

5.1.37. Methyl 7-(((4-(butylcarbamoyl)quinolin-2-yl)methyl)amino)-7-oxo heptanoate (8h)

Yield: 40%, mp: 120-122 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.74 (t, J = 5.4 Hz, 1H), 8.54 (t, J = 6 Hz, 1H), 8.02 (t, J = 7.8 Hz, 2H), 7.78 (t, J = 8.4 Hz, 1H), 7.61 (t, J = 8.3 Hz, 1H), 7.39 (s, 1H), 4.56 (d, J = 6 Hz, 2H), 3.58 (s, 3H), 3.36-3.30 (m, 2H), 2.29 (t, J = 7.4 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.61-1.53 (m, 6H), 1.51-1.32 (m, 2H), 1.29-1.21 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ESI-MS m/z: 414.5 $[M+H]^+$.

5.1.38. Methyl 8-(((4-(butylcarbamoyl)quinolin-2-yl)methyl)amino)-8-oxo octanoate (8i)

Yield: 22%, mp: 116-118 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.73 (t, J = 5.6 Hz, 1H), 8.52 (t, J = 5.9 Hz, 1H), 8.02 (t, J = 9 Hz, 2H), 7.78 (t, J = 8.4 Hz, 1H), 7.61 (t, J = 8.3 Hz, 1H), 7.39 (s, 1H), 4.56 (d, J = 5.7 Hz, 2H), 3.58 (s, 3H), 3.36-3.30 (m, 2H), 2.28 (t, J = 7.4 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.60-1.44 (m, 6H), 1.42-1.32 (m, 2H), 1.29-1.26 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H). ESI-MS m/z: 428.6 $[M+H]^+$.

5.1.39. Methyl 7-(((4-(methylcarbamoyl)quinolin-2-yl)methyl)amino)-7-oxo heptanoate (8j)

Yield: 58%, mp: 156-158 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.70 (q, J = 4.8 Hz, 1H), 8.53 (t, J = 6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.78 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 8.3 Hz, 1H), 7.42 (s, 1H), 4.56 (d, J = 6 Hz, 2H), 3.58 (s, 3H), 2.87 (d, J = 4.5 Hz, 3H), 2.29 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.61-1.48 (m, 4H), 1.34-1.24 (m, 2H). ESI-MS m/z: 372.4 $[M+H]^+$.

5.1.40. Methyl 8-(((4-(methylcarbamoyl)quinolin-2-yl)methyl)amino)-8-oxo octanoate (8k)

Yield: 47%, mp: 136-138 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.70 (q, J = 4.8 Hz, 1H), 8.53 (t, J = 6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.78 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 8.3 Hz, 1H), 7.41 (s, 1H), 4.56 (d, J = 6 Hz, 2H), 3.58 (s, 3H), 2.86 (d, J = 4.8 Hz, 3H), 2.28 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.57-1.47 (m, 4H), 1.33-1.25 (m, 4H). ESI-MS m/z: 386.6 $[M+H]^+$.

5.1.41. Methyl 7-(((4- (benzylcarbamoyl)-6-bromoquinolin-2-yl)methyl)amino)-7-oxoheptanoate (8l)

Yield: 75%, mp: 150-152 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.44 (t, J = 6 Hz, 1H),

8.55 (t, *J* = 6 Hz, 1H), 8.26 (d, *J* = 2.1 Hz, 1H), 7.99-7.89 (m, 2H), 7.55 (s, 1H), 7.42-7.31 (m, 4H), 7.30-7.27 (m, 1H), 4.57 (d, *J* = 5.7 Hz, 4H), 3.58 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.61-1.48 (m, 4H), 1.34-1.23 (m, 2H). ESI-MS m/z: 527.4 $[M+H]^+$.

5.1.42. Methyl 8-(((4- (benzylcarbamoyl)-6-bromoquinolin-2-yl)methyl)amino)-8-oxooctanoate (8m)

Yield: 43%, mp: 146-148 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.43 (t, *J* = 5.6 Hz, 1H), 8.55 (t, *J* = 5.4 Hz, 1H), 8.26 (s, 1H), 7.98-7.92 (m, 2H), 7.55 (s, 1H), 7.40-7.30 (m, 5H), 4.57 (d, *J* = 5.6 Hz, 4H), 3.58 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.55-1.49 (m, 4H), 1.28 (m, 4H). ESI-MS m/z: 541.5 $[M+H]^+$.

5.1.43. Methyl 9-(((4- (benzylcarbamoyl)-6-bromoquinolin-2-yl)methyl)amino)-9-oxononanoate (8n)

Yield: 65%, mp: 156-158 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.43 (t, *J* = 6 Hz, 1H), 8.55 (t, *J* = 5.8 Hz, 1H), 8.25 (d, *J* = 2 Hz, 1H), 7.98-7.91 (m, 2H), 7.55 (s, 1H), 7.41-7.30 (m, 5H), 4.56 (d, *J* = 6 Hz, 4H), 3.57 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 1.56-1.46 (m, 4H), 1.26 (m, 6H). ESI-MS m/z: 555.5 $[M+H]^+$.

5.1.44. Methyl 7-(((6-bromo-4- (phenylcarbamoyl)quinolin-2-yl)methyl)amino)-7-oxoheptanoate (8o)

Yield: 80%, mp: 162-164 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.58 (t, *J* = 6 Hz, 1H), 8.27 (d, *J* = 2 Hz, 1H), 8.02-7.95 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.67 (s, 1H), 7.41 (t, *J* = 8 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.60 (d, *J* = 6 Hz, 2H), 3.57 (s, 3H), 2.28-2.20 (m, 4H), 1.59-1.48 (m, 4H), 1.32-1.24 (m, 2H). ESI-MS m/z: 513.4 $[M+H]^+$.

5.1.45. Methyl 8-(((6-bromo-4- (phenylcarbamoyl)quinolin-2-yl)methyl)amino)-8-oxooctanoate (8p)

Yield: 67%, mp: 168-170 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.58 (t, *J* = 6 Hz, 1H), 8.27 (d, *J* = 2 Hz, 1H), 8.02-7.95 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.66 (s, 1H), 7.40 (t, *J* = 8 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.60 (d, *J* = 6 Hz, 2H), 3.56 (s, 3H), 2.25-2.19 (m, 4H), 1.58-1.44 (m, 4H), 1.27-1.24 (m, 4H). ESI-MS m/z: 527.4 $[M+H]^+$.

5.1.46. Methyl 5-oxo-5- ((quinolin-2-ylmethyl) amino)pentanoate (8q)

Yield: 45%, mp: 101-102 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 4.54 (d, *J* = 6 Hz, 2H), 3.60 (s, 3H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.25 (t, *J* = 7.4 Hz, 2H), 1.81 (m, 2H). ESI-MS m/z: 287.3 $[M+H]^+$.

5.1.47. Methyl 6-oxo-6- ((quinolin-2-ylmethyl) amino) hexanoate (8r)

Yield: 15%, mp: 88-90 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (t, *J* = 5.9 Hz, 1H),

8.34 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.78-7.72 (m, 1H), 7.60-7.55 (m, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 4.54 (d, *J* = 6 Hz, 2H), 3.58 (s, 3H), 2.33 (t, *J* = 6.9 Hz, 2H), 2.22 (t, *J* = 6.8 Hz, 2H), 1.56 (m, 4H). ESI-MS m/z: 301.5 $[M+H]^+$.

5.1.48. Methyl 7-oxo-7- ((quinolin-2-ylmethyl) amino) heptanoate (8s)
Yield: 26%, mp: 88-89 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (t, *J* = 5.7 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.78-7.71 (m, 1H), 7.60-7.55 (m, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 4.54 (d, *J* = 6 Hz, 2H), 3.58 (s, 3H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.61-1.49 (m, 4H), 1.34-1.23 (m, 2H). ESI-MS m/z: 315.3 $[M+H]^+$.

5.1.49. Methyl 8-oxo-8- ((quinolin-2-ylmethyl) amino) octanoate (8t)
Yield: 61%, mp: 86-88 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (t, *J* = 6 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.97-7.94 (m, 2H), 7.78-7.72 (m, 1H), 7.60-7.55 (m, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 4.54 (d, *J* = 6 Hz, 2H), 3.58 (s, 3H), 2.28 (t, *J* = 7.35 Hz, 2H), 2.20 (t, *J* = 7.35 Hz, 2H), 1.54-1.49 (m, 4H), 1.30-1.25 (m, 4H). ESI-MS m/z: 329.5 $[M+H]^+$.

5.1.50. Methyl 7- (((6-fluoroquinolin-2-yl)methyl)amino)-7-oxoheptanoate (8u)
Yield: 71%, mp: 72-74 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.54 (t, *J* = 6 Hz, 1H), 8.34 (d, *J* = 8.8 Hz, 1H), 8.04-8.00 (m, 1H), 7.79 (dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H), 7.69 (td, J_1 = 8.1 Hz, J_2 = 2.8 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 4.53 (d, *J* = 6 Hz, 2H), 3.58 (s, 3H), 2.29 (t, *J* = 7.2 Hz, 2H), 2.20 (t, *J* = 7.2 Hz, 2H), 1.59-1.50 (m, 4H), 1.32-1.29 (m, 2H). ESI-MS m/z: 333.4 $[M+H]^+$.

5.1.51. Methyl 7- (((6-chloroquinolin-2-yl)methyl)amino)-7-oxoheptanoate (8v)
Yield: 92%, mp: 88-90 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.52 (t, *J* = 6 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 7.99 (d, *J* = 9 Hz, 1H), 7.77-7.73 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 4.53 (d, *J* = 6 Hz, 2H), 3.58 (s, 3H), 2.29 (t, *J* = 7.2 Hz, 2H), 2.20 (t, *J* = 7.2 Hz, 2H), 1.60-1.49 (m, 4H), 1.33-1.17 (m, 2H). ESI-MS m/z: 349.9 $[M+H]^+$.

5.1.52. Methyl 7- (((6-bromoquinolin-2-yl)methyl)amino)-7-oxoheptanoate (8w)
Yield: 50%, mp: 92-94 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.52 (t, *J* = 5.9 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 1.8 Hz, 1H), 7.92-7.84 (m, 2H), 7.49 (d, *J* = 8.7 Hz, 1H), 4.52 (d, *J* = 5.7 Hz, 2H), 3.58 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.60-1.49 (m, 4H), 1.33-1.24 (m, 2H). ESI-MS m/z: 394.3 $[M+H]^+$.

5.1.53. Methyl 8- (((6-bromoquinolin-2-yl)methyl)amino)-8-oxooctanoate (8x)
Yield: 43%, mp: 104-106 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.53 (t, *J* = 5.9 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 7.92-7.84 (m, 2H), 7.50 (d, *J* = 8.7 Hz, 1H), 4.53 (d, *J* = 6 Hz, 2H), 3.58 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.54-1.49 (m, 4H), 1.30-1.26 (m, 4H). ESI-MS m/z: 408.3 $[M+H]^+$.

5.1.54. Methyl 7- (((6-iodoquinolin-2-yl)methyl)amino)-7-oxoheptanoate (8y)

Yield: 86%, mp: 79-80 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.53 (t, J = 6 Hz, 1H), 8.43 (d, J = 1.8 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.00 (dd, J_1 = 9 Hz, J_2 = 1.8 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 4.52 (d, J = 6 Hz, 2H), 3.58 (s, 3H), 2.29 (t, J = 7.2 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.60-1.47 (m, 4H), 1.33-1.23 (m, 2H). ESI-MS m/z: 441.4 $[M+H]^+$.

5.1.55. N^1-((4-(benzylcarbamoyl)quinolin-2-yl)methyl)-N^5-hydroxyglutaramide (9a)

Preparation of hydroxylamine in methanol:

To a solution of hydroxylamine hydrochloride (4.67 g, 67 mmol) in methanol (24 mL) at 0 °C was added slowly dropwise potassium hydroxide (6.60 g, 100 mmol) in methanol (14 mL). The reaction mixture was stirred at 0 °C for 0.5 h and filtered to give a solution of hydroxylamine in methanol.

Compound **8a** (0.32 g, 0.77 mmol) was dissolved in the solution of hydroxylamine in methanol (8 mL), and then the reaction mixture was stirred at room temperature for 1 h. The mixture was acidified with 2M HCl to pH 7. The mixture was filtrated to give a residue and purified by chromatography on silica gel to give **9a** (0.15 g, 47%) as a white solid. Mp: 174-175 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.33 (t, J = 6 Hz, 1H), 8.69 (s, 1H), 8.53 (t, J = 6 Hz, 1H), 8.07-8.00 (m, 2H), 7.80 (t, J = 8.2 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.48 (s, 1H), 7.42-7.32 (m, 4H), 7.30-7.26 (m, 1H), 4.57 (d, J = 6 Hz, 4H), 2.24 (t, J = 7.5 Hz, 2H), 2.00 (t, J = 7.5 Hz, 2H), 1.83-1.73 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.1, 168.8, 166.7, 159.2, 147.2, 142.8, 139.1, 129.9, 128.8, 128.4, 127.3, 127.0, 126.8, 125.2, 123.2, 117.3, 44.7, 42.6, 34.7, 31.8, 21.4; HRMS (AP-ESI) m/z calcd for $C_{23}H_{24}N_4O_4$ $[M+H]^+$ 421.1870, found: 421.1867.

Compounds **9b-9y** and **11a-11b** were synthesized by the same method described above.

5.1.56. N^1-((4-(benzylcarbamoyl)quinolin-2-yl)methyl)-N^6-hydroxyadipamide(9b)

Yield: 73%, mp: 178-180 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.32 (t, J = 5.7 Hz, 1H), 8.65 (s, 1H), 8.53 (t, J = 6 Hz, 1H), 8.04 (t, J = 9 Hz, 2H), 7.80 (t, J = 8.2 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.48 (s, 1H), 7.42-7.32 (m, 4H), 7.30-7.26 (m, 1H), 4.57 (d, J = 6 Hz, 4H), 2.21 (t, J = 7.5 Hz, 2H), 1.96 (t, J = 7.5 Hz, 2H), 1.60-1.45 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.4, 169.0, 166.8, 159.2, 147.2, 142.8, 139.1, 129.9, 128.9, 128.4, 127.3, 126.9, 126.8, 125.2, 123.2, 117.3, 44.7, 42.6, 35.1, 32.1, 24.9, 24.8; HRMS (AP-ESI) m/z calcd for $C_{24}H_{26}N_4O_4$ $[M+H]^+$ 435.2027, found: 435.2024.

5.1.57. N^1-((4- (benzylcarbamoyl)quinolin-2-yl)methyl)-N^7-hydroxy heptanediamide (9c)

Yield: 83%, mp: 162-164 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1H), 9.33 (t, J = 6 Hz, 1H), 8.64 (s, 1H), 8.53 (t, J = 6 Hz, 1H), 8.07-8.00 (m, 2H), 7.80 (t, J = 8.2 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.47 (s, 1H), 7.41-7.32 (m, 4H), 7.30-7.26 (m, 1H),

4.57 (d, *J* = 6 Hz, 4H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.60-1.45 (m, 4H), 1.31-1.21 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 166.7, 159.3, 147.2, 142.8, 139.1, 129.9, 128.8, 128.4, 127.3, 126.9, 126.8, 125.2, 123.2, 117.3, 44.7, 42.6, 35.2, 32.1, 28.3, 24.9, 24.9; HRMS (AP-ESI) m/z calcd for $C_{25}H2_8N_4O_4$ $[M+H]^+$ 449.2183, found: 449.2190.

5.1.58. N^1-((4-(benzylcarbamoyl)quinolin-2-yl)methyl)-N^8-hydroxy octanediamide (9d)

Yield: 67%, mp: 150-152 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.33 (t, *J* = 6 Hz, 1H), 8.53 (t, *J* = 6 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.47 (s, 1H), 7.41-7.32 (m, 4H), 7.30-7.26 (m, 1H), 4.57 (d, *J* = 5.7 Hz, 4H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.57-1.45 (m, 4H), 1.27-1.26 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 166.7, 159.3, 147.1, 142.9, 139.1, 129.9, 128.8, 128.4, 127.3, 126.9, 126.8, 125.2, 123.2, 117.3, 44.6, 42.6, 35.3, 32.2, 28.4, 28.4, 25.2, 25.0; HRMS (AP-ESI) m/z calcd for $C_{26}H_{30}N_4O_4$ $[M+H]^+$ 463.2340, found: 463.2344.

5.1.59. N^1-((4-(benzylcarbamoyl)quinolin-2-yl)methyl)-N^9-hydroxy nonanediamide (9e)

Yield: 73%, mp: 136-137 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.34 (t, *J* = 6 Hz, 1H), 8.65 (s, 1H), 8.54 (t, *J* = 6 Hz, 1H), 8.06-8.00 (m, 2H), 7.79 (t, *J* = 6.8 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.47 (s, 1H), 7.41-7.31 (m, 5H), 4.56 (d, *J* = 5.6 Hz, 4H), 2.20 (t, *J* = 7.2 Hz, 2H), 1.93 (t, *J* = 7.2 Hz, 2H), 1.56-1.43 (m, 4H), 1.29-1.22 (m, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.6, 169.1, 166.8, 159.3, 147.2, 142.8, 139.1, 129.9, 128.8, 128.4, 127.3, 126.9, 126.8, 125.2, 123.2, 117.3, 44.7, 42.6, 35.3, 32.2, 28.6, 28.5, 28.5, 25.2, 25.1; HRMS (AP-ESI) m/z calcd for $C_{27}H_{32}N_4O_4$ $[M+H]^+$ 477.2496, found: 477.2502.

5.1.60. N^1-hydroxy-N^7-((4-(phenylcarbamoyl)quinolin-2-yl)methyl) heptanediamide (9f)

Yield: 49%, mp: 164-166 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.87 (s, 1H), 10.32 (s, 1H), 8.57 (s, 1H), 8.09-8.04 (m, 2H), 7.85-7.78 (m, 3H), 7.67-7.59 (m, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 4.61 (d, *J* = 6 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.94 (t, *J* = 7.5 Hz, 2H), 1.57-1.47 (m, 4H), 1.27 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.6, 169.1, 165.4, 159.4, 147.3, 142.8, 138.7, 130.1, 128.9, 128.9, 127.1, 125.1, 124.2, 123.0, 119.9, 117.4, 44.7, 35.2, 32.2, 28.3, 24.9, 24.9; HRMS (AP-ESI) m/z calcd for $C_{24}H_{26}N_4O_4$ $[M+H]^+$ 435.2027, found: 435.2036.

5.1.61.N^1-hydroxy-N^8-((4- (phenylcarbamoyl)quinolin-2-yl)methyl)octanediamide (9g)

Yield: 40%, mp: 176-178 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 10.30 (s, 1H), 8.63 (s, 1H), 8.55 (t, *J* = 6 Hz, 1H), 8.08-8.04 (m, 2H), 7.85-7.76 (m, 3H), 7.67 (t, *J* = 8.3 Hz, 1H), 7.58 (s, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 4.61 (d, *J* = 6 Hz, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.90 (t, *J* = 7.5 Hz, 2H),

1.57-1.41 (m, 4H), 1.25-1.24 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.6, 169.1, 165.4, 159.4, 147.2, 142.8, 138.7, 130.1, 128.9, 128.8, 127.1, 125.0, 124.1, 123.0, 119.9, 117.3, 44.7, 35.3, 32.2, 28.4, 28.4, 25.2, 24.9; HRMS (AP-ESI) m/z calcd for $C_{25}H_{28}N_4O_4$ $[M+H]^+$ 449.2183, found: 449.2189.

5.1.62.N^1-((4- (butylcarbamoyl)quinolin-2-yl)methyl)-N^7-hydroxyheptanediamide (9h)

Yield: 88%, mp: 170-172 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.75 (t, J = 5.6 Hz, 1H), 8.64 (s, 1H), 8.53 (t, J = 6 Hz, 1H), 8.04 (t, J = 8.4 Hz, 2H), 7.79 (t, J = 8.2 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.39 (s, 1H), 4.56 (d, J = 5.7 Hz, 2H), 3.37-3.31 (m, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.94 (t, J = 7.5 Hz, 2H), 1.60-1.50 (m, 6H), 1.40-1.32 (m, 2H), 1.27-1.26 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.0, 166.6, 159.3, 147.2, 143.4, 129.9, 128.8, 126.7, 125.2, 123.2, 117.1, 44.7, 38.7, 35.2, 32.1, 31.0, 28.3, 24.9, 24.9, 19.6, 13.7; HRMS (AP-ESI) m/z calcd for $C_{22}H_{30}N_4O_4$ $[M+H]^+$ 415.2340, found: 415.2334.

5.1.63. N^1-((4-(butylcarbamoyl)quinolin-2-yl)methyl)-N^8-hydroxyoctanediamide (9i)

Yield: 56%, mp: 158-160 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.75 (t, J = 5.7 Hz, 1H), 8.65 (s, 1H), 8.54 (t, J = 6 Hz, 1H), 8.02 (d, J = 7.7 Hz, 2H), 7.79 (t, J = 8.2 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.39 (s, 1H), 4.56 (d, J = 6 Hz, 2H), 3.36-3.31 (m, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 7.5 Hz, 2H), 1.60-1.50 (m, 6H), 1.40-1.32 (m, 2H), 1.27-1.26 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 166.6, 159.3, 147.2, 143.3, 129.9, 128.8, 126.7, 125.2, 123.2, 117.1, 44.7, 38.7, 35.3, 32.2, 31.0, 28.4, 25.2, 24.9, 19.6, 13.7; HRMS (AP-ESI) m/z calcd for $C_{23}H_{32}N_4O_4$ $[M+H]^+$ 429.2496, found: 429.2487.

5.1.64. N^1-hydroxy-N^7-((4- (methylcarbamoyl)quinolin-2-yl)methyl) heptanediamide (9j)

Yield: 57%, mp: 154-156 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.71 (q, J = 4.2 Hz, 1H), 8.54 (t, J = 5.7 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 8.4 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.42 (s, 1H), 4.56 (d, J = 6 Hz, 2H), 2.87 (d, J = 4.5 Hz, 3H), 2.20 (t, J = 7.5 Hz, 2H), 1.94 (t, J = 7.5 Hz, 2H), 1.57-1.45 (m, 4H), 1.37-1.24 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 167.1, 159.2, 147.2, 143.1, 129.9, 128.8, 126.7, 125.3, 123.2, 117.2, 44.7, 35.2, 32.2, 28.3, 26.0, 24.9, 24.9; HRMS (AP-ESI) m/z calcd for $C_{19}H_{24}N_4O_4$ $[M+H]^+$ 373.1870, found: 373.1867.

5.1.65. N^1-hydroxy-N^8-((4-(methylcarbamoyl)quinolin-2-yl)methyl) octanediamide (9k)

Yield: 50%, mp: 160-162 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.70 (q, J = 4.5 Hz, 1H), 8.64 (s, 1H), 8.52 (t, J = 6 Hz, 1H), 8.08 (d, J = 7.2 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.78 (t, J = 8.4 Hz, 1H), 7.61 (t, J = 8.2 Hz, 1H), 7.42 (s, 1H), 4.56 (d, J = 6 Hz, 2H), 2.87 (d, J = 4.5 Hz, 3H), 2.20 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 7.5

Hz, 2H), 1.57-1.43 (m, 4H), 1.27-1.25 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 167.1, 159.3, 147.2, 143.1, 129.9, 128.8, 126.7, 125.3, 123.2, 117.2, 44.7, 35.3, 32.2, 28.4, 26.0, 25.1, 25.0; HRMS (AP-ESI) m/z calcd for $C_{20}H_{26}N_4O_4$ $[M+H]^+$ 387.2027, found: 387.2033.

5.1.66. N^1-((4-(benzylcarbamoyl)-6-bromoquinolin-2-yl)methyl)-N^7-hydroxy heptanediamide (9l)

Yield: 37%, mp: 174-176 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 9.47 (t, J = 6 Hz, 1H), 8.59 (t, J = 6 Hz, 1H), 8.26 (d, J = 2 Hz, 1H), 7.99-7.91 (m, 2H), 7.56 (s, 1H), 7.43-7.29 (m, 5H), 4.57 (d, J = 5.6 Hz, 4H), 2.21 (t, J = 7.2 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 1.57-1.46 (m, 4H), 1.30-1.24 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.6, 169.1, 166.2, 160.1, 145.9, 141.5, 138.9, 133.0, 131.1, 128.5, 127.4, 127.3, 127.1, 124.5, 120.0, 118.5, 44.7, 42.7, 35.2, 32.2, 28.3, 24.9, 24.9; HRMS (AP-ESI) m/z calcd for $C_{25}H_{27}BrN_4O_4$ $[M+H]^+$ 527.1288, found: 527.1296.

5.1.67. N^1-((4-(benzylcarbamoyl)-6-bromoquinolin-2-yl)methyl)-N^8-hydroxy octanediamide (9m)

Yield: 70%, mp: 136-138 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 9.54 (t, J = 6 Hz, 1H), 8.66 (t, J = 5.6 Hz, 1H), 8.27 (d, J = 2 Hz, 1H), 8.00-7.93 (m, 2H), 7.60 (s, 1H), 7.42-7.29 (m, 5H), 4.57-4.55 (m, 4H), 2.22 (t, J = 7.2 Hz, 2H), 1.95 (t, J = 7.2 Hz, 2H), 1.56-1.46 (m, 4H), 1.29-1.22 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.7, 169.1, 166.1, 160.1, 145.6, 141.5, 138.9, 133.1, 130.8, 128.4, 127.4, 127.2, 127.0, 124.5, 120.0, 118.5, 44.5, 42.6, 35.2, 32.2, 28.4, 28.3, 25.1, 24.9; HRMS (AP-ESI) m/z calcd for $C_{26}H_{29}BrN_4O_4$ $[M+H]^+$ 541.1445, found: 541.1435.

5.1.68. N^1-((4-(benzylcarbamoyl)-6-bromoquinolin-2-yl)methyl)-N^9-hydroxy nonanediamide (9n)

Yield: 91%, mp: 162-164 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.44 (t, J = 6 Hz, 1H), 8.66 (s, 1H), 8.55 (t, J = 5.6 Hz, 1H), 8.25 (d, J = 2 Hz, 1H), 7.98-7.92 (m, 2H), 7.54 (s, 1H), 7.41-7.31 (m, 5H), 4.56-4.55 (m, 4H), 2.20 (t, J = 7.2 Hz, 2H), 1.93 (t, J = 7.2 Hz, 2H), 1.56-1.45 (m, 4H), 1.29-1.22 (m, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.6, 169.1, 166.1, 160.1, 145.9, 141.5, 138.9, 132.9, 131.1, 128.4, 127.4, 127.2, 127.0, 124.5, 119.9, 118.4, 44.6, 42.7, 35.3, 32.3, 28.6, 28.5, 28.5, 25.2, 25.1; HRMS (AP-ESI) m/z calcd for $C_{27}H_{31}BrN_4O_4$ $[M+H]^+$ 555.1601, found: 555.1608.

5.1.69. N^1-((6-bromo-4-(phenylcarbamoyl)quinolin-2-yl)methyl)-N^7-hydroxy heptanediamide (9o)

Yield: 92%, mp: 174-176 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 10.35 (s, 1H), 8.67 (s, 1H), 8.62 (t, J = 5.6 Hz, 1H), 8.29 (d, J = 2 Hz, 1H), 8.03-7.95 (m, 2H), 7.80 (d, J = 7.6 Hz, 2H), 7.70 (s, 1H), 7.41 (t, J = 8 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 4.60 (d, J = 6 Hz, 2H), 2.22 (t, J = 7.2 Hz, 2H), 1.93 (t, J = 7.2 Hz, 2H), 1.58-1.45 (m, 4H), 1.30-1.22 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.7, 169.1, 164.8, 160.2, 145.9, 141.3, 138.6, 133.1, 131.2, 128.8, 127.1, 124.3, 120.2,

120.1, 118.8, 44.7, 35.2, 32.2, 28.3, 24.9, 24.9; HRMS (AP-ESI) m/z calcd for $C_{24}H_{25}BrN_4O_4$ $[M+H]^+$ 513.1132, found: 513.1132.

5.1.70. N^1-((6-bromo-4-(phenylcarbamoyl)quinolin-2-yl)methyl)-N^8-hydroxy octanediamide (9p)

Yield: 93%, mp: 170-172 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 10.36 (s, 1H), 8.62 (t, J = 6 Hz, 1H), 8.29 (d, J = 1.6 Hz, 1H), 8.03-7.95 (m, 2H), 7.80 (d, J = 7.6 Hz, 2H), 7.69 (s, 1H), 7.41 (t, J = 8 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 4.61 (d, J = 5.6 Hz, 2H), 2.22 (t, J = 7.2 Hz, 2H), 1.91 (t, J = 7.2 Hz, 2H), 1.56-1.44 (m, 4H), 1.28-1.22 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.7, 169.1, 164.7, 160.2, 145.9, 141.4, 138.6, 133.2, 131.2, 128.9, 127.1, 124.3, 120.2, 120.1, 118.7, 44.7, 35.3, 32.2, 28.4, 28.4, 25.1, 24.9; HRMS (AP-ESI) m/z calcd for $C_{25}H_{27}BrN_4O_4$ $[M+H]^+$ 527.1288, found: 527.1281.

5.1.71. N^1-hydroxy-N^5-(quinolin-2-ylmethyl)glutaramide (9q)

Yield: 85%, mp: 178-180 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (d, J = 1.2 Hz, 1H), 8.71 (d, J = 1.5 Hz, 1H), 8.56 (t, J = 5.85 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.98-7.94 (m, 2H), 7.78-7.72 (m, 1H), 7.60-7.55 (m, 1H), 7.45 (d, J = 8.4 Hz, 1H), 4.54 (d, J = 6 Hz, 2H), 2.21 (t, J = 7.35 Hz, 2H), 2.00 (t, J = 7.5 Hz, 2H), 1.82-1.72 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.0, 168.8, 159.5, 146.9, 136.7, 129.6, 128.3, 127.8, 126.9, 126.1, 119.6, 44.8, 34.7, 31.8, 21.5; HRMS (AP-ESI) m/z calcd for $C_{15}H_{17}N_3O_3$ $[M+H]^+$ 288.1343, found: 288.1341.

5.1.72. N^1-hydroxy-N^6-(quinolin-2-ylmethyl)adipamide (9r)

Yield: 44%, mp: 162-164 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ10.36 (s, 1H), 8.73 (s, 1H), 8.56 (t, J = 5.85 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 7.98-7.94 (m, 2H), 7.78-7.72 (m, 1H), 7.60-7.55 (m, 1H), 7.45 (d, J = 8.4 Hz, 1H), 4.54 (d, J = 6 Hz, 2H), 2.20 (t, J = 7.35 Hz, 2H), 1.96 (t, J = 6.6 Hz, 2H), 1.53-1.51 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.4, 168.9, 159.5, 146.9, 136.6, 129.6, 128.4, 127.8, 126.8, 126.1, 119.6, 44.8, 35.1, 32.1, 24.9, 24.9; HRMS (AP-ESI) m/z calcd for $C_{16}H_{19}N_3O_3$ $[M+H]^+$ 302.1499, found: 302.1500.

5.1.73. N^1-hydroxy-N^7-(quinolin-2-ylmethyl)heptanediamide (9s)

Yield: 64%, mp: 156-158 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.69 (d, J = 1.2 Hz, 1H), 8.55 (t, J = 5.85 Hz, 1H), 8.35 (d, J = 8.7 Hz, 1H), 7.97-7.94 (m, 2H), 7.75 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 4.53 (d, J = 6 Hz, 2H), 2.20 (t, J = 7.35 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 1.59-1.45 (m, 4H), 1.30-1.20 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 159.6, 146.7, 136.9, 129.7, 128.2, 127.8, 126.9, 126.1, 119.6, 44.7, 35.2, 32.1, 28.3, 25.0, 24.9; HRMS (AP-ESI) m/z calcd for $C_{17}H_{21}N_3O_3$ $[M+H]^+$ 316.1656, found: 316.1659.

5.1.74. N^1-hydroxy-N^8-(quinolin-2-ylmethyl)octanediamide (9t)

Yield: 61%, mp: 134-136 ºC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.67 (s, 1H), 8.54 (t, J = 5.85 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 7.98-7.95 (m, 2H), 7.79 (td,

J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1H), 7.61-7.56 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 4.54 (d, J = 6 Hz, 2H), 2.20 (t, J = 7.35 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 1.57-1.43 (m, 4H), 1.27-1.25 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.6, 169.1, 159.5, 145.9, 137.6, 130.1, 127.9, 127.5, 126.9, 126.4, 119.7, 44.4, 35.3, 32.2, 28.4, 28.4, 25.1, 25.0; HRMS (AP-ESI) m/z calcd for $C_{18}H_{23}N_3O_3$ $[M+H]^+$ 330.1812, found: 330.1819.

5.1.75. N^1-((6-fluoroquinolin-2-yl)methyl)-N^7-hydroxyheptanediamide (9u)
Yield: 86%, mp: 181-182 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.67 (d, J = 1.5 Hz, 1H), 8.52 (t, J = 6 Hz, 1H), 8.35 (d, J = 8.7 Hz, 1H), 8.05-8.00 (m, 1H), 7.78 (dd, J_1 = 9.3 Hz, J_2 = 3 Hz, 1H), 7.67 (td, J_1 = 10.5 Hz, J_2 = 3 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 4.53 (d, J = 6 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 1.59-1.45 (m, 4H), 1.30-1.20 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.2, 159.4 (d, J = 243.1 Hz), 159.2 (d, J = 26 Hz), 144.1, 136.3, 136.2, 131.1 (d, J = 9.2 Hz), 127.5 (d, J = 10.3 Hz), 120.4, 119.5 (d, J = 25.6 Hz), 110.9 (d, J = 21.6 Hz), 44.7, 35.2, 32.2, 28.3, 25.0, 24.9; HRMS (AP-ESI) m/z calcd for $C_{17}H_{20}FN_3O_3$ $[M+H]^+$ 334.1561, found: 334.1553.

5.1.76. N^1-((6-chloroquinolin-2-yl)methyl)-N^7-hydroxyheptanediamide (9v)
Yield: 84%, mp: 179-180 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.67 (s, 1H), 8.53 (t, J = 6 Hz, 1H), 8.34 (d, J = 8.7 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.99 (d, J = 9 Hz, 1H), 7.78 (dd, J_1 = 9 Hz, J_2 = 2.4 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 4.53 (d, J = 5.7 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.94 (t, J = 7.5 Hz, 2H), 1.59-1.45 (m, 4H), 1.30-1.21 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.6, 169.1, 160.3, 145.4, 136.0, 130.5, 130.4, 130.1, 127.6, 126.5, 120.6, 44.8, 35.2, 32.2, 28.3, 25.0, 24.9; HRMS (AP-ESI) m/z calcd for $C_{17}H_{20}ClN_3O_3$ $[M+H]^+$350.1266, found: 350.1262.

5.1.77. N^1-((6-bromoquinolin-2-yl)methyl)-N^7-hydroxyheptanediamide (9w)
Yield: 90%, mp: 180-182 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.65 (d, J = 1.5 Hz, 1H), 8.51 (t, J = 6 Hz, 1H), 8.34 (d, J = 8.7 Hz, 1H), 8.25 (d, J = 2.1 Hz, 1H), 7.92-7.84 (m, 2H), 7.49 (d, J = 8.7 Hz, 1H), 4.52 (d, J = 5.7 Hz, 2H), 2.19 (t, J = 7.5 Hz, 2H), 1.94 (t, J = 7.5 Hz, 2H), 1.59-1.45 (m, 4H), 1.31-1.21 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 160.3, 145.5, 135.9, 132.6, 130.6, 129.8, 128.2, 120.5, 118.9, 44.8, 35.2, 32.2, 28.3, 25.0, 24.9; HRMS (AP-ESI) m/z calcd for $C_{17}H_{20}BrN_3O_3$ $[M+H]^+$ 394.0761, found: 394.0766.

5.1.78. N^1-((6-bromoquinolin-2-yl)methyl)-N^8-hydroxyoctanediamide (9x)
Yield: 71%, mp: 158-160 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.51 (t, J = 5.7 Hz, 1H), 8.34 (d, J = 8.7 Hz, 1H), 8.25 (d, J = 1.8 Hz, 1H), 7.92-7.84 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H), 4.52 (d, J = 6 Hz, 2H), 2.19 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 7.5 Hz, 2H), 1.56-1.46 (m, 4H), 1.27-1.24 (m, 4H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.6, 169.1, 160.3, 145.3, 136.0, 132.7, 130.4, 129.8, 128.2, 120.5, 118.9, 44.7, 35.3, 32.2, 28.4, 28.4, 25.2, 25.0; HRMS (AP-ESI) m/z calcd for $C_{18}H_{22}BrN_3O_3$ $[M+H]^+$ 408.0917, found: 408.0936.

5.1.79. N^1-hydroxy-N^7-((6-iodoquinolin-2-yl)methyl)heptanediamide (9y)

Yield: 95%, mp: 160-162 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.66 (d, J = 1.2 Hz, 1H), 8.51 (t, J = 6 Hz, 1H), 8.42 (d, J = 1.5 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.01 (dd, J_1 = 9 Hz, J_2 = 1.8 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 4.51 (d, J = 5.7 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 1.59-1.45 (m, 4H), 1.30-1.23 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 160.3, 137.9, 136.3, 135.6, 131.5, 131.4, 130.3, 128.8, 128.7, 120.3, 44.8, 35.2, 32.2, 28.3, 25.0, 24.9. HRMS (AP-ESI) m/z calcd for $C_{17}H_{20}IN_3O_3$ $[M+H]^+$ 442.0622, found: 442.0613.

5.1.80. Methyl 7-(((4-(benzylcarbamoyl)-6-phenylquinolin-2-yl)methyl)amino)-7-oxoheptanoate (10a)

To a nitrogen degassed solution of compound **8l** (0.55 g, 1.1 mmol) in toluene (25 mL) were successively added phenylboronic acid (0.16 g, 1.3 mmol), sodium carbonate (0.35 g, 3.3 mmol), PPh_3 (0.05 epuiv) and $Pd(OAc)_2$ (0.05 equiv). The reaction mixture was refluxed overnight. And water (100 mL) was added. After extraction with EtOAc (3*50 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography to afford white solid **10a** (0.17 g, 30%). Mp: 155-157 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.42 (t, J = 6 Hz, 1H), 8.58 (t, J = 6 Hz, 1H), 8.19 (d, J = 2.4 Hz, 1H), 8.14-8.11 (m, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.54-7.50 (m, 3H), 7.45-7.43 (m, 3H), 7.41-7.40 (m, 3H), 7.35-7.30 (m, 1H), 4.58-4.54 (m, 4H), 3.58 (s, 3H), 2.30 (t, J = 7.4 Hz, 2H), 2.22 (t, J = 7.2 Hz, 2H), 1.60-1.49 (m, 4H), 1.34-1.26 (m, 2H). ESI-MS m/z: 524.8 $[M+H]^+$.

Compound **10b** was synthesized by the same method described above.

5.1.81. Methyl 7-oxo-7-(((6-phenylquinolin-2-yl)methyl)amino)heptanoate (10b)

Yield: 60%, mp: 112-114 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.53 (t, J = 6 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 1.2 Hz, 1H), 8.11-8.02 (m, 2H), 7.85-7.82 (m, 2H), 7.55-7.40 (m, 4H), 4.55 (d, J = 6 Hz, 2H), 3.58 (s, 3H), 2.21 (t, J = 7.5 Hz, 2H), 1.95 (t, J = 7.5 Hz, 2H), 1.62-1.49 (m, 4H), 1.35-1.27 (m, 2H). ESI-MS m/z: 391.5 $[M+H]^+$.

5.1.82. N^1-((4-(benzylcarbamoyl)-6-phenylquinolin-2-yl)methyl)-N^7-hydroxy heptanediamide (11a)

Yield: 76%, mp: 174-176 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.45 (t, J = 6 Hz, 1H), 8.68 (s, 1H), 8.59 (t, J = 6 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 8.12-8.11 (m, 1H), 7.67 (d, J = 7.2 Hz, 2H), 7.53-7.46 (m, 3H), 7.41-7.40 (m, 3H), 7.39-7.37 (m, 3H), 7.34-7.31 (m, 1H), 4.59-4.57 (m, 4H), 2.22 (t, J = 7.2 Hz, 2H), 1.95 (t, J = 7.2 Hz, 2H), 1.58-1.49 (m, 4H), 1.31-1.24 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.5, 169.1, 166.7, 159.5, 146.6, 143.1, 139.2, 139.2, 138.2, 129.2, 128.5, 128.4, 127.9, 127.5, 127.4, 127.1, 126.9, 123.4, 122.3, 117.7, 44.7, 42.7, 35.2, 32.2, 28.3, 25.0, 24.9; HRMS (AP-ESI) m/z calcd for $C_{31}H_{32}N_4O_4$ $[M+H]^+$ 525.2496, found: 525.2502.

5.1.83. N^1-hydroxy-N^7-((6-phenylquinolin-2-yl)methyl)heptanediamide (11b)
Yield: 64%, mp: 158-160 ºC. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.65 (s, 1H), 8.52 (t, J = 6 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 1.2 Hz, 1H), 8.11-8.02 (m, 2H), 7.85-7.82 (m, 2H), 7.55-7.40 (m, 4H), 4.55 (d, J = 6 Hz, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.95 (t, J = 7.5 Hz, 2H), 1.61-1.46 (m, 4H), 1.32-1.27 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.4, 169.1, 159.7, 146.3, 139.3, 137.6, 137.0, 129.1, 128.9, 128.7, 127.8, 127.1, 127.0, 125.2, 120.0, 44.5, 35.2, 32.2, 28.3, 25.0, 24.9; HRMS (AP-ESI) m/z calcd for $C_{23}H_{25}N_3O_3$ $[M+H]^+$ 392.1969, found: 392.1995.

5.2. In vitro HDAC enzymatic assay

HDAC inhibitory activities of all quinoline hydroxamic acid derivatives were evaluated by the Color de Lys™ assay (BML-AK501, Enzo® Life Sciences) including HDAC1&2. Based on the HDAC kit instruction, HDAC1&2 (HeLa cell nucleus extracts), substrate and tested compounds (including positive control compound) were diluted to needed concentrations. Firstly, HDAC1&2 (15 μL/well) and tested compounds (10 μL/well) with different concentrations were incubated at 37 °C for 5 minutes in the 96-well plate. After addition of substrate (25 μL/well), the resulting mixture kept up incubating at 37 °C for 0.5 h. Nextly, the mixture (50 μL/well) of Color de Lys Developer and TSA was added. After incubation for 0.5 h, absorbance values were measured in a microtiter-plate reader at 405 nm. The inhibition rates were calculated from the ultraviolet absorption values of inhibited wells and positive control wells. Finally, the IC_{50} values were gained using a regression analysis method between the concentration and inhibition rate.

5.3. Molecular docking

Surflex-dock was used for the molecular docking of **9w** and all the parameters were set to the default except mentioned. The HDAC2 active site was gained based on the co-crystal structure of HDAC2-SAHA (PDB code: 4LXZ). Compound **9w** was optimized using concord method and then assigned with AM1-BCC charges[17]. Other detail method referred to literature.[16]

5.4. MTT Assay

MDA-MB-231 (breast cancer cell), PC-3 (prostate cancer cell), K562 (chronic myelogenous leukaemia cell) and A549 (lung cancer cell) were respectively cultured in RPMI1640 medium (10% FBS) at 37 °C in 5% CO_2 humid incubator. Cell anti-proliferative assay was determined by MTT [(3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2H-tetrazolium bromide)] method. Medium (100 μL/well) including cancer cells (4000 cells/well) was plated in 96-well plates. After incubation for 8 h, different concentrations of inhibitors (100 μL/well) were added. Followed by 48 h incubation, 0.5% MTT (10 μL/well) was used. After 4 h, DMSO (150 μL) was added and rocked for 10 min at 37 °C in a shaker. At last, the optical density values were read with a microtiter-plate reader at 570 nm.

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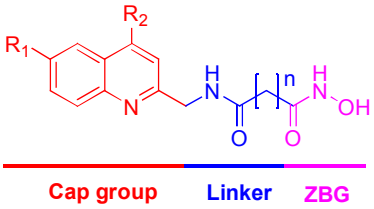
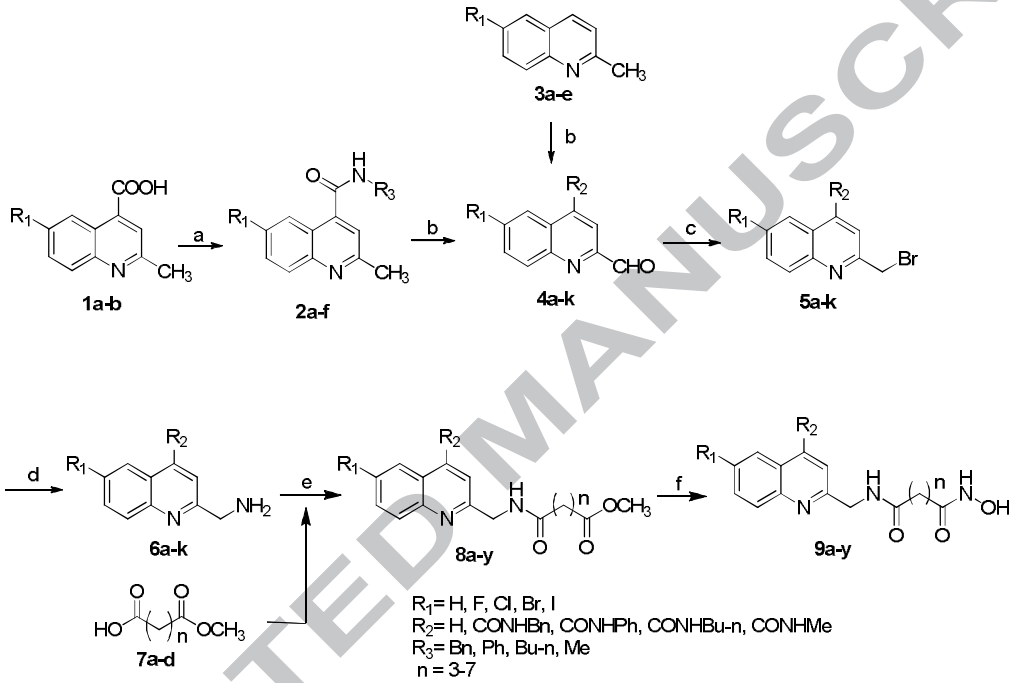
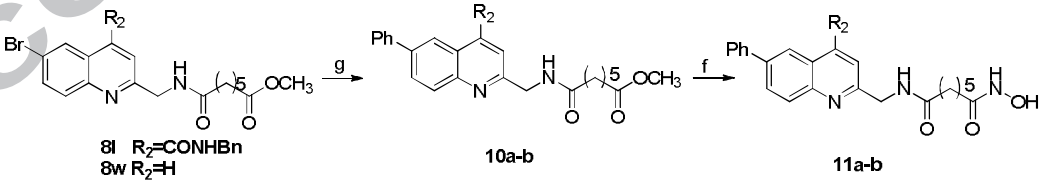


Fig.1 HDAC inhibitor pharmacophore model and our substituted quinoline hydroxamic acid derivative



Scheme 1. Reagents and conditions: (a) EDCI, HOBT, Et_3N, CH_2Cl_2, substituted aniline, 0 °C to rt, overnight; (b) SeO_2, 1,4-dixoane, reflux, 1 h; (c) (i) $NaBH_4$, MeOH, rt, 15 min; (ii) PBr_3, CH_2Cl_2, rt, overnight; (d) (i) NaN_3, DMF, rt, overnight; (ii) PPh_3, THF, rt, 5 h; (e) EDCI, HOBT, Et_3N, CH_2Cl_2, 0 °C to RT, overnight; (f) $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 1 h.



Scheme 2. Reagents and conditions: (g) $Pd(OAc)_2$, PPh_3, phenylboronic acid, Na_2CO_3, toluene, reflux, overnight; (f) $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 1 h.

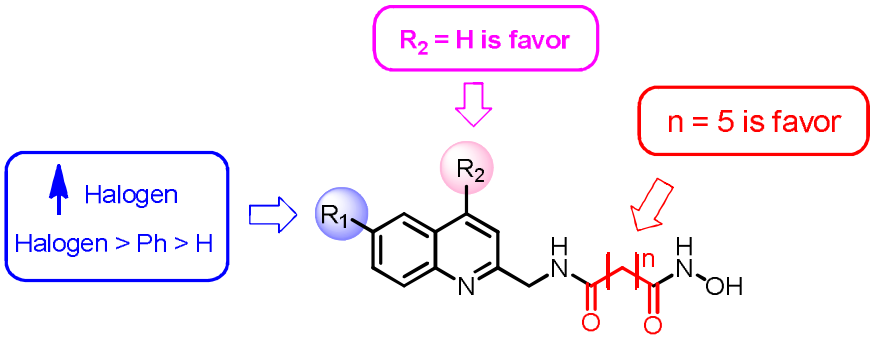


Figure 2. Compounds SARs analysis.

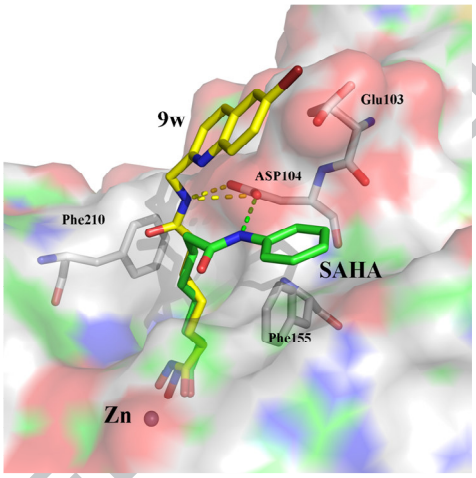
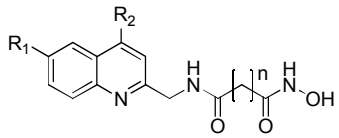


Figure 3 The molecular binding mode of compound **9w** and SAHA in the active site of HDAC2 using surflex dock software

Tab.1 the structures and HDACs inhibitory activities of quinoline hydroxamate derivatives



Compd	R_1	R_2	n	IC_{50}[a] of HDACs (nM)
9a	H	-CONHBn	3	> 1000
9b	H	-CONHBn	4	> 1000
9c	H	-CONHBn	5	399 ± 26
9d	H	-CONHBn	6	780 ± 285
9e	H	-CONHBn	7	> 1000
9f	H	-CONHPh	5	301 ± 166
9g	H	-CONHPh	6	562 ± 177
9h	H	-CONHBu-n	5	444 ± 40
9i	H	-CONHBu-n	6	> 1000
9j	H	-CONHMe	5	642 ± 237
9k	H	-CONHMe	6	> 1000
9l	Br	-CONHBn	5	343 ± 86
9m	Br	-CONHBn	6	> 1000
9n	Br	-CONHBn	7	> 1000
9o	Br	-CONHPh	5	196 ± 43
9p	Br	-CONHPh	6	> 1000
9q	H	H	3	> 1000
9r	H	H	4	> 1000
9s	H	H	5	266 ± 110
9t	H	H	6	678 ± 332
9u	F	H	5	155 ± 58
9v	Cl	H	5	120 ± 15
9w	Br	H	5	85 ± 32
9x	Br	H	6	146 ± 31
9y	I	H	5	132 ± 29
11a	Ph	-CONHBn	5	341 ± 46
11b	Ph	H	5	152 ± 43
SAHA				161 ± 51

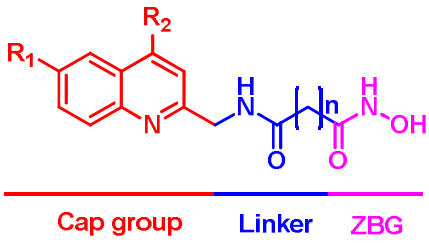
[a] Values are the mean of three independent determinations and expressed with standard deviations.

Tab.2 Anti-proliferative activities against MDA-MB231, PC3, K562 and A549 cell lines

Compd.	$IC_{50}(\mu M)^a$			
	MDA-MB-231	PC-3	K562	A549
9v	1.84 ± 0.11	9.13 ± 1.91	3.39 ± 0.38	2.71 ± 0.34
9w	0.90 ± 0.25	9.26 ± 0.50	4.86 ± 1.38	3.89 ± 0.72
9y	1.41 ± 0.37	8.48 ± 1.29	2.45 ± 0.59	2.58 ± 0.31
SAHA	2.02 ± 0.30	7.30 ± 0.20	3.94 ± 0.39	5.32 ± 1.64

[a] Values are the mean of three independent determinations and expressed with standard deviations.

Graphic Abstract



	R_1	R_2	n	HDACs (nM)	anti-proliferative activities (μM)			
					MDA-MB-231	PC-3	K562	A549
9w	Br	H	5	85	0.90	9.26	4.86	3.89
9y	I	H	5	132	1.41	8.48	2.45	2.58
SAHA				161	2.02	7.30	3.94	5.32