

Supporting Information

Design, synthesis, and biological evaluation of tetrahydroisoquinoline-based histone deacetylase 8 selective inhibitors

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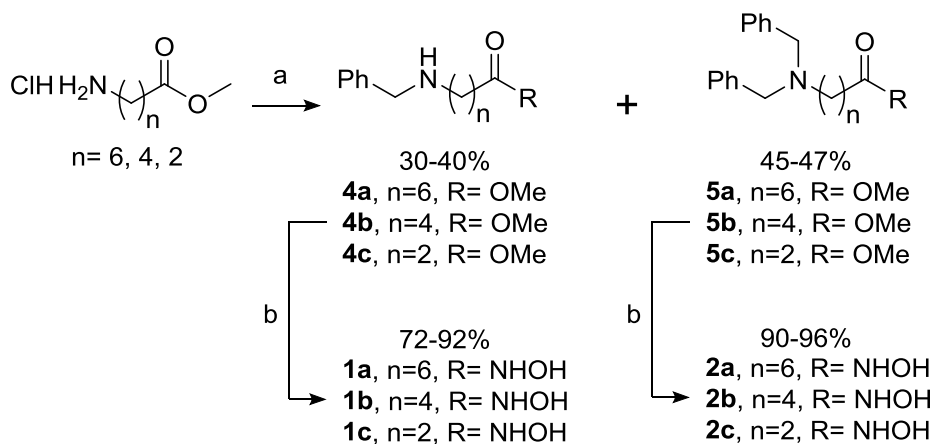
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Chemical methods and experimental

General materials and methods: All reagents and solvents were obtained from commercial sources and used without further purification. ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers at 400 MHz and 100 MHz, respectively. Chemical shifts were reported on δ scale in ppm with solvent indicated as the internal reference. Coupling constants were reported in Hertz (Hz) and the standard abbreviations indicating multiplicity were used as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. High resolution mass spectrometry (HRMS) experiments were recorded with electrospray ionization (ESI) on Synapt G2-Si mass spectrometer. The purity of all the final compounds was confirmed to be $\geq 95\%$ by NMR (as described above) and LCMS using Shimadzu LCMS-2020 with UV detector at 214 and 254 nm containing Kinetex C18 column (100 \times 3.0 mm, 2.6 μm) eluting with gradient of water/acetonitrile and methanol. Thin layer chromatography (TLC) was performed with Merck 60F₂₅₄ silica gel plates. Products were visualized using ninhydrin (1% w/v in ethanol) with heating for 2 min, UV irradiation at 254 nm, or iodine oxidation. Flash chromatography purification was performed on Biotage-Isolera Four using pre-filled KP-Sil (normal phase) and KP-C18-HS (reversed phase) SNAP cartridges with UV detection at 254 and 280 nm. Ethyl acetate/hexanes and methanol/dichloromethane solvent systems were used as eluent for normal phase chromatography and methanol/water for reversed phase chromatography unless indicated otherwise. All the TIQ intermediates and final compounds with substituents at position 1 were enantiomeric mixtures and were used for biological evaluation without separation.

Synthetic procedure for amine-based histone deacetylase (HDAC) inhibitors

Scheme 1. Synthesis of amine-based HDAC inhibitors.^a



^aReagents and conditions: a) benzyl bromide (1.5 eq), Et_3N (1.5 eq), CH_3CN , rt, 12 h; b) $NH_2OH \cdot HCl$ (20 eq), KOH (25 eq), $MeOH$, $0^\circ C$ -rt, 5 h.

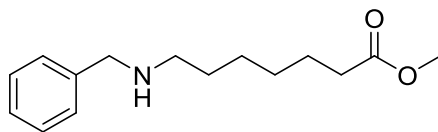
General procedure for step a: Appropriate amine (1.0 eq) was suspended in acetonitrile (15 mL) and triethylamine (1.5 eq) was added. The mixture was stirred at room temperature for 5 minutes followed by dropwise addition of benzyl bromide (1.5 eq). The solution was stirred at room temperature for 12 hours. The solution was concentrated *in vacuo*, water was added and the product was extracted with dichloromethane (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent eliminated *in vacuo*. The crude products were purified by flash chromatography eluting a gradient of ethyl acetate:hexanes (3:7 to 10:0) to afford secondary and tertiary amines.

General procedure for step b: To an ice-cooled solution of hydroxylamine hydrochloride (20 eq) in methanol (25 mL) was added powdered KOH (25 eq) portionwise and the resulting mixture was stirred at room temperature for 1 hour after the addition of KOH was completed.

The precipitate was filtered off and the filtrate was added dropwise to an ice-cooled solution of methyl ester (1.0 eq) in methanol (5 mL). An additional amount of KOH (10 eq) was added to the reaction solution and the reaction was monitored by TLC using methanol:dichloromethane (1:9) solvent system. After reaction completion, the solution was concentrated *in vacuo* and water was added. The pH of the solution was adjusted to pH 8.0 by dropwise addition of 1 M HCl and the product was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The product was purified by reversed phase flash chromatography eluting a gradient of methanol:water (10:90 to 90:10).

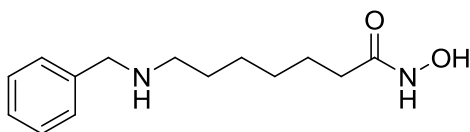
Characterization of intermediates and final products of amine-based HDAC inhibitors:

Methyl 7-(benzylamino)heptanoate (**4a**):



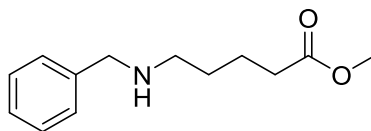
According to general procedure for step a, employing methyl-7-aminoheptanoate hydrochloride and benzyl bromide afforded **4a** as a yellow oil (40% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.35–7.26 (m, 5H), 3.80 (s, 2H), 3.68 (s, 3H), 2.64 (t, $J = 7.2$ Hz, 2H), 2.32 (t, $J = 7.5$ Hz, 2H), 1.66–1.52 (m, 4H), 1.39–1.31 (m, 4H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 174.2, 140.6, 128.4 (2C), 128.1 (2C), 126.9, 54.1, 51.5, 49.4, 34.0, 30.0, 29.1, 27.0, 24.9.

7-(benzylamino)-*N*-hydroxyheptanamide (**1a**):



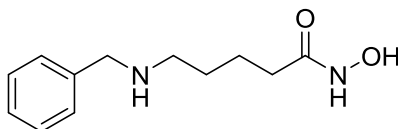
According to general procedure for step b, employing **4a** and hydroxylamine hydrochloride afforded **1a** as a yellow semisolid (85% yield). ^1H NMR (400 MHz, methanol-*d*₄): δ 7.49–7.46 (m, 5H), 4.20 (s, 2H), 3.03 (t, $J = 7.2$ Hz, 2H), 2.12 (t, $J = 7.2$ Hz, 2H), 1.72–1.63 (m, 4H), 1.41–1.30 (m, 4H). ^{13}C NMR (100 MHz, methanol-*d*₄): δ 171.3, 131.3, 129.5 (2C), 129.2, 128.8 (2C), 50.9, 47.1, 32.0, 28.0, 25.7, 25.5, 24.9. HRMS m/z calculated for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 251.1754; found: 251.1759.

Methyl 5-(benzylamino)pentanoate (**4b**):



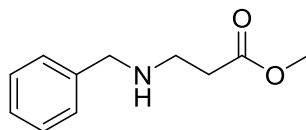
According to general procedure for step a, employing methyl-7-aminopentanoate hydrochloride and benzyl bromide afforded **4b** as a yellow oil (30% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.62–7.40 (m, 5H), 4.12 (s, 2H), 3.66 (s, 3H), 2.86 (m, 2H), 2.33 (m, 2H), 1.94–1.66 (m, 4H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 173.4, 130.4 (2C), 129.9, 129.6, 129.2 (2C), 51.7, 50.5, 45.6, 33.1, 31.5, 22.2.

5-(benzylamino)-*N*-hydroxypentanamide (**1b**):



According to general procedure for step b, employing **4b** and hydroxylamine hydrochloride afforded **1b** as a yellow oil (92% yield). ^1H NMR (400 MHz, methanol-*d*₄): δ 7.49–7.45 (m, 5H), 4.19 (s, 2H), 3.05 (t, $J = 7.1$ Hz, 2H), 2.17 (t, $J = 6.7$ Hz, 2H), 1.78–1.61 (m, 4H). ^{13}C NMR (100 MHz, methanol-*d*₄): δ 172.1, 132.5, 131.0 (2C), 130.7, 130.3 (2C), 52.4, 48.1, 32.8, 26.5, 23.5. HRMS m/z calculated for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 223.1441; found: 223.1450.

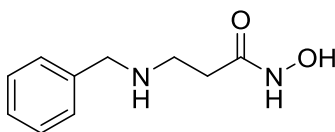
Methyl 3-(benzylamino)propanoate (**4c**):



According to general procedure for step a, employing methyl-7-aminopropanoate hydrochloride and benzyl bromide afforded **4c** as a yellow oil (39% yield). ^1H NMR (400 MHz, chloroform-*d*):

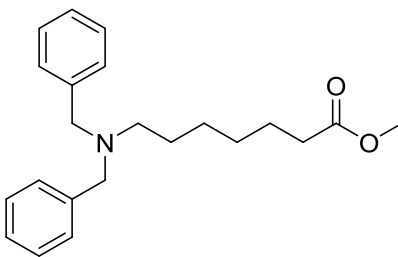
δ 7.35–7.27 (m, 5H), 3.83 (s, 2H), 3.70 (s, 3H), 2.93 (m, 2H), 2.57 (m, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 173.2, 140.0, 128.4 (2C), 128.1 (2C), 127.0, 53.7, 51.6, 44.4, 34.5.

3-(benzylamino)-N-hydroxypropanamide (**1c**):



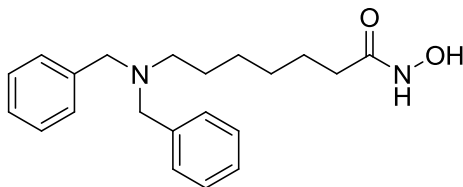
According to general procedure for step b, employing **4c** and hydroxylamine hydrochloride afforded **1c** as a yellow semisolid (72% yield). ^1H NMR (400 MHz, methanol-*d*₄): δ 7.52–7.46 (m, 5H), 4.22 (s, 2H), 3.28 (t, $J = 6.1$ Hz, 2H), 2.55 (d, $J = 7.0$ Hz, 2H). ^{13}C NMR (100 MHz, methanol-*d*₄): δ 171.3, 135.3, 131.0 (2C), 130.5, 130.1 (2C), 52.4, 47.1, 32.5. HRMS m/z calculated for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 195.1128; found: 195.1133.

Methyl 7-(dibenzylamino)heptanoate (**5a**):



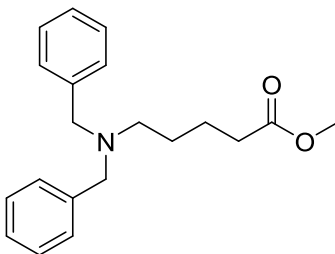
According to general procedure for step a, employing methyl-7-aminoheptanoate hydrochloride and benzyl bromide afforded **5a** as a colorless oil (47% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.40–7.23 (m, 10H), 3.69 (s, 4H), 3.57 (s, 3H), 2.43 (m, 2H), 2.29 (t, $J = 7.6$ Hz, 2H), 1.63–1.24 (m, 8H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 174.3, 140.1, 128.8 (2C), 128.2 (2C), 126.7, 58.3 (2C), 53.2, 51.5, 34.1, 29.0, 26.9, 26.8, 25.0.

7-(dibenzylamino)-N-hydroxyheptanamide (**2a**):



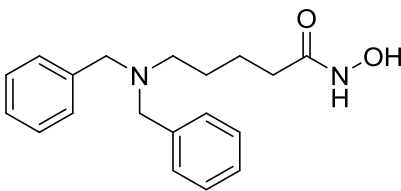
According to general procedure for step b, employing **5a** and hydroxylamine hydrochloride afforded **2a** as a colorless oil (90% yield). ^1H NMR (400 MHz, methanol- d_4): δ 7.35–7.20 (m, 10H), 3.53 (s, 4H), 2.38 (t, $J = 7.2$ Hz, 2H), 2.03 (t, $J = 7.2$ Hz, 2H), 1.57–1.50 (m, 4H), 1.28–1.25 (m, 4H). ^{13}C NMR (100 MHz, methanol- d_4): δ 169.5, 137.4 (2C), 126.6 (4C), 125.8 (4C), 124.5 (2C) 56.0 (2C), 50.8, 30.3, 26.5, 24.6, 24.3, 23.3. HRMS m/z calculated for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 341.2224; found: 341.2229.

Methyl 5-(dibenzylamino)pentanoate (**5b**):



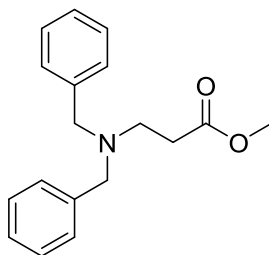
According to general procedure for step a, employing methyl-7-aminopentanoate hydrochloride and benzyl bromide afforded **5b** as a colorless oil (45% yield). ^1H NMR (400 MHz, chloroform- d): δ 7.39–7.23 (m, 10H), 3.67 (s, 3H), 3.51 (s, 4H), 2.44 (t, $J = 6.7$ Hz, 2H), 2.24 (t, $J = 7.2$ Hz, 2H), 1.67–1.54 (m, 4H). ^{13}C NMR (100 MHz, chloroform- d): δ 174.2, 139.9, 128.8 (2C), 128.2 (2C), 126.8, 58.3 (2C), 53.4, 51.4, 33.8, 26.50, 22.57.

5-(dibenzylamino)-N-hydroxypentanamide (**2b**):



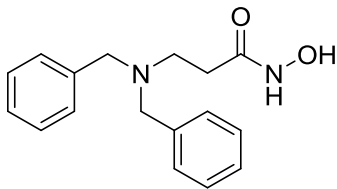
According to general procedure for step b, employing **5b** and hydroxylamine hydrochloride afforded **2b** as a colorless oil (96% yield). ^1H NMR (400 MHz, methanol- d_4): δ 7.37–7.24 (m, 8H), 7.20 (t, $J = 7.3$ Hz, 2H), 3.52 (s, 4H), 2.41 (t, $J = 7.0$ Hz, 2H), 2.01 (t, $J = 6.9$ Hz, 2H), 1.56 (m, 4H). ^{13}C NMR (100 MHz, methanol- d_4): δ 171.9, 139.8 (2C), 129.1 (4C), 128.3 (4C), 127.0 (2C), 58.4 (2C), 53.0, 32.7, 26.5, 23.6. HRMS m/z calculated for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 313.1911; found: 313.1912.

Methyl 3-(dibenzylamino)propanoate (**5c**):



According to general procedure for step a, employing methyl-7-aminopropanoate hydrochloride and benzyl bromide afforded **5c** as a colorless oil (46% yield). ^1H NMR (400 MHz, chloroform- d): δ 7.37–7.26 (m, 10H), 3.64 (s, 3H), 3.61 (s, 4H), 2.83 (t, $J = 7.2$ Hz, 2H), 2.53 (t, $J = 7.1$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform- d): δ 173.0, 139.3, 128.8 (2C), 128.2 (2C), 127.0, 58.1 (2C), 51.5, 49.2, 32.7.

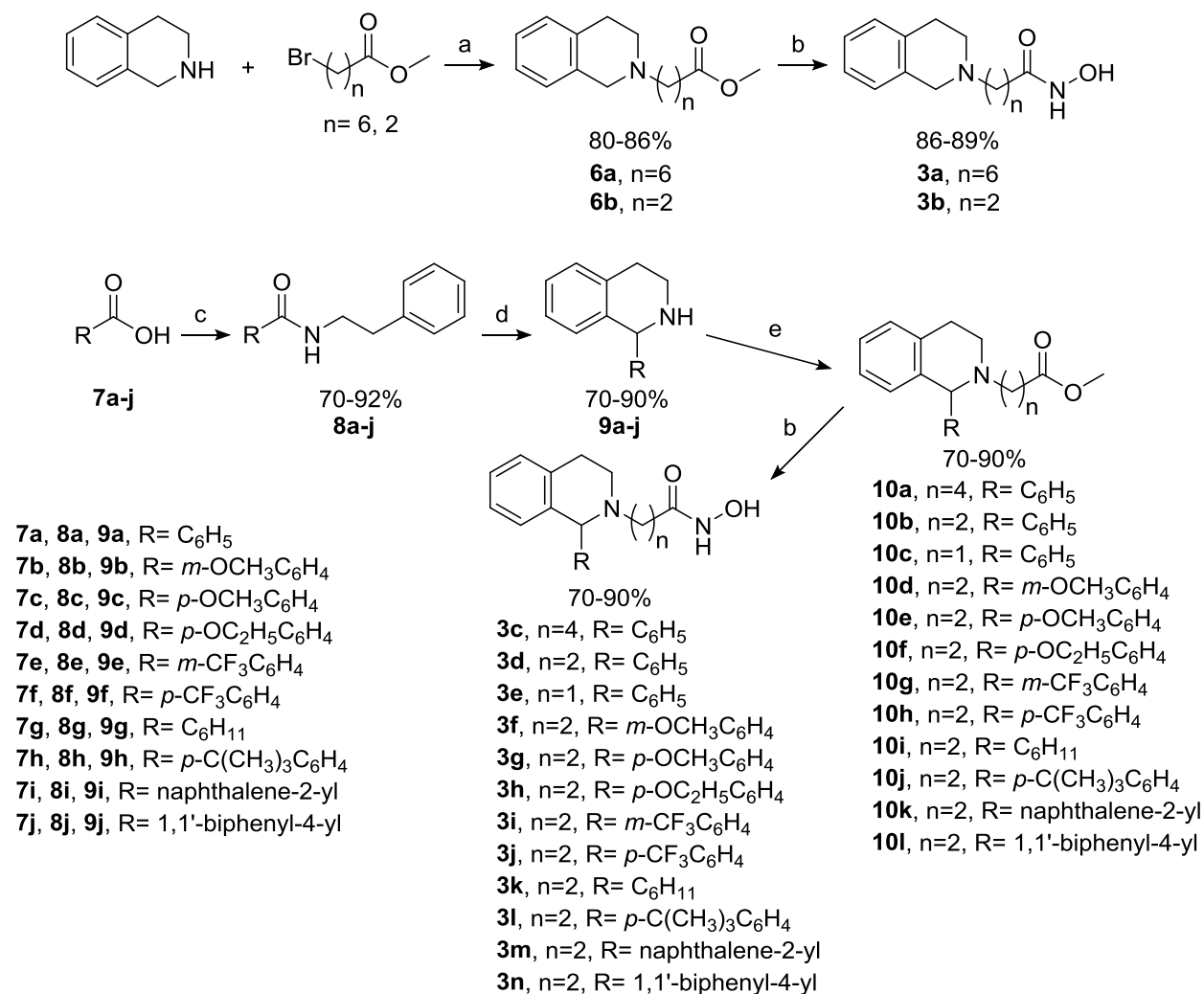
3-(dibenzylamino)-N-hydroxypropanamide (**2c**):



According to general procedure for step b, employing **5c** and hydroxylamine hydrochloride afforded **2c** as a colorless oil (96% yield). ^1H NMR (400 MHz, methanol- d_4): δ 7.36–7.27 (m, 8H), 7.24–7.19 (m, 2H), 3.54 (s, 4H), 2.75 (t, $J = 7.0$ Hz, 2H), 2.33 (t, $J = 7.0$ Hz, 2H). ^{13}C NMR (100 MHz, methanol- d_4): δ 171.7, 140.2 (2C), 130.1 (2C), 130.1 (2C), 129.4 (2C), 129.4 (2C), 128.2, 128.1, 58.8 (2C), 50.5, 31.8. HRMS m/z calculated for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 285.1598; found: 285.1602.

Synthetic procedure for TIQ-based HDAC inhibitors

Scheme 2. Synthesis of TIQ-based HDAC inhibitors.^a



^aReagents and conditions: a) K₂CO₃ (2.0 eq), CH₃CN, rt, 12 h; b) NH₂OH·HCl (20 eq), KOH (25 eq), MeOH, 0 °C–rt, 5 h; c) (i) (COCl)₂ (1.5 eq), cat. DMF, CH₂Cl₂, 0 °C, 3 h; (ii) phenethylamine (1.0 eq), Et₃N (1.5 eq), CH₂Cl₂, 0 °C, 4 h; d) (i) P₂O₅ (2.5 eq), POCl₃ (3.0 eq), xylene, reflux, 160 °C, 6 h; (ii) H₂/PtO₂, ethanol, rt, 12 h; e) methyl 2-bromoethanoate, methyl 3-bromopropanoate, or methyl 5-bromopentanoate (1.2 eq), K₂CO₃ (2.0 eq), CH₃CN, rt, 12 h.

General procedure for step a:

To a solution of 1,2,3,4-tetrahydroisoquinoline (1.0 eq) in acetonitrile (10mL) were added K_2CO_3 (2.0 eq) and methyl 3-bromopropanoate or methyl 3-bromoheptanoate (1.2 eq). The mixture was stirred for 12 hours at 40 °C. The reaction was then cooled to room temperature and the solvent eliminated *in vacuo*. Water was added and the product was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was used in the next reaction without further purification.

General procedure for step b:

To an ice-cooled solution of hydroxylamine hydrochloride (20 eq) in methanol (50 mL) was added powdered KOH (25 eq) portionwise and the resulting mixture was stirred at room temperature for 1 hour after the addition of KOH was completed. The precipitate was filtered off and the filtrate was added dropwise to an ice-cooled solution of methyl ester **6a-b** or **10a-l** (1.0 eq) in methanol (5 mL). An additional amount of KOH (10 eq) was added to the reaction solution and the reaction was monitored by TLC using hexanes:ethyl acetate (2:8) solvent system. After reaction completion, the solution was concentrated *in vacuo* and then diluted with dichloromethane. The solution was washed 3 times each with water and brine and then dried over Na_2SO_4 . The combined organic extracts were concentrated *in vacuo* and the product was purified by flash chromatography eluting dichloromethane:methanol (50:1).

General procedure for step c:

Acid **7a-j** (1.0 eq) was dissolved in dichloromethane (50 mL) and the solution was cooled to 0 °C. To this solution were added oxalyl chloride (1.5 eq) and catalytic amount of dimethylformamide (10 μ L). The solution was stirred for 3 hours at 0 °C and then the solvent was removed *in vacuo* to afford the corresponding acid chloride. The crude acid chloride product (1.0 eq) was dissolved in dichloromethane (50 mL) and phenethylamine (1.0 eq) was added. The solution was cooled to 0 °C and triethylamine (1.5 eq) was added dropwise. The solution was stirred at 0 °C to room temperature for 4 hours. The solution was diluted with ethyl acetate and washed with 10% aqueous HCl, saturated aqueous NaHCO₃, and brine. The ethyl acetate solution was dried over Na₂SO₄, and the solvent was removed *in vacuo* to afford the target amide **8a-j**, which was used in the next reaction without further purification.

General procedure for step d:

To a solution of amide **8a-j** (1.0 eq) in xylene (75 mL) were added phosphoric pentoxide (2.5 eq) and phosphorus oxychloride (3.0 eq). The reaction solution was refluxed at 160 °C for 6 hours. The solution was then carefully poured into ice water and a solution of 20% aqueous KOH (10 mL) was added. The mixture was stirred at room temperature for 5 minutes and an additional amount of KOH solution was added to achieve pH 7. Ethyl acetate (50 mL) was added and the mixture was stirred at room temperature for 15 minutes. The organic layer was collected and the aqueous layer extracted with additional ethyl acetate (2 \times 50 mL). The combined organic extracts were dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude dihydroisoquinoline (1.0 eq) was dissolved in ethanol (15 mL) and PtO₂ (0.1 eq) was added. The reaction mixture was degassed by nitrogen and stirred at room temperature under hydrogen balloon for 12 hours. The PtO₂ was filtered off through Celite and the resultant solution was concentrated *in vacuo*. The

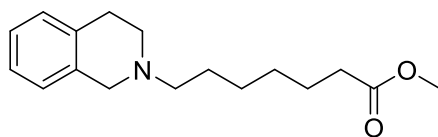
crude product was purified by silica gel flash chromatography eluting hexanes:ethyl acetate (10:1) to afford tetrahydroisoquinoline **9a-j** as racemic mixtures.

General procedure for step e:

To a solution of tetrahydroisoquinoline **9a-j** (1.0 eq) in acetonitrile (10mL) were added K_2CO_3 (2.0 eq) and methyl 3-bromopropanoate or methyl 3-bromopentanoate or methyl 3-bromoheptanoate (1.2 eq). The mixture was stirred for 12 hours at 40 °C. The reaction was then cooled to room temperature and the solvent eliminated *in vacuo*. Water was added and the product was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was used in the next reaction without further purification.

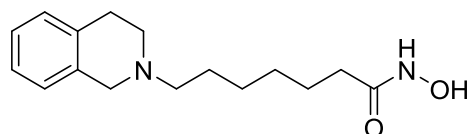
Characterization of intermediates and final products of TIQ-based HDAC inhibitors:

Methyl 7-(3,4-dihydroisoquinolin-2(1*H*)-yl)heptanoate (**6a**):



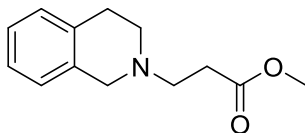
According to general procedure for step a, employing 1,2,3,4-tetrahydroisoquinoline and methyl 7-bromoheptanoate afforded **6a** as a colorless oil (80% yield). ¹H NMR (400 MHz, chloroform-*d*): δ 7.28-7.00 (m, 4H), 3.71 (s, 2H), 3.64 (s, 3H), 2.93 (t, *J* = 5.82 Hz, 2H), 2.82 (t, *J* = 5.84 Hz, 2H), 2.57 (m, 2H), 2.29 (m, 2H), 1.69-1.60 (m, 4H), 1.39-1.31 (m, 4H). ¹³C NMR (100 MHz, chloroform-*d*): δ 174.1, 133.7, 133.5, 128.6, 126.6, 126.4, 125.8, 57.8, 55.6, 51.4, 50.6, 34.0, 28.9, 28.3, 27.1, 26.5, 24.8. HRMS *m/z* calculated for C₁₇H₂₅NO₂ [M+H]⁺: 276.1958; found: 276.1949.

7-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-*N*-hydroxyheptanamide (**3a**):



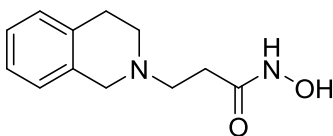
According to general procedure for step b, employing **6a** and hydroxylamine hydrochloride afforded **3a** as a white solid (86% yield). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.10-7.03 (m, 4H), 3.51 (s, 2H), 2.79 (t, *J* = 5.70 Hz, 2H), 2.62 (t, *J* = 5.83 Hz, 2H), 2.41 (t, *J* = 7.29 Hz, 2H), 2.29 (t, *J* = 7.34 Hz, 2H), 1.55-1.42 (m, 4H), 1.36-1.21 (m, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 169.6, 135.5, 134.7, 128.8, 126.8, 126.3, 125.9, 58.2, 56.1, 51.0, 32.7, 29.2, 29.02, 27.2, 26.9, 25.6. HRMS *m/z* calculated for C₁₆H₂₄N₂O₂ [M+H]⁺: 277.1911; found: 277.1898.

Methyl 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**6b**):



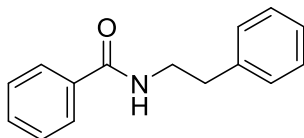
According to general procedure for step a, employing 1,2,3,4-tetrahydroisoquinoline and methyl 3-bromopropanoate afforded **6b** as a colorless oil (86% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.18-7.04 (m, 4H), 3.86 (s, 2H), 3.71 (s, 3H), 3.07-2.97 (m, 6H), 2.79 (t, $J = 7.32$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 172.2, 133.1, 132.2, 128.7, 126.8, 126.7, 126.2, 54.9, 52.5, 51.9, 50.4, 31.5, 27.7. HRMS m/z calculated for $\text{C}_{13}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 220.1332; found: 220.1329.

3-(3,4-Dihydroisoquinolin-2(1H)-yl)-*N*-hydroxypropanamide (**3b**):



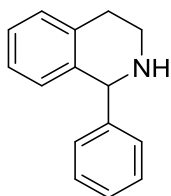
According to general procedure for step b, employing **6b** and hydroxylamine hydrochloride afforded **3b** as a white solid (89% yield). ^1H NMR (400 MHz, DMSO- d_6): δ 7.23-7.16 (m, 4H), 3.39 (t, $J = 7.56$ Hz, 2H), 3.32 (t, $J = 7.56$ Hz, 2H), 3.10-2.85 (m, 4H), 2.65 (t, $J = 5.60$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 172.3, 132.1, 129.6, 128.9, 127.8, 127.0, 126.9, 52.4, 52.0, 49.2, 27.8, 25.7. HRMS m/z calculated for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 221.1285; found: 221.1286.

N-Phenethylbenzamide (**8a**):



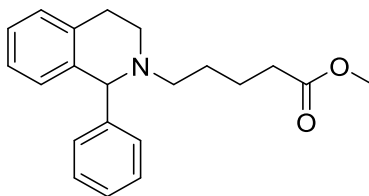
According to general procedure for step c, employing **7a** and phenethylamine afforded **8a** as a white solid (85% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.7 (d, J = 6.80 Hz, 2H), 7.5 (t, J = 6.80 Hz, 1H), 7.4 (t, J = 6.40 Hz, 2H), 7.32 (t, J = 7.40 Hz, 2H), 7.25 (t, J = 7.73 Hz, 3H), 6.30 (brs, 1H), 3.73 (t, J = 6.88 Hz, 2H), 2.96 (t, J = 6.94 Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 167.5, 138.9, 134.7, 131.4, 128.8 (2C), 128.7 (2C), 128.6 (2C), 126.8 (2C), 126.6, 41.2, 35.7. HRMS m/z calculated for $\text{C}_{15}\text{H}_{15}\text{NO}$ $[\text{M}+\text{H}]^+$: 226.1226; found: 226.1217.

1-phenyl-1,2,3,4-tetrahydroisoquinoline (**9a**):



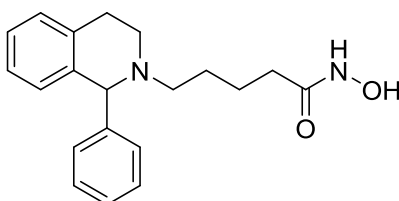
According to general procedure for step d, employing **8a**, phosphorus pentoxide and phosphoryl chloride afforded **9a** as a white solid (90% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.3 (m, 5H), 7.17 (d, J = 4.40 Hz, 2H), 7.08 (m, 1H), 6.79 (d, J = 7.60 Hz, 1H), 5.14 (s, 1H), 3.34-3.30 (m, 1H), 3.17-3.04 (m, 2H), 2.89-2.84 (m, 1H), 1.93 (brs, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 144.9, 138.3, 135.5, 129.04, 128.99 (2C), 128.4 (2C), 128.1, 127.4, 126.2, 125.6, 62.1, 42.3, 29.8. HRMS m/z calculated for $\text{C}_{15}\text{H}_{15}\text{N}$ $[\text{M}+\text{H}]^+$: 210.1277; found: 210.1272.

Methyl 5-(1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)pentanoate (**10a**):



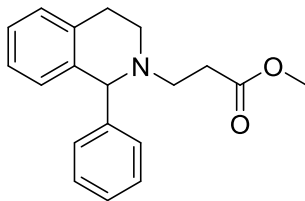
According to general procedure for step e, employing **9a** and methyl 5-bromopentanoate afforded **10a** as a colorless oil (90% yield). ¹H NMR (400 MHz, chloroform-*d*): δ 7.36 (d, *J* = 4.03 Hz, 1H), 7.34-7.30 (m, 4H), 7.20-7.10 (m, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.60 Hz, 1H), 4.62 (s, 1H), 3.70 (s, 3H), 3.31-3.22 (m, 2H), 2.66-2.62 (m, 2H), 2.40-2.26 (m, 4H), 1.79-1.59 (m, 4H). ¹³C NMR (100 MHz, chloroform-*d*): δ 174.0, 144.6, 138.8, 134.8, 129.8 (2C), 129.0, 128.5, 128.2 (2C), 127.2, 125.9, 125.7, 69.1, 53.7, 51.4, 47.3, 33.7, 29.4, 26.2, 22.6. HRMS *m/z* calculated for C₂₁H₂₅NO₂ [M+H]⁺: 324.1958; found: 324.1943.

N-hydroxy-5-(1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)pentanamide (**3c**):



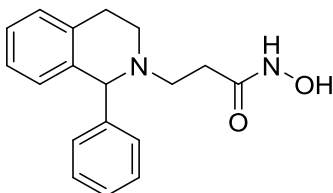
According to general procedure for step b, employing **10a** and hydroxylamine hydrochloride afforded **3c** as a white solid (70% yield). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.28 (brs, 1H), 8.64 (brs, 1H), 7.30-7.21 (m, 5H), 7.10 (d, *J* = 7.60 Hz, 1H), 7.05 (t, *J* = 7.20 Hz, 1H), 6.89 (t, *J* = 7.60 Hz, 1H), 6.62 (d, *J* = 7.90 Hz, 1H), 4.53 (s, 1H), 3.14-2.96 (m, 2H), 2.47-2.21 (m, 4H), 1.85 (d, *J* = 6.4 Hz, 2H), 1.41-1.16 (m, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 169.5, 144.8, 138.8, 134.9, 129.7 (2C), 128.9, 128.8, 128.5 (2C), 127.4, 126.2, 125.9, 68.2, 53.9, 46.9, 32.6, 29.1, 26.2, 23.5. HRMS *m/z* calculated for C₂₀H₂₄N₂O₂ [M+H]⁺: 325.1911; found: 325.1897.

Methyl 3-(1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10b**):



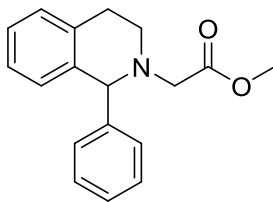
According to general procedure for step e, employing **9a** and methyl 3-bromopropanoate afforded **10b** as a colorless oil (80% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.32 (m, 5H), 7.13-7.08 (m, 2H), 7.01 (t, $J = 7.60$ Hz, 1H), 6.79 (d, $J = 7.60$ Hz, 1H), 4.62 (s, 1H), 3.63 (s, 3H), 3.23-3.08 (m, 2H), 2.97-2.84 (m, 2H), 2.72-2.65 (m, 2H), 2.50 (t, $J = 7.18$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 173.0, 143.9, 138.2, 134.6, 129.6 (2C), 128.8, 128.4, 128.2 (2C), 127.2, 125.9, 125.6, 68.2, 51.5, 49.9, 47.2, 32.3, 29.0. HRMS m/z calculated for $\text{C}_{19}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 296.1645; found: 296.1634.

N-hydroxy-3-(1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (**3d**):



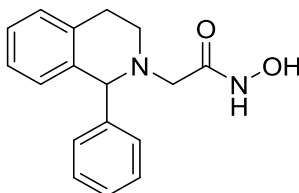
According to general procedure for step b, employing **10b** and hydroxylamine hydrochloride afforded **3d** as a white solid (80% yield). ^1H NMR (400 MHz, DMSO-*d*₆): δ 10.35 (brs, 1H), 8.67 (brs, 1H), 7.30-7.25 (m, 5H), 7.12-7.06 (m, 2H), 6.96 (t, $J = 7.60$ Hz, 1H), 6.62 (d, $J = 7.60$ Hz, 1H), 4.63 (s, 1H), 3.10-2.90 (m, 2H), 2.70-2.55 (m, 2H), 2.26-2.16 (m, 2H), 2.14-2.02 (m, 2H). ^{13}C NMR (100 MHz, DMSO-*d*₆): δ 168.4, 144.2, 138.6, 134.8, 129.7 (2C), 128.9, 128.5, 127.5 (2C), 126.2, 125.9, 125.1, 67.0, 50.5, 46.7, 30.3, 28.9. HRMS m/z calculated for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 297.1598; found: 297.1588.

Methyl 2-(1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (**10c**):



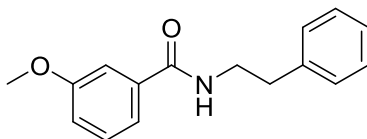
According to general procedure for step e, employing **9a** and methyl 2-bromoethanoate afforded **10c** as a colorless oil (88% yield). ¹H NMR (400 MHz, chloroform-*d*): δ 7.37-7.29 (m, 5H), 7.20-7.13 (m, 2H), 7.04 (t, *J* = 7.59 Hz, 1H), 6.74 (d, *J* = 7.60 Hz, 1H), 5.02 (s, 1H), 3.72 (s, 3H), 3.41 (s, 2H), 3.30-2.88 (m, 4H). ¹³C NMR (100 MHz, chloroform-*d*): δ 171.1, 143.1, 137.8, 134.0, 129.4 (2C), 128.4, 128.2, 128.0 (2C), 127.2, 125.6, 125.4, 66.4, 55.2, 51.0, 29.0. HRMS *m/z* calculated for C₁₈H₁₉NO₂ [M+H]⁺: 282.1489; found: 282.1475.

N-hydroxy-2-(1-phenyl-3,4-dihydroisoquinolin-2(1*H*)-yl)acetamide (**3e**):



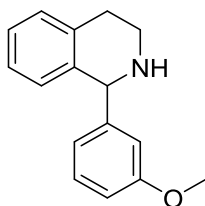
According to general procedure for step b, employing **10c** and hydroxylamine hydrochloride afforded **3e** as a white solid (75% yield). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.32 (brs, 1H), 8.73 (brs, 1H), 7.35-7.25 (m, 5H), 7.15-7.05 (m, 2H), 6.97 (t, *J* = 7.22 Hz, 1H), 6.59 (d, *J* = 7.66 Hz, 1H), 4.75 (s, 1H), 3.15 (s, 2H), 2.97-2.70 (m, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 166.3, 143.6, 138.1, 134.3, 129.5 (2C), 128.4, 128.4, 128.2 (2C), 127.3, 125.8, 125.6, 66.8, 55.6, 48.2, 28.7. HRMS *m/z* calculated for C₁₇H₁₈N₂O₂ [M+H]⁺: 283.1441; found: 283.1427.

3-methoxy-*N*-phenethylbenzamide (**8b**):



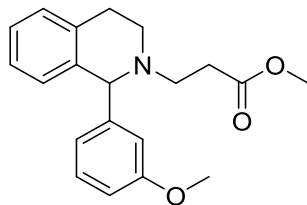
According to general procedure for step c, employing **7b** and phenethylamine afforded **8b** as a white solid (88% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.36-7.31 (m, 3H), 7.28-7.20 (m, 5H), 7.02 (d, $J = 7.66$ Hz, 1H), 6.34 (brs, 1H), 3.83 (s, 3H), 3.75-3.65 (m, 2H), 2.95 (t, $J = 6.94$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 167.4, 159.8, 138.9, 136.2, 129.5, 128.8 (2C), 128.7 (2C), 126.6, 118.6, 117.6, 112.2, 55.4, 41.2, 35.7. HRMS m/z calculated for $\text{C}_{16}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 256.1332; found: 256.1321.

1-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**9b**):



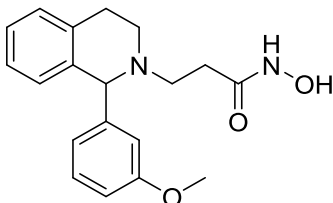
According to general procedure for step d, employing **8b**, phosphorus pentoxide and phosphoryl chloride afforded **9b** as a white solid (78% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.32-7.25 (m, 1H), 7.17-7.13 (m, 2H), 7.09-7.04 (m, 1H), 6.86-6.78 (m, 4H), 5.10 (s, 1H), 3.80 (s, 3H), 3.32-3.29 (m, 1H), 3.15-3.02 (m, 2H), 2.87-2.82 (m, 1H), 1.98 (brs, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 159.7, 146.5, 138.1, 135.4, 129.4, 129.0, 128.0, 126.3, 125.7, 121.4, 114.6, 112.8, 62.1, 55.2, 42.3, 29.8. HRMS m/z calculated for $\text{C}_{16}\text{H}_{17}\text{NO}$ $[\text{M}+\text{H}]^+$: 240.1383; found: 240.1384.

Methyl 3-(1-(3-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10d**):



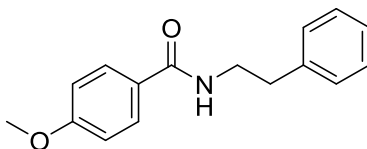
According to general procedure for step e, employing **9b** and methyl 3-bromopropanoate afforded **10d** as a colorless oil (70% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.42-7.35 (m, 3H), 7.33-7.25 (m, 2H), 7.09-6.98 (m, 1H), 6.89-6.80 (m, 2H), 5.10 (s, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.31-3.03 (m, 4H), 2.86-2.81 (m, 4H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 173.5, 159.3, 145.0, 137.3, 134.2, 128.7, 128.5, 128.2, 125.5, 125.3, 121.7, 114.9, 112.1, 68.2, 54.9, 51.1, 44.5, 47.0, 31.9, 28.5. HRMS m/z calculated for $\text{C}_{20}\text{H}_{23}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 326.1751; found: 326.1736.

N-hydroxy-3-(1-(3-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide propanoate (**3f**):



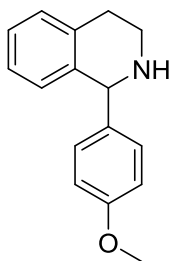
According to general procedure for step b, employing **10d** and hydroxylamine hydrochloride afforded **3f** as a white solid (90% yield). ^1H NMR (400 MHz, DMSO-*d*₆): δ 10.36 (brs, 1H), 8.60 (brs, 1H), 7.21 (t, $J = 7.96$ Hz, 1H), 7.15-7.05 (m, 2H), 7.01 (t, $J = 6.88$ Hz, 1H), 6.82 (d, $J = 6.80$ Hz, 3H), 6.66 (d, $J = 8.01$ Hz, 1H), 4.60 (s, 1H), 3.72 (s, 3H), 3.05-3.02 (m, 1H), 2.98-2.96 (m, 1H), 2.82-2.78 (m, 1H), 2.65-2.62 (m, 1H), 2.58-2.52 (m, 2H), 2.23-2.08 (m, 2H). ^{13}C NMR (100 MHz, DMSO-*d*₆): δ 168.2, 159.2, 145.1, 137.8, 135.1, 133.6, 129.1, 128.2, 127.6, 126.5, 123.2, 114.2, 112.3, 66.2, 55.2, 51.5, 46.3, 28.1, 27.1. HRMS m/z calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 327.1703; found: 327.1694.

4-methoxy-*N*-phenethylbenzamide (**8c**):



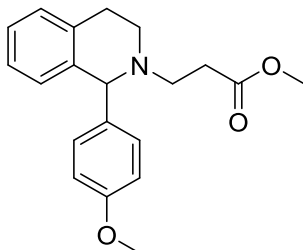
According to general procedure for step c, employing **7c** and phenethylamine afforded **8c** as a white solid (70% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.68 (d, $J = 8.73$ Hz, 2H), 7.35 (t, $J = 7.23$ Hz, 2H), 7.26 (t, $J = 7.66$ Hz, 3H), 6.92 (d, $J = 8.73$ Hz, 2H), 6.07 (brs, 1H), 3.86 (s, 3H), 3.73 (m, 2H), 2.95 (t, $J = 6.87$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 173.5, 159.3, 137.3, 128.7 (2C), 128.5 (2C), 128.2 (2C), 125.5, 125.3, 114.9 (2C), 55.4, 41.1, 31.9. HRMS m/z calculated for $\text{C}_{16}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 256.1332; found: 256.1333.

1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**9c**):



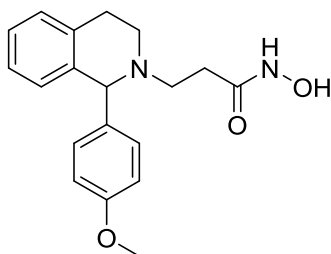
According to general procedure for step d, employing **8c**, phosphorus pentoxide and phosphoryl chloride afforded **9c** as a white solid (77% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.22 (d, $J = 8.33$ Hz, 2H), 7.15 (d, $J = 4.43$ Hz, 2H), 7.06 (m, 1H), 6.88 (d, $J = 8.49$ Hz, 2H), 6.79 (d, $J = 7.66$ Hz, 1H), 5.09 (s, 1H), 3.83 (s, 3H), 3.31-3.28 (m, 1H), 3.13-3.05 (m, 2H), 2.87-2.84 (m, 1H), 2.14 (brs, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 158.9, 138.5, 137.0, 135.4, 130.0 (2C), 129.0, 128.1, 126.2, 125.6, 113.8 (2C), 61.4, 55.3, 42.3, 29.7. HRMS m/z calculated for $\text{C}_{16}\text{H}_{17}\text{NO}$ $[\text{M}+\text{H}]^+$: 240.1383; found: 240.1380.

Methyl 3-(1-(4-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10e**):



According to general procedure for step e, employing **9c** and methyl 3-bromopropanoate afforded **10e** as a colorless oil (79% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.18 (d, J = 8.42 Hz, 2H), 7.15-7.10 (m, 2H), 7.01 (m, 1H), 6.85 (d, J = 8.49 Hz, 2H), 6.72 (d, J = 7.66 Hz, 1H), 4.56 (s, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 3.20-3.06 (m, 2H), 2.96-2.82 (m, 2H), 2.71-2.64 (m, 2H), 2.50 (t, J = 8.80 Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 172.2, 158.1, 138.1, 135.9, 134.9, 130.0 (2C), 128.2, 128.1, 125.3, 125.0, 113.6 (2C), 67.1, 54.7, 51.3, 49.3, 47.0, 31.9, 28.2. HRMS m/z calculated for $\text{C}_{20}\text{H}_{23}\text{NO}_3$ [$\text{M}+\text{H}$] $^+$: 326.1751; found: 326.1741.

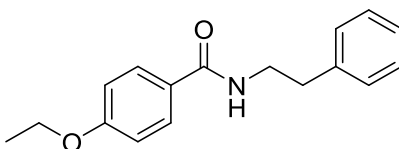
N-hydroxy-3-(1-(4-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (**3g**):



According to general procedure for step b, employing **10e** and hydroxylamine hydrochloride afforded **3g** as a white solid (80% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 9.66 (brs, 1H), 7.27 (brs, 1H), 7.15 (d, J = 4.40 Hz, 2H), 7.10 (d, J = 8.42 Hz, 2H), 7.05-7.03 (m, 1H), 6.86 (d, J = 8.26 Hz, 2H), 6.72 (d, J = 7.67 Hz, 1H), 4.57 (s, 1H), 3.78 (s, 3H), 3.21-3.05 (m, 2H), 2.93-

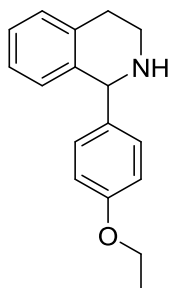
2.78 (m, 2H), 2.60-2.48 (m, 3H), 2.29-2.25 (m, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 169.6, 158.7, 137.1, 133.9, 133.6, 130.4 (2C), 128.5, 128.1, 126.0, 125.6, 113.6 (2C), 67.7, 54.8, 48.8, 45.2, 30.0, 27.8. HRMS m/z calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 327.1703; found: 327.1688.

4-ethoxy-*N*-phenethylbenzamide (**8d**):



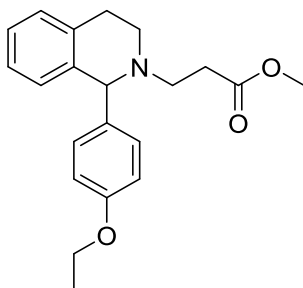
According to general procedure for step c, employing **7d** and phenethylamine afforded **8d** as a white solid (83% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.65 (d, $J = 6.80$ Hz, 2H), 7.33 (t, $J = 7.61$ Hz, 2H), 7.27-7.25 (m, 3H), 6.85 (d, $J = 6.80$ Hz, 2H), 6.18 (brs, 1H), 4.05 (q, $J = 7.20$ Hz, 2H), 3.75-3.67 (m, 2H), 2.90 (t, $J = 6.80$ Hz, 2H), 1.45 (t, $J = 6.80$ Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 166.7, 161.1, 138.7, 128.4 (2C), 128.3 (2C), 128.2 (2C), 126.3, 126.1, 113.8 (2C), 63.2, 40.7, 35.4, 14.2. HRMS m/z calculated for $\text{C}_{17}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 270.1489; found: 270.1479.

1-(4-ethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**9d**):



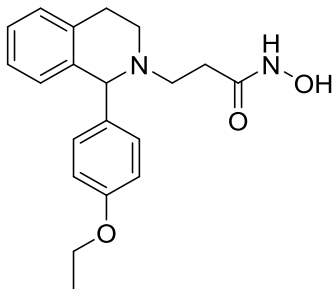
According to general procedure for step d, employing **8d**, phosphorus pentoxide and phosphoryl chloride afforded **9d** as a white solid (77% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.28-7.15 (m, 4H), 7.10 (t, $J = 6.81$ Hz, 1H), 6.85 (d, $J = 8.80$ Hz, 2H), 6.80 (d, $J = 7.60$ Hz, 1H), 5.27 (s, 1H), 4.00 (q, $J = 7.20$ Hz, 2H), 3.25-3.20 (m, 2H), 3.05-2.95 (m, 2H), 2.29 (brs, 1H), 1.40 (t, $J = 6.80$ Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 158.8, 133.6, 133.0, 130.9, 130.7 (2C), 128.6, 127.8, 127.0, 126.0, 113.8 (2C), 63.1, 59.4, 40.0, 26.1, 14.8. HRMS m/z calculated for $\text{C}_{17}\text{H}_{19}\text{NO}$ $[\text{M}+\text{H}]^+$: 254.1539; found: 254.1539.

Methyl 3-(1-(4-ethoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10f**):



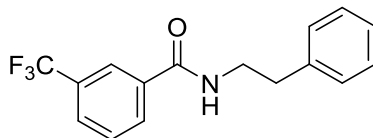
According to general procedure for step e, employing **9d** and methyl 3-bromopropanoate afforded **10f** as a colorless oil (85% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.22 (d, $J = 7.65$ Hz, 2H), 7.15-7.09 (m, 2H), 7.03 (t, $J = 7.58$ Hz, 1H), 6.85 (d, $J = 8.80$ Hz, 2H), 6.75 (d, $J = 7.60$ Hz, 1H), 4.60 (s, 1H), 4.05 (q, $J = 6.80$ Hz, 2H), 3.64 (s, 3H), 3.24-3.10 (m, 2H), 2.96-2.85 (m, 2H), 2.72-2.65 (m, 2H), 2.53 (t, $J = 7.60$ Hz, 2H), 1.44 (t, $J = 6.80$ Hz, 3H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 172.6, 157.8, 138.3, 135.4, 134.2, 130.2 (2C), 128.5, 128.0, 125.5, 125.2, 113.7 (2C), 67.2, 62.9, 51.1, 49.4, 40.9, 31.9, 28.6, 14.9. HRMS m/z calculated for $\text{C}_{21}\text{H}_{25}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 340.1907; found: 340.1893.

3-(1-(4-ethoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-hydroxypropanamide (**3h**):



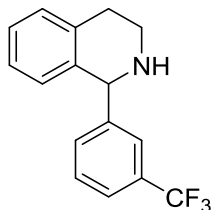
According to general procedure for step b, employing **10f** and hydroxylamine hydrochloride afforded **3h** as a white solid (88% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.35 (brs, 1H), 8.62 (brs, 1H), 7.31-6.98 (m, 5H), 6.82 (d, $J = 8.20$ Hz, 2H), 6.61 (d, $J = 7.60$ Hz, 1H), 4.52 (s, 1H), 4.01 (q, $J = 6.40$ Hz, 2H), 3.11-3.01 (m, 2H), 2.81-2.55 (m, 4H), 2.21-2.11 (m, 2H), 1.30 (t, $J = 6.80$ Hz, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 168.1, 157.6, 138.6, 135.5, 134.4, 130.3, 128.5 (2C), 128.4, 125.7, 125.5, 113.9 (2C), 66.0, 62.9, 50.0, 46.3, 30.0, 28.5, 14.9. HRMS m/z calculated for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 341.1860; found: 341.1844.

N-phenethyl-3-(trifluoromethyl)benzamide (**8e**):



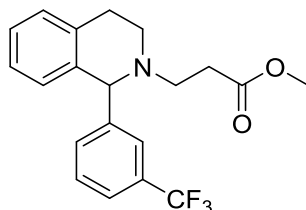
According to general procedure for step c, employing **7e** and phenethylamine afforded **8e** as a white solid (92% yield). ^1H NMR (400 MHz, chloroform- d): δ 7.98 (s, 1H), 7.88 (d, $J = 7.77$ Hz, 1H), 7.75 (d, $J = 7.70$ Hz, 1H), 7.56 (t, $J = 7.77$ Hz, 1H), 7.35 (t, $J = 7.26$ Hz, 2H), 7.29-7.25 (m, 3H), 6.30 (brs, 1H), 3.75 (m, 2H), 2.97 (t, $J = 6.93$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform- d): δ 166.1, 138.7, 135.5, 131.3 (q, $J_{(F,C)} = 4.04$ Hz), 130.9, 130.1, 129.2, 128.8 (2C), 128.0, 126.7, 125.0, 123.9, 41.3, 35.6. HRMS m/z calculated for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{NO}$ $[\text{M}+\text{H}]^+$: 294.1100; found: 294.1090.

1-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**9e**):



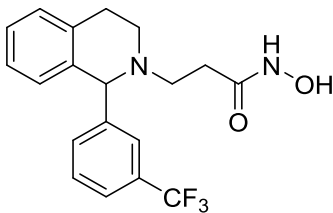
According to general procedure for step d, employing **8e**, phosphorus pentoxide and phosphoryl chloride afforded **9e** as a white solid (85% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.66 (s, 1H), 7.61 (d, $J = 7.65$ Hz, 1H), 7.50-7.43 (m, 2H), 7.20 (d, $J = 4.30$ Hz, 2H), 7.10-7.08 (m, 1H), 6.73 (d, $J = 7.60$ Hz, 1H), 5.20 (s, 1H), 3.32-3.26 (m, 1H), 3.18-3.07 (m, 2H), 2.91-2.84 (m, 1H), 2.01 (brs, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 145.5, 137.0, 135.1, 132.1 (q, $J_{(F, C)} = 4.01$ Hz), 130.4, 128.9, 128.5, 127.5, 126.2, 125.4, 125.3, 123.9, 61.4, 42.0, 29.3. HRMS m/z calculated for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{N}$ $[\text{M}+\text{H}]^+$: 278.1151; found: 278.1144.

Methyl 3-(1-(3-(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)propanoate (**10g**):



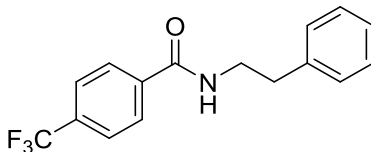
According to general procedure for step e, employing **9e** and methyl 3-bromopropanoate afforded **10g** as a colorless oil (80% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.58-7.53 (m, 2H), 7.47-7.42 (m, 2H), 7.17-7.11 (m, 2H), 7.05 (t, $J = 7.60$ Hz, 1H), 6.69 (d, $J = 7.60$ Hz, 1H), 4.60 (s, 1H), 3.62 (s, 3H), 3.21-3.09 (m, 2H), 2.91-2.85 (m, 2H), 2.69-2.65 (m, 2H), 2.48 (t, $J = 6.80$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 172.2, 144.9, 136.7, 134.2, 132.4 (q, $J_{(F, C)} = 4.05$ Hz), 128.3 (2C), 125.9 (2C), 125.7, 125.4 (2C), 123.8, 67.5, 51.1, 49.5, 46.6, 32.0, 27.7. HRMS m/z calculated for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$: 364.1519; found: 364.1511.

N-hydroxy-3-(1-(3-(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (**3i**):



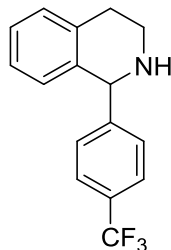
According to general procedure for step b, employing **10g** and hydroxylamine hydrochloride afforded **3i** as a white solid (90% yield). ^1H NMR (400 MHz, DMSO- d_6): δ 10.43 (brs, 1H), 8.65 (brs, 1H), 7.55 (d, $J = 7.65$ Hz, 2H), 7.46 (d, $J = 7.60$ Hz, 2H), 7.18-7.06 (m, 2H), 7.01 (t, $J = 6.89$ Hz, 1H), 6.61 (t, $J = 7.61$ Hz, 1H), 4.76 (s, 1H), 3.07-2.95 (m, 2H), 2.83-2.79 (m, 2H), 2.65-2.53 (m, 2H), 2.20-2.06 (m, 2H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 169.3, 153.7, 142.0, 139.3, 134.8 (2C), 133.4, 133.2, 132.5 (q, $J_{(F, C)} = 4.01$ Hz), 130.7, 130.5, 128.9, 128.4, 70.8, 54.9, 50.9, 34.7, 33.14. HRMS m/z calculated for $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 365.1471; found: 365.1456.

N-phenethyl-4-(trifluoromethyl)benzamide (**8f**):



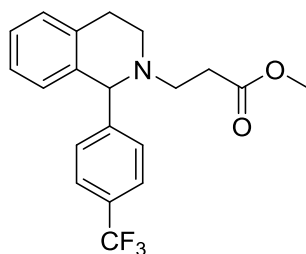
According to general procedure for step c, employing **7f** and phenethylamine afforded **8f** as a white solid (90% yield). ^1H NMR (400 MHz, chloroform- d): δ 7.81 (d, $J = 8.13$ Hz, 2H), 7.69 (d, $J = 8.19$ Hz, 2H), 7.38 (t, $J = 7.70$ Hz, 2H), 7.30-7.25 (m, 3H), 6.19 (brs, 1H), 3.76 (m, 2H), 2.98 (t, $J = 6.81$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform- d): δ 166.2, 138.6, 137.9, 133.2 (q, $J_{(F, C)} = 4.08$ Hz), 128.8 (2C), 127.7, 127.3 (2C), 126.8, 125.7, 125.0, 122.3, 41.3, 35.6. HRMS m/z calculated for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{NO}$ $[\text{M}+\text{H}]^+$: 294.1100; found: 294.1089.

1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**9f**):



According to general procedure for step d, employing **8f**, phosphorus pentoxide and phosphoryl chloride afforded **9f** as a white solid (85% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.58 (d, $J = 7.95$ Hz, 2H), 7.40 (d, $J = 7.90$ Hz, 2H), 7.20 (d, $J = 8.80$ Hz, 2H), 7.08-7.05 (m, 1H), 6.70 (d, $J = 7.72$ Hz, 1H), 5.16 (s, 1H), 3.27-3.23 (m, 1H), 3.12-3.03 (m, 2H), 2.86-2.82 (m, 1H), 1.26 (brs, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 148.5, 136.9, 135.2, 128.91 (2C), 128.88, 127.5, 127.2, 126.2, 125.3, 124.9 (q, $J_{(F, C)} = 4.08$ Hz), 122.4, 61.1, 41.5, 29.3. HRMS m/z calculated for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{N}$ $[\text{M}+\text{H}]^+$: 278.1151; found: 278.1142.

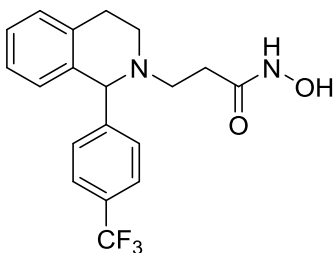
Methyl 3-(1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10h**):



According to general procedure for step e, employing **9f** and methyl 3-bromopropanoate afforded **10h** as a colorless oil (80% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 7.59 (d, $J = 8.09$ Hz, 2H), 7.42 (d, $J = 8.04$ Hz, 2H), 7.17-7.09 (m, 2H), 7.05 (t, $J = 8.60$ Hz, 1H), 6.69 (d, $J = 7.77$ Hz, 1H), 4.69 (s, 1H), 3.63 (s, 3H), 3.23-3.09 (m, 2H), 2.95-2.85 (m, 2H), 2.73-2.65 (m, 2H), 2.52 (t, $J = 7.09$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 172.4, 148.0, 136.8, 134.2,

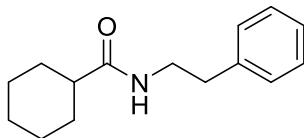
129.4 (2C), 129.2, 128.9, 128.3, 125.9, 125.5, 125.2, 124.8 (q, $J_{(F,C)} = 4.07$ Hz), 67.4, 51.1, 49.5, 46.6, 32.0, 28.4. HRMS m/z calculated for $C_{20}H_{20}F_3NO_2$ $[M+H]^+$: 364.1519; found: 364.1505.

N-hydroxy-3-(1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (**3j**):



According to general procedure for step b, employing **10h** and hydroxylamine hydrochloride afforded **3j** as a white solid (70% yield). 1H NMR (400 MHz, chloroform-*d*): δ 7.59 (d, $J = 6.95$ Hz, 2H), 7.33 (d, $J = 6.82$ Hz, 2H), 7.16 (d, $J = 4.40$ Hz, 2H), 7.09-7.04 (m, 1H), 6.66 (d, $J = 7.58$ Hz, 1H), 4.70 (s, 1H), 3.17-3.05 (m, 2H), 2.98-2.90 (m, 1H), 2.62-2.55 (m, 4H), 2.35-2.31 (m, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 169.6, 146.2, 135.7, 133.7, 129.6 (2C), 129.3, 128.3, 126.4, 125.8, 125.2 (q, $J_{(F,C)} = 4.03$ Hz), 125.0, 122.3, 67.7, 48.9, 45.0, 30.0, 27.5. HRMS m/z calculated for $C_{19}H_{19}F_3N_2O_2$ $[M+H]^+$: 365.1471; found: 365.1466.

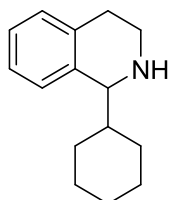
N-phenethylcyclohexanecarboxamide (**8g**):



According to general procedure for step c, employing **7g** and phenethylamine afforded **8g** as a white solid (80% yield). 1H NMR (400 MHz, chloroform-*d*): δ 7.34-7.19 (m, 5H), 5.58 (brs, 1H), 3.52 (m, 2H), 2.82 (t, $J = 6.91$ Hz, 2H), 2.06-1.99 (m, 1H), 1.83-1.65 (m, 5H), 1.45-1.36 (m, 2H), 1.30-1.16 (m, 3H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 176.0, 139.0, 128.8 (2C), 128.6

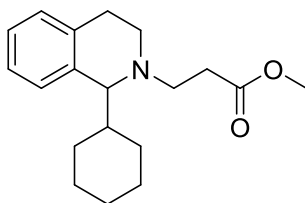
(2C), 126.4, 45.5, 40.4, 35.7, 29.7 (2C), 25.7 (3C). HRMS m/z calculated for $C_{15}H_{21}NO$ $[M+H]^+$: 232.1696; found: 232.1687.

1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline (**9g**):



According to general procedure for step d, employing **8g**, phosphorus pentoxide and phosphoryl chloride afforded **9g** as a white solid (85% yield). 1H NMR (400 MHz, chloroform-*d*): δ 7.28-7.08 (m, 4H), 3.93 (d, $J = 3.79$ Hz, 1H), 3.31-3.27 (m, 1H), 2.97-2.86 (m, 2H), 2.73-2.67 (m, 1H), 1.97-1.69 (m, 6H), 1.45-1.30 (m, 3H), 1.22-1.10 (m, 3H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 138.5, 136.2, 129.1, 126.1, 125.60, 125.56, 60.8, 43.0, 42.3, 31.0, 30.3, 27.1, 26.7, 26.6, 26.4. HRMS m/z calculated for $C_{15}H_{21}N$ $[M+H]^+$: 216.1747; found: 216.1748.

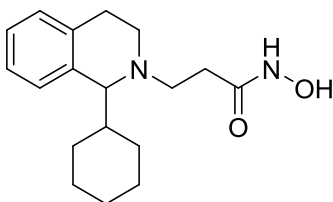
Methyl 3-(1-cyclohexyl-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10i**):



According to general procedure for step e, employing **9g** and methyl 3-bromopropanoate afforded **10i** as a colorless oil (88% yield). 1H NMR (400 MHz, chloroform-*d*): δ 7.28-7.01 (m, 4H), 3.69 (s, 3H), 3.47-3.28 (m, 1H), 3.22 (d, $J = 7.67$ Hz, 1H), 2.90-2.76 (m, 4H), 2.64-2.59 (m, 1H), 2.51 (t, $J = 7.03$ Hz, 2H), 2.02-1.99 (m, 1H), 1.75-1.46 (m, 5H), 1.19-0.92 (m, 5H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 173.3, 136.8, 135.2, 129.5, 128.7, 126.0, 124.7, 67.0, 51.5,

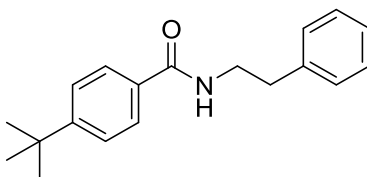
50.3, 44.2, 43.4, 33.8, 30.8, 30.7, 26.7, 26.6, 26.6, 24.5. HRMS m/z calculated for $C_{19}H_{27}NO_2$ $[M+H]^+$: 302.2115; found: 302.2100.

3-(1-Cyclohexyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-hydroxypropanamide (**3k**):



According to general procedure for step b, employing **10i** and hydroxylamine hydrochloride afforded **3k** as a white solid (70% yield). 1H NMR (400 MHz, chloroform-*d*): δ 10.35 (brs, 1H), 8.66 (brs, 1H), 7.13-6.99 (m, 4H), 3.21 (d, $J = 7.54$ Hz, 1H), 3.17-3.12 (m, 1H), 2.82-2.54 (m, 5H), 2.13 (t, $J = 7.18$ Hz, 2H), 1.95-1.91 (m, 1H), 1.77-1.42 (m, 5H), 1.20-0.95 (m, 5H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 168.5, 137.0, 135.4, 129.7, 128.9, 126.3, 125.1, 66.2, 50.9, 44.2, 43.3, 32.2, 30.8, 30.6, 26.7, 26.6, 26.5, 24.4. HRMS m/z calculated for $C_{18}H_{26}N_2O_2$ $[M+H]^+$: 303.2067; found: 303.2061.

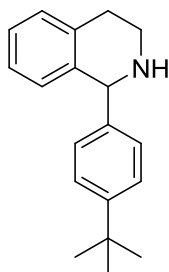
4-(*tert*-butyl)-*N*-phenethylbenzamide (**8h**):



According to general procedure for step c, employing **7h** and phenethylamine afforded **8h** as a white solid (84% yield). 1H NMR (400 MHz, chloroform-*d*): δ 7.65 (d, $J = 8.80$ Hz, 2H), 7.42 (d, $J = 8.80$ Hz, 2H), 7.32 (t, $J = 8.23$ Hz, 2H), 7.25 (t, $J = 8.66$ Hz, 3H), 6.20 (brs, 1H), 3.71 (m, 2H), 2.91 (t, $J = 7.20$ Hz, 2H), 1.3 (s, 9H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 167.0, 154.5,

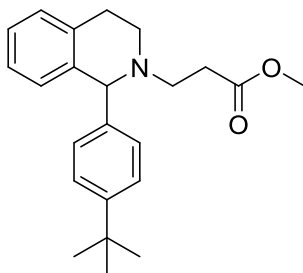
138.6, 131.4, 131.1, 128.4 (2C), 126.3 (2C), 126.2, 125.6, 125.1 (2C), 40.7, 35.4, 34.5, 30.8 (3C). HRMS m/z calculated for $C_{19}H_{23}NO$ $[M+H]^+$: 282.1852; found: 282.1846.

1-(4-(*tert*-butyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**9h**):



According to general procedure for step d, employing **8h**, phosphorus pentoxide and phosphoryl chloride afforded **9h** as a white solid (70% yield). 1H NMR (400 MHz, chloroform-*d*): δ 7.35 (d, $J = 8.80$ Hz, 2H), 7.22-7.15 (m, 4H), 7.10-7.05 (m, 1H), 6.81 (d, $J = 8.80$ Hz, 1H), 5.12 (s, 1H), 3.30-3.15 (m, 1H), 3.14-3.00 (m, 2H), 2.90-2.81 (m, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 149.8, 141.5, 138.0, 135.1, 128.6, 128.2 (2C), 127.8, 125.8, 125.2 (2C), 124.9, 61.2, 41.8, 34.1, 31.0 (3C), 29.9. HRMS m/z calculated for $C_{19}H_{23}N$ $[M+H]^+$: 266.1903; found: 266.1891.

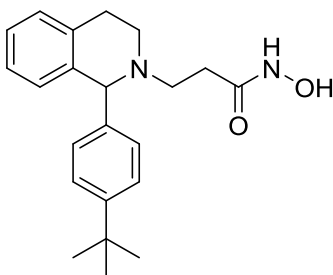
Methyl 3-(1-(4-(*tert*-butyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10j**):



According to general procedure for step e, employing **9h** and methyl 3-bromopropanoate afforded **10j** as a colorless oil (80% yield). White solid, 85% yield. 1H NMR (400 MHz,

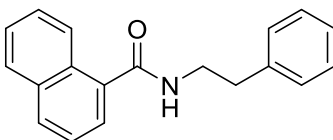
chloroform-*d*): δ 7.35 (d, $J = 8.80$ Hz, 2H), 7.21-7.13 (m, 4H), 7.01 (t, $J = 7.60$ Hz, 1H), 6.82 (d, $J = 7.60$ Hz, 1H), 4.60 (s, 1H), 3.60 (s, 3H), 3.21-3.11 (m, 2H), 2.99-2.91 (m, 2H), 2.78-2.71 (m, 2H), 2.5 (t, $J = 7.20$ Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 172.5, 149.5, 140.3, 137.9, 134.2, 128.8, 128.6, 128.1 (2C), 125.6, 125.2 (2C), 124.6, 67.1, 51.1, 49.4, 46.4, 34.1, 32.0, 31.1 (3C), 28.3. HRMS m/z calculated for $\text{C}_{23}\text{H}_{29}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 352.2271; found: 352.2261.

3-(1-(4-(*tert*-butyl)phenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-hydroxypropanamide (**3l**):



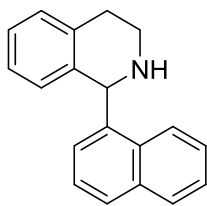
According to general procedure for step b, employing **10j** and hydroxylamine hydrochloride afforded **3l** as a white solid (75% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.21 (brs, 1H), 8.50 (brs, 1H), 7.30 (d, $J = 8.40$ Hz, 2H), 7.15-7.05 (m, 4H), 6.95 (t, $J = 7.23$ Hz, 1H), 6.63 (d, $J = 7.60$ Hz, 1H), 4.58 (s, 1H), 3.08-2.91 (m, 2H), 2.78-2.68 (m, 2H), 2.58-2.41 (m, 4H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 172.1, 149.2, 140.8, 138.2, 134.4, 129.0 (2C), 128.5, 128.4, 125.8, 125.5, 124.8 (2C), 66.6, 51.2, 49.5, 46.2, 34.2, 31.6, 31.2 (3C). HRMS m/z calculated for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 353.2224; found: 353.2236.

N-Phenethyl-1-naphthamide (**8i**):



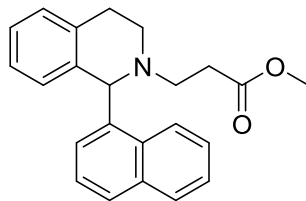
According to general procedure for step c, employing **7i** and phenethylamine afforded **8i** as a white solid (85% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 8.22 (dd, $J = 3.44, 6.26$ Hz, 1H), 7.91-7.86 (m, 2H), 7.61-7.48 (m, 3H), 7.42 (dd, $J = 7.15, 8.07$ Hz, 1H), 7.37-7.25 (m, 5H), 6.07 (brs, 1H), 3.96-3.74 (m, 2H), 3.01 (t, $J = 6.89$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 169.5, 138.8, 134.6, 133.6, 130.5, 130.1, 128.9 (2C), 128.7 (2C), 128.3, 127.0, 126.6, 126.4, 125.4, 124.8, 124.7, 41.1, 35.7. HRMS m/z calculated for $\text{C}_{19}\text{H}_{17}\text{NO}$ $[\text{M}+\text{H}]^+$: 276.1383; found: 276.1371.

1-(Naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (**9i**):



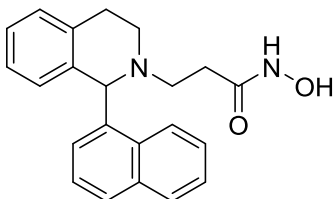
According to general procedure for step d, employing **8i**, phosphorus pentoxide and phosphoryl chloride afforded **9i** as a white solid (90% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 8.29-8.27 (m, 1H), 7.95-7.88 (m, 1H), 7.85-7.79 (m, 1H), 7.54-7.47 (m, 2H), 7.44-7.38 (m, 1H), 7.29-7.17 (m, 3H), 7.05 (t, $J = 6.84$ Hz, 1H), 6.81 (d, $J = 7.72$ Hz, 1H), 5.90 (s, 1H), 3.33-3.27 (m, 1H), 3.21-3.11 (m, 2H), 3.01-2.95 (m, 1H), 2.01 (brs, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 139.6, 137.9, 135.1, 134.0, 131.3, 128.7, 128.5, 127.8, 127.5, 127.4, 125.9, 125.8, 125.4, 125.2, 124.7, 124.0, 61.9, 41.8, 29.5. HRMS m/z calculated for $\text{C}_{19}\text{H}_{17}\text{N}$ $[\text{M}+\text{H}]^+$: 260.1434; found: 260.1423.

Methyl 3-(1-(naphthalen-1-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10k**):



According to general procedure for step e, employing **9i** and methyl 3-bromopropanoate afforded **10k** as a colorless oil (80% yield). ^1H NMR (400 MHz, chloroform-*d*): δ 8.38 (d, $J = 8.46$ Hz, 1H), 7.91-7.87 (m, 2H), 7.51-7.30 (m, 4H), 7.24 (d, $J = 7.45$ Hz, 1H), 7.15 (t, $J = 7.32$ Hz, 1H), 6.94 (t, $J = 7.39$ Hz, 1H), 6.70 (d, $J = 7.79$ Hz, 1H), 5.20 (s, 1H), 3.42 (s, 3H), 3.40-3.30 (m, 2H), 3.10-2.99 (m, 2H), 2.81-2.64 (m, 2H), 2.53-2.46 (m, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 172.8, 139.1, 138.6, 134.6, 134.3, 131.9, 129.2, 128.50 (2C), 128.47 (2C), 127.8, 126.1, 126.0, 125.5 (2C), 125.0, 68.8, 51.3, 50.3, 48.3, 32.3, 29.0. HRMS m/z calculated for $\text{C}_{23}\text{H}_{23}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 346.1802; found: 346.1788.

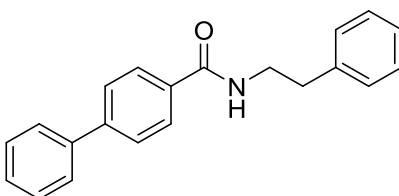
N-Hydroxy-3-(1-(naphthalen-1-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanamide (**3m**):



According to general procedure for step b, employing **10k** and hydroxylamine hydrochloride afforded **3m** as a white solid (82% yield). ^1H NMR (400 MHz, DMSO-*d*₆): δ 10.30 (brs, 1H), 8.59 (brs, 1H), 8.33 (d, $J = 8.42$ Hz, 1H), 7.91-7.86 (m, 2H), 7.48 (d, $J = 4.86$ Hz, 2H), 7.43 (t, $J = 7.38$ Hz, 1H), 7.35 (t, $J = 7.35$ Hz, 1H), 7.18 (d, $J = 7.48$ Hz, 1H), 7.06 (t, $J = 7.22$ Hz, 1H), 6.87 (t, $J = 7.36$ Hz, 1H), 6.47 (d, $J = 7.62$ Hz, 1H), 5.16 (s, 1H), 3.25-3.19 (m, 2H), 2.93-2.67 (m, 4H), 2.22-1.99 (m, 2H). ^{13}C NMR (100 MHz, DMSO-*d*₆): δ 168.4, 138.9, 134.6, 134.5,

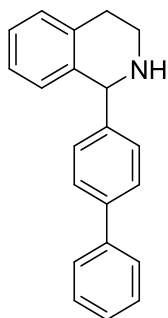
131.5, 130.6, 129.4, 128.9, 128.8, 128.6, 127.6, 126.5, 126.3, 126.1, 125.9, 125.7, 125.6, 60.2, 50.8, 29.9, 21.2, 14.6. HRMS m/z calculated for $C_{22}H_{22}N_2O_2$ $[M+H]^+$: 347.1754; 347.1745.

N-phenethyl-[1,1'-biphenyl]-4-carboxamide (**8j**):



According to general procedure for step c, employing **7j** and phenethylamine afforded **8j** as a white solid (90% yield). 1H NMR (400 MHz, chloroform-*d*): δ 7.78 (d, $J = 7.60$ Hz, 2H), 7.65-7.62 (m, 4H), 7.48 (t, $J = 7.20$ Hz, 2H), 7.40-7.35 (m, 3H), 7.31-7.25 (m, 3H), 6.22 (brs, 1H), 3.79-3.74 (m, 2H), 2.98 (t, $J = 6.80$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 166.8, 143.9, 139.6, 138.5, 132.9, 128.51 (2C), 128.46 (2C), 128.36 (2C), 127.6, 126.94 (2C), 126.84 (2C), 126.79 (2C), 126.2, 40.8, 35.3. HRMS m/z calculated for $C_{21}H_{19}NO$ $[M+H]^+$: 302.1539; found: 302.1527.

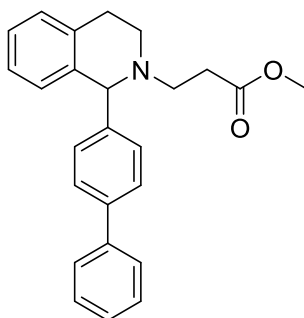
1-([1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydroisoquinoline (**9j**):



According to general procedure for step d, employing **8j**, phosphorus pentoxide and phosphoryl chloride afforded **9j** as a white solid (84% yield). 1H NMR (400 MHz, chloroform-*d*): δ 7.64-

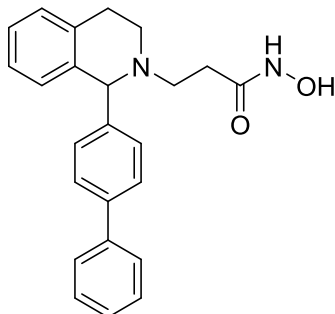
7.55 (m, 3H), 7.45 (t, $J = 7.60$ Hz, 2H), 7.35 (d, $J = 8.51$ Hz, 2H), 7.20 (d, $J = 4.40$ Hz, 1H), 7.15-7.05 (m, 4H), 6.85 (d, $J = 7.23$ Hz, 1H), 5.2 (s, 1H), 3.55-3.31 (m, 1H), 3.18-3.01 (m, 2H), 2.91-2.85 (m, 1H), 1.98 (brs, 1H). ^{13}C NMR (100 MHz, chloroform- d): δ 143.62, 140.5, 139.9, 137.8, 135.1, 129.6, 129.0 (2C), 128.7, 128.2 (2C), 127.8, 126.9 (2C), 126.8, 126.7, 125.9, 125.3, 61.4, 41.9, 29.2. HRMS m/z calculated for $\text{C}_{21}\text{H}_{19}\text{N}$ $[\text{M}+\text{H}]^+$: 286.1590; found: 286.1584.

Methyl 3-(1-([1,1'-biphenyl]-4-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate (**10l**):



According to general procedure for step e, employing **9j** and methyl 3-bromopropanoate afforded **10l** as a colorless oil (90% yield). ^1H NMR (400 MHz, chloroform- d): δ 7.62 (d, $J = 7.60$ Hz, 2H), 7.58 (d, $J = 8.04$ Hz, 2H), 7.45 (t, $J = 7.55$ Hz, 2H), 7.35 (t, $J = 7.24$ Hz, 2H), 7.21-7.14 (m, 2H), 7.05 (t, $J = 7.23$ Hz, 2H), 6.80 (d, $J = 8.00$ Hz, 1H), 4.70 (s, 1H), 3.65 (s, 3H), 3.22-3.15 (m, 2H), 3.01-2.86 (m, 2H), 2.78-2.71 (m, 2H), 2.52 (t, $J = 7.20$ Hz, 2H). ^{13}C NMR (100 MHz, chloroform- d): δ 173.2, 142.7, 140.5, 139.7, 137.7, 134.2, 129.6 (2C), 128.5, 128.3 (2C), 128.1, 126.8, 126.7 (2C), 126.5 (2C), 125.7, 125.3, 67.4, 51.1, 49.5, 46.7, 32.0, 28.3. HRMS m/z calculated for $\text{C}_{25}\text{H}_{25}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 372.1958; found: 372.1940.

3-(1-([1,1'-biphenyl]-4-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-hydroxypropanamide (**3n**):



According to general procedure for step b, employing **10l** and hydroxylamine hydrochloride afforded **3n** as a white solid (75% yield). ^1H NMR (400 MHz, DMSO- d_6): δ 10.41 (brs, 1H), 8.70 (brs, 1H), 7.65 (d, $J = 7.54$ Hz, 2H), 7.61 (d, $J = 7.60$ Hz, 2H), 7.45 (t, $J = 7.34$ Hz, 2H), 7.39-7.30 (m, 3H), 7.15 (d, $J = 7.65$ Hz, 1H), 7.11 (t, $J = 7.31$ Hz, 1H), 7.01 (t, $J = 7.29$ Hz, 1H), 6.70 (d, $J = 7.60$ Hz, 1H), 4.71 (s, 1H), 3.11-3.01 (m, 2H), 2.83-2.82 (m, 1H), 2.71-2.61 (m, 3H), 2.25-2.11 (m, 2H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 168.1, 143.1, 140.0, 138.9, 138.1, 134.5, 129.9, 129.0, 128.9, 128.53 (2C), 128.50, 127.4, 126.7 (2C), 126.5 (2C), 125.9, 125.6, 66.2, 50.2, 46.2, 30.0, 28.1. HRMS m/z calculated for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 373.1911; found: 373.1900.

Biology methods

Fluorogenic enzymatic assays for HDAC isoforms:

The inhibitory effect of the compounds on the activity of class I HDACs was determined *in vitro* using an optimized assay performed in 96-well opaque half-area microplate (Corning).

Recombinant, full-length human HDAC1 (BPS Biosciences #50051), 2 (BPS Biosciences #50002), 3 (BPS Biosciences #50003), and 8 (purified from *Escherichia coli* as described previously¹) were diluted in assay buffer 1 (25 mM Tris-HCl, 137 mM NaCl, 2.7 mM KCl, 1 mM MgCl₂, and 1 mg/mL BSA, pH 8.0) to give 4, 5, 1, 8.5 ng/μL stock solutions, respectively. Serial dilutions of inhibitors were made in assay buffer 2 (25 mM Tris-HCl, 137 mM NaCl, 2.7 mM KCl, 1 mM MgCl₂, pH 8.0). The reaction was initiated by mixing 10 μL of each enzyme stock to 30 μL of inhibitor and pre-incubated for 5 min at room temperature. After pre-incubation, 10 μL of 125 μM HDAC substrate Boc-L-Lys(Ac)-AMC (Chem-Impex, used for HDAC1, 2 and 3) or 10 μL of 25 μM Fluor de Lys[®] (Enzo Life Sciences BML-KI178, used for HDAC8, based on residues 379-382 of p53 (Arg-His-Lys(Ac)-Lys(Ac))) was added. The mixture was incubated for 35 min at room temperature. For HDAC1, 2, and 3, the reaction was quenched with 50 μL of 1 mg/mL trypsin and 5 μM trichostatin A dissolved in assay buffer 2. For HDAC8, the reaction was quenched with 50 μL of 50 μg/ml trypsin and 5 μM Trichostatin A dissolved in assay buffer 2. The mixture was further incubated at room temperature for 35 min. Fluorescence measurements were obtained with Synergy 4 Hybrid microplate reader (Bio-Tek) at excitation wavelength 360 nm and emission wavelength 460 nm. The experiments were repeated at least twice with each experiment containing three replicates. Replicate raw data were analyzed using the GraphPad Prism 7 software (GraphPad Software Inc., La Jolla, CA) to determine the IC₅₀ values for the inhibitors.

The inhibitory activity of the TIQ-based compounds for HDAC6 was determined using HDAC6 Fluorogenic Assay kit (BPS Biosciences #50076) per the manufacturer's instructions. Percent inhibition was calculated as absolute signal difference between wells treated with inhibitor and wells without inhibitor divided by signal of wells without inhibitor (positive control) times 100. Trichostatin A and SAHA were utilized as inhibitor positive controls with both showing >99% inhibition.

In vitro IC₅₀ data for TIQ-based HDAC inhibitors and PCI-34051

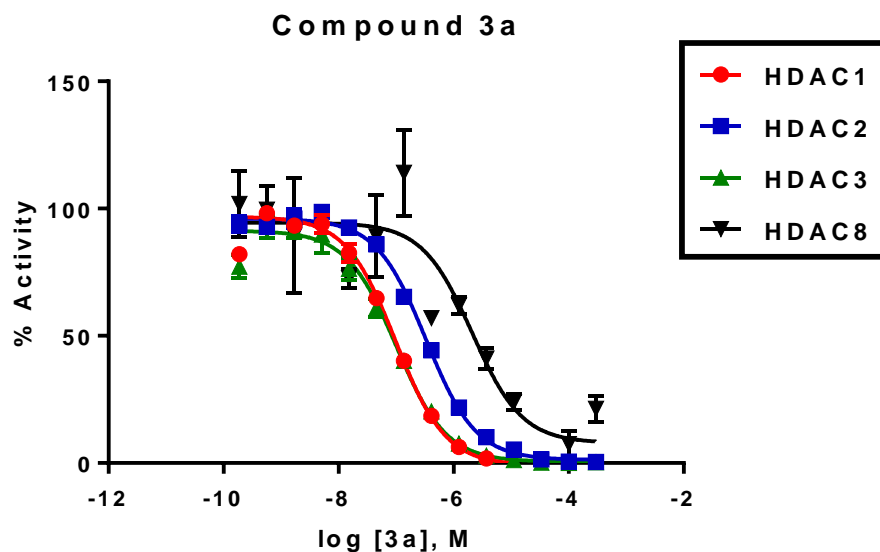


Figure S1. IC₅₀ analysis of compound **3a** for class I HDAC isoforms. Data plotted as mean ± standard deviation of percent activity of at least two independent experiments.

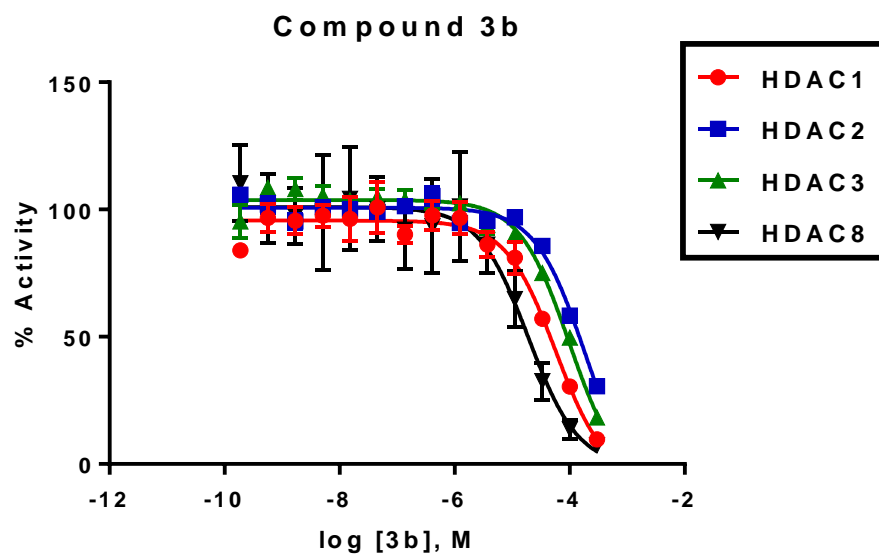


Figure S2. IC₅₀ analysis of compound **3b** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

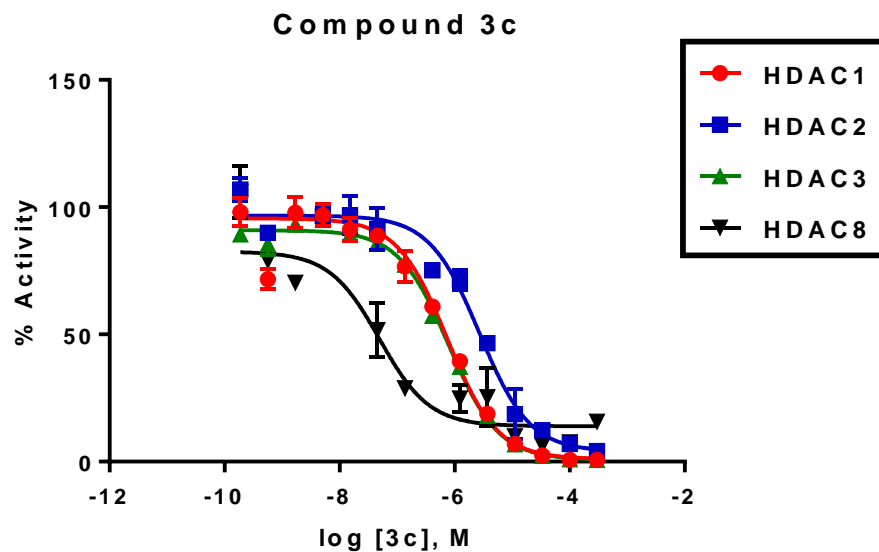


Figure S3. IC₅₀ analysis of compound **3c** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

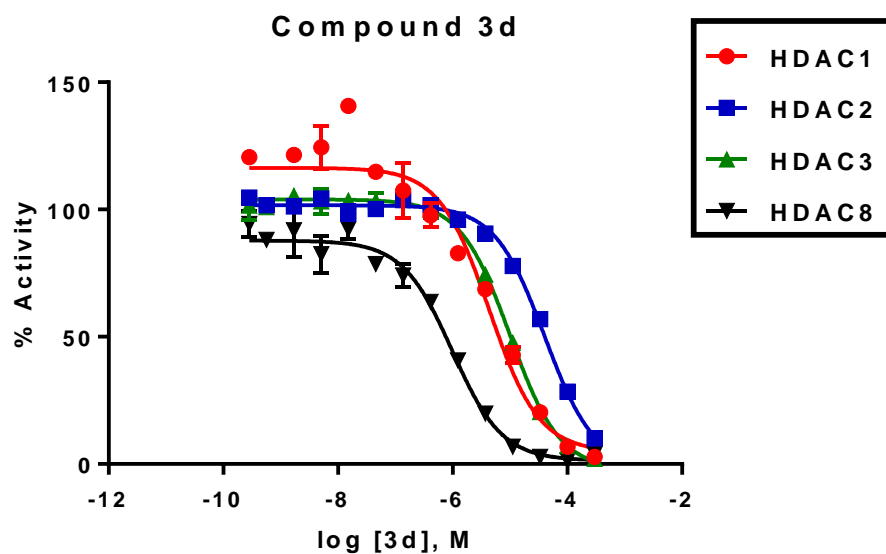


Figure S4. IC₅₀ analysis of compound **3d** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

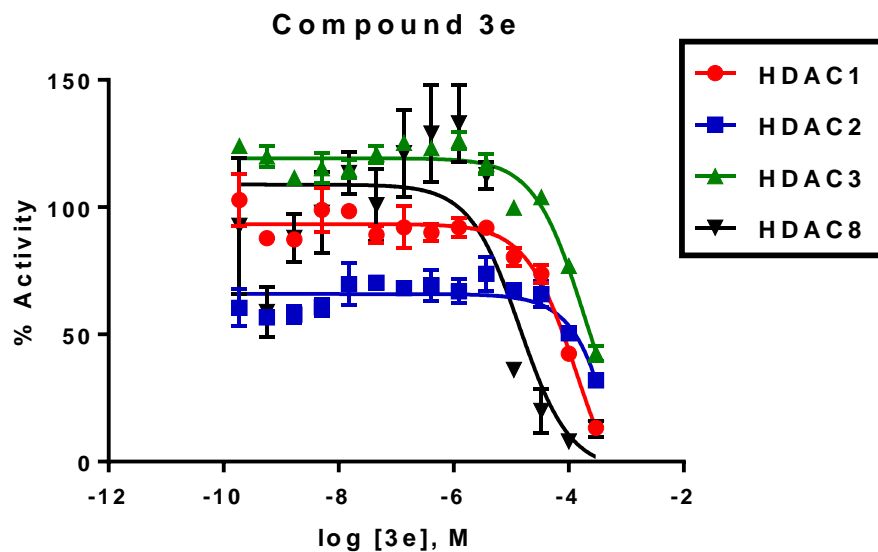


Figure S5. IC₅₀ analysis of compound **3e** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

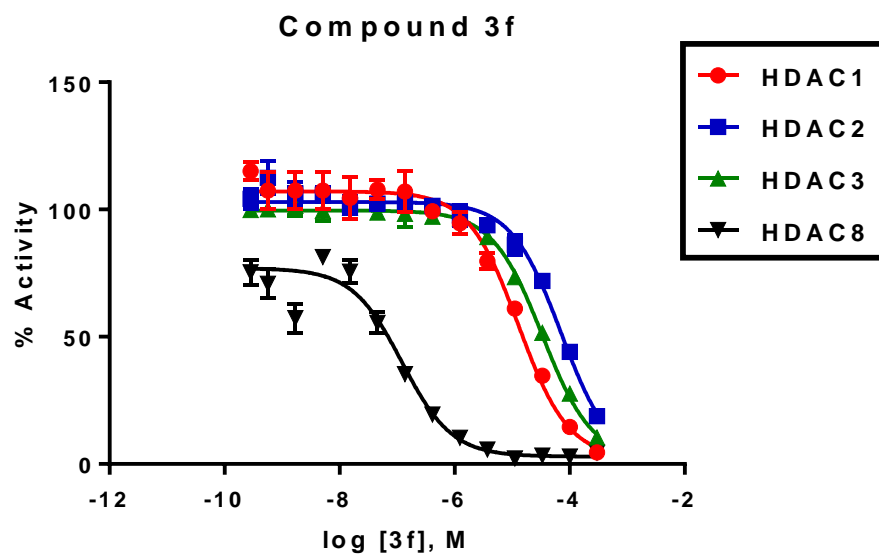


Figure S6. IC₅₀ analysis of compound **3f** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

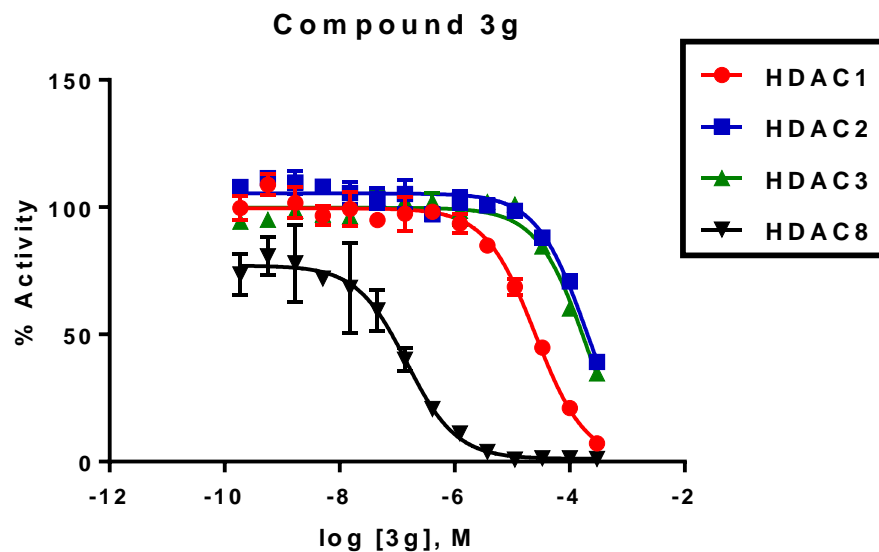


Figure S7. IC₅₀ analysis of compound **3g** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

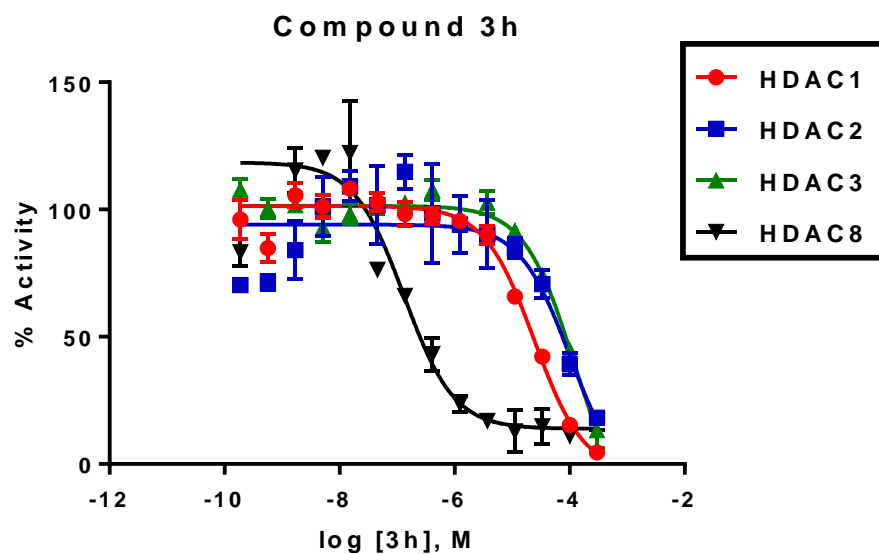


Figure S8. IC₅₀ analysis of compound **3h** for class I HDAC isoforms. Data plotted as mean ± standard deviation of percent activity of at least two independent experiments.

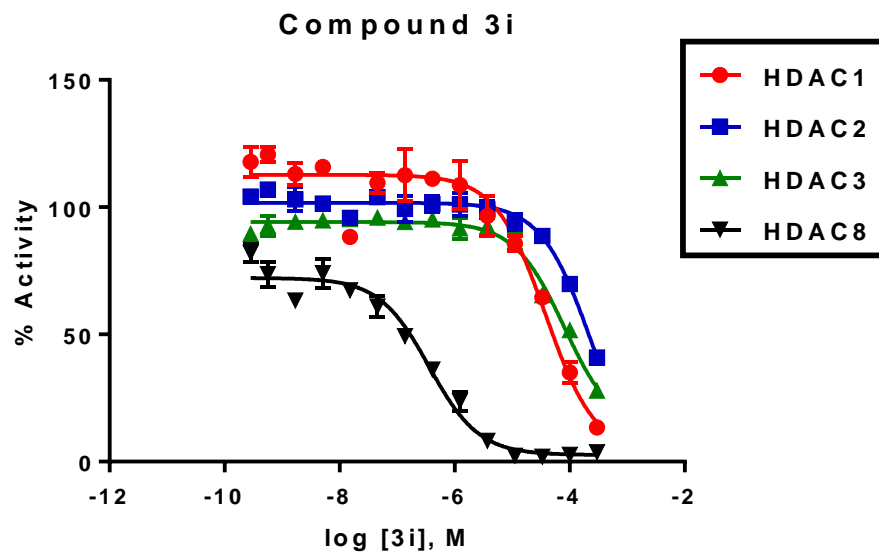


Figure S9. IC₅₀ analysis of compound **3i** for class I HDAC isoforms. Data plotted as mean ± standard deviation of percent activity of at least two independent experiments.

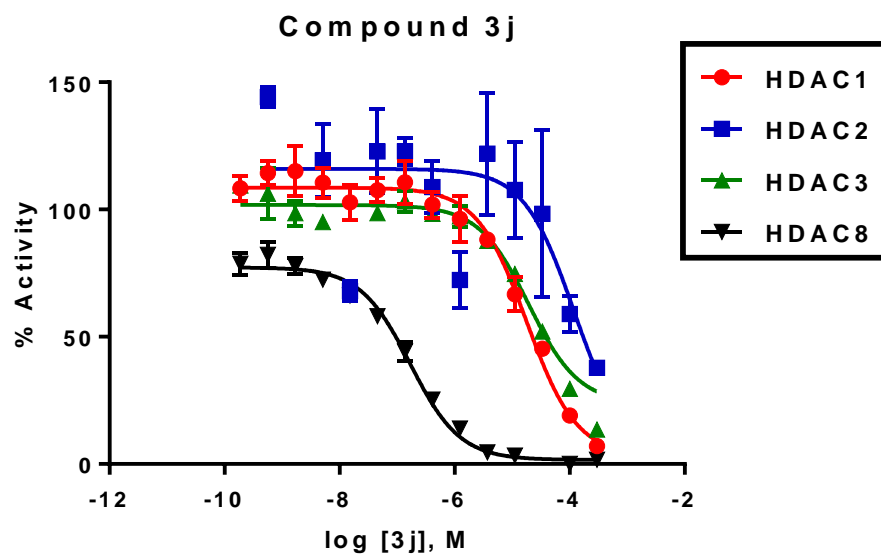


Figure S10. IC₅₀ analysis of compound **3j** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

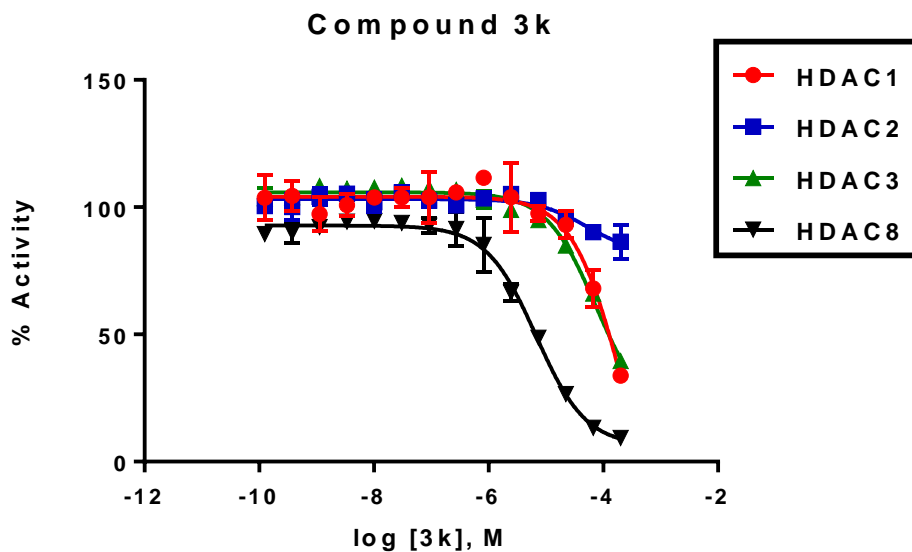


Figure S11. IC₅₀ analysis of compound **3k** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

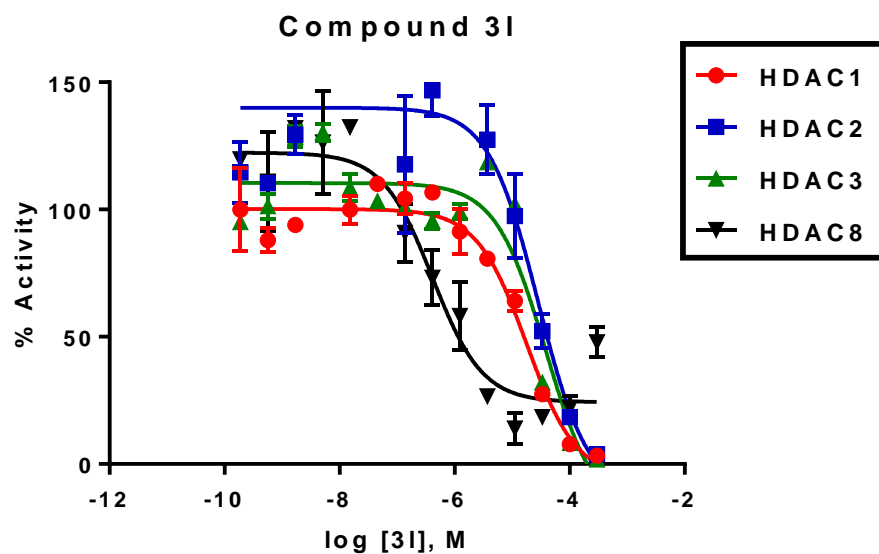


Figure S12. IC₅₀ analysis of compound **3l** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

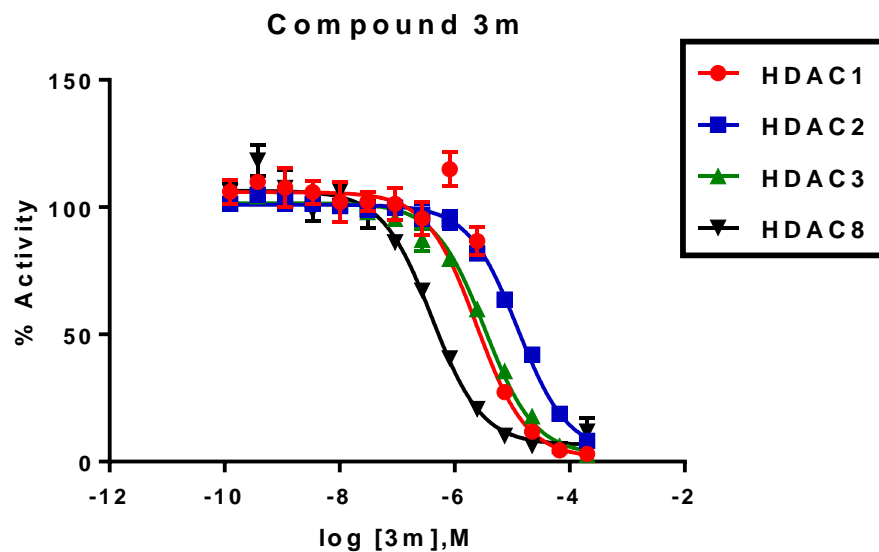


Figure S13. IC₅₀ analysis of compound **3m** for class I HDAC isoforms. Data plotted as mean \pm standard deviation of percent activity of at least two independent experiments.

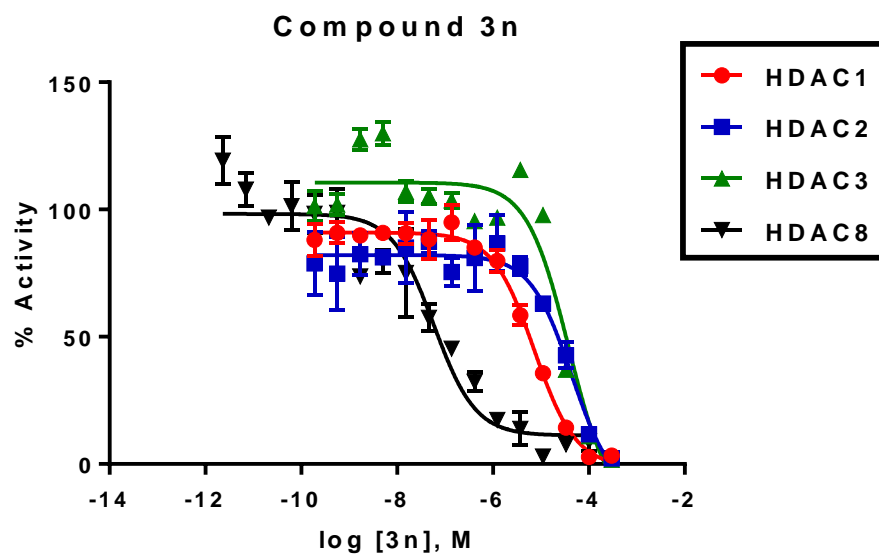


Figure S14. IC₅₀ analysis of compound **3n** for class I HDAC isoforms. Data plotted as mean ± standard deviation of percent activity of at least two independent experiments.

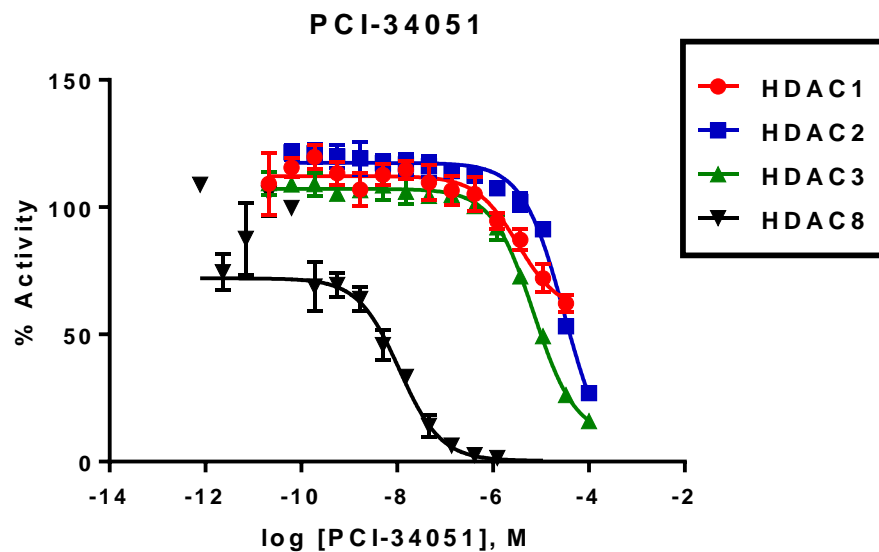


Figure S15. IC₅₀ analysis of **PCI-34051** for class I HDAC isoforms. Data plotted as mean ± standard deviation of percent activity of at least two independent experiments.

Cell Culture, Compound Treatment, and Cytotoxicity Assays

Human neuroblastoma *MYCN* amplified cell lines, IMR5 and Kelly, and non-*MYCN* amplified cell lines, SKNAS and SH-SY5Y, were used in this study. IMR5 and SH-SY5Y have wild type *TP53*, whereas Kelly and SKNAS harbor *TP53* mutations. IMR5, a clone of IMR32, was a gift of Roger H. Kennett (University of Pennsylvania, PA, USA). Kelly cell line was obtained from Sigma (St. Louis, MO, USA). SKNAS cell line was a gift of Susan L. Cohn (University of Chicago, IL, USA). SH-SY5Y was purchased from ATTC (CRL-2266). IMR5, SKNAS and Kelly were maintained in RPMI 1640 with 5% fetal bovine serum (FBS), 1% OPI (oxaloacetate pyruvate insulin, Sigma-Aldrich), and 1% penicillin-streptomycin at 37 °C in a humidified atmosphere of 5% CO₂. SH-SY5Y were cultured in Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F12) supplemented with 10% FBS and 1% penicillin-streptomycin at 37 °C in a humidified atmosphere of 5% CO₂.

For cytotoxicity studies, cells were seeded at 2×10^4 cells per 50 μ L per well in a 96-well plate one day prior to addition of compounds. After overnight incubation, cells were incubated with varying concentrations of compounds for defined periods of time. If incubating for more than 48 hours, on the third day half of the media was replaced with compound-containing fresh medium. Cell viability was determined by MTS using CellTiter 96[®] Aqueous One Solution Cell Proliferation Assay (Promega) according to the manufacturer's instructions. DMSO-treated cells served as a negative control. The experiments were performed in triplicate and repeated at least two times.

Cytotoxicity Data for 3g and 3n

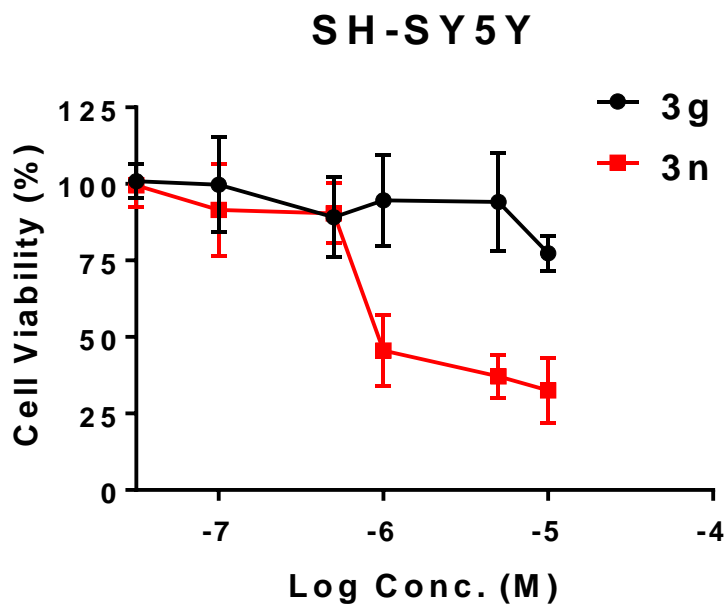


Figure S16. Concentration-dependent cytotoxicity analysis of **3g** and **3n** in SH-SY5Y cells after 48-hour treatment. Data plotted as mean \pm standard deviation of percent cell viability of at least two independent experiments.

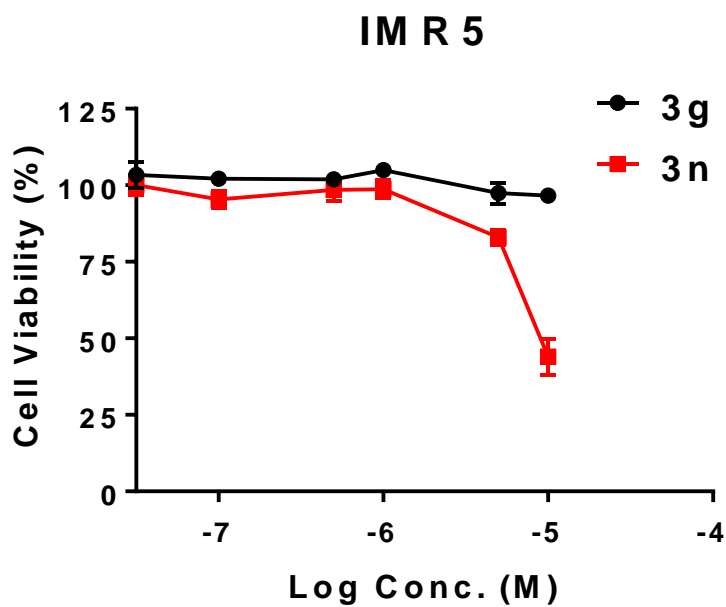


Figure S17. Concentration-dependent cytotoxicity analysis of **3g** and **3n** in IMR5 cells after 48-hour treatment. Data plotted as mean \pm standard deviation of percent cell viability of at least two independent experiments.

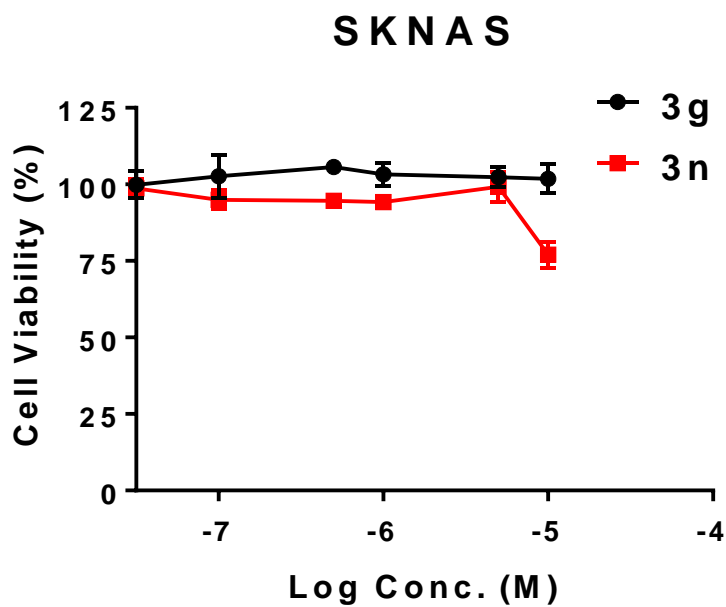


Figure S18. Concentration-dependent cytotoxicity analysis of **3g** and **3n** in SKNAS cells after 48-hour treatment. Data plotted as mean \pm standard deviation of percent cell viability of at least two independent experiments.

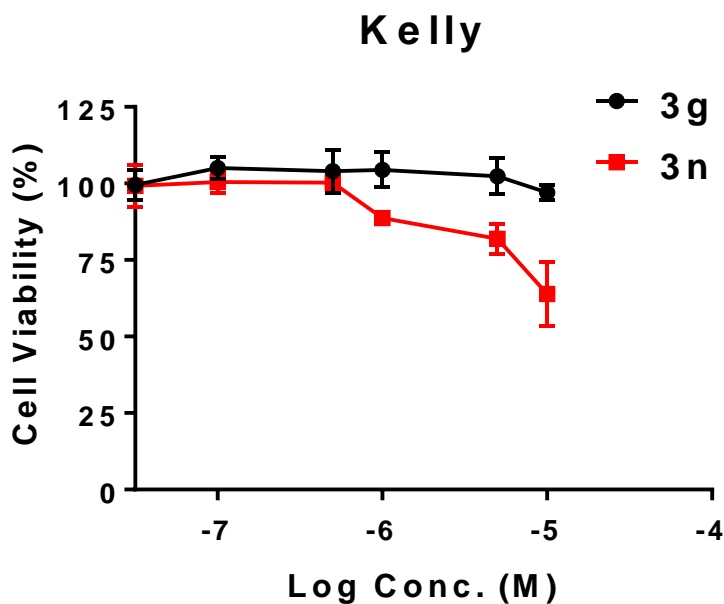


Figure S19. Concentration-dependent cytotoxicity analysis of **3g** and **3n** in Kelly cells after 48-hour treatment. Data plotted as mean \pm standard deviation of percent cell viability of at least two independent experiments.

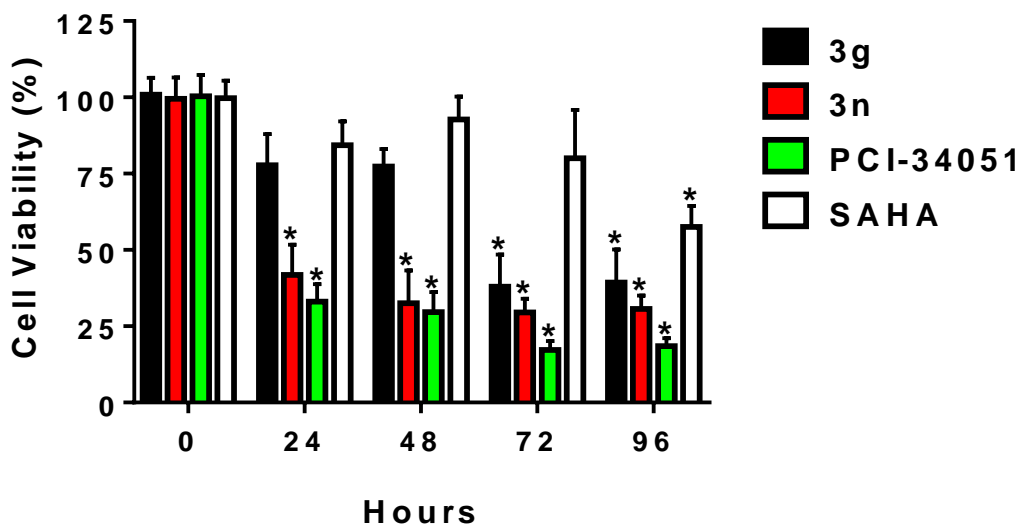


Figure S20. Time-dependent cytotoxicity analysis of **3g**, **3n**, PCI-34051, and SAHA in SH-SY5Y cells after treatment with 10 μ M of each compound for indicated timepoints. Data plotted as mean \pm standard deviation of percent cell viability of at least two independent experiments. * Statistically significant difference compared with DMSO control (Student's t-test, $p < 0.01$).

Western Blot

SH-SY5Y cells were cultured up to 90% confluence in 6-well plates and treated with varying concentrations of compounds for defined periods of time. At termination of treatment, cells were washed twice with ice-cold PBS and protein was extracted by adding ice-cold RIPA buffer (Cell Signaling Technology) supplemented with protease and phosphatase inhibitors (Calbiochem). Cells were scraped and the cell lysate was centrifuged at 10,000g for 10 min at 4 °C. Protein concentration was characterized with the Pierce BCA Assay Kit (Thermo Fischer). Proteins were diluted 3:1 with 4X Laemmli sample buffer containing 5% β -mercaptoethanol (Bio-Rad), boiled for 5 minutes, loaded onto a 12% polyacrylamide gel and separated by electrophoresis (100 V, 1.5 hours). Proteins were transferred to a nitrocellulose membrane (iBlot 2 (Invitrogen) mode P3

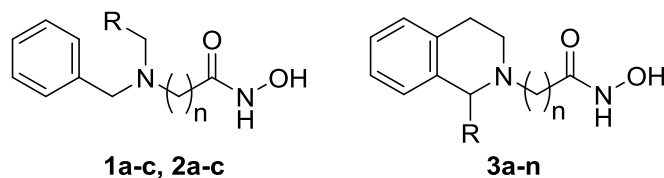
for 7 minutes). Equal protein loading was confirmed with Ponceau S staining solution (Sigma-Aldrich). The membranes were then blocked with Odyssey blocking buffer (Li-Cor) for 2 hours at room temperature, and then incubated with primary antibodies in blocking buffer for acetyl α -tubulin (Santa Cruz, sc-23950), acetyl histone H3 (Millipore Sigma, 06-599), histone H3 (Abcam, ab1791), and GAPDH (Abcam, ab128915) overnight at 4 °C. The membranes were then washed three times with PBS containing 0.1% Tween-20 (PBST) for 5 minutes at room temperature. The membranes were then incubated with an anti-rabbit or anti-mouse IRDye-conjugated secondary antibody (Li-Cor) for 1 hour at RT. The membranes were then washed 3 times with PBST for 5 minutes and visualized using the Odyssey Sa scanner (Li-Cor).

Modeling methods:

Coordinates of X-ray models of class I HDAC1 (5ICN),² HDAC2 (3MAX),³ HDAC3 (4A69),⁴ HDAC8 (1T69 and 1VKG)⁵ and class II HDAC6 (5EDU)⁶ were downloaded from the protein data bank (PDB). All molecular modeling studies were performed in Molecular Operating Environment (MOE).⁷ The proteins were subjected to the “structure preparation” procedure. Hydrogen atoms were added using the Protonate3D algorithm. The energy of the resulting structure was minimized utilizing AMBER12EHT forcefield.^{8,9} The ligands were assigned MMFF94x charges and minimized using the MMFF94x forcefield until the RMS gradient was less than 0.001 kcal/mol/Å². The MOE docking module “Dock” was used for docking/scoring using the default parameters and settings. SAHA was used to define the binding site. Docking was performed using the “induced fit” and the “rigid receptor” algorithms, “Triangle Matcher” for placement, “London dG” for scoring of the binding poses after placement, and “GBVI/WSA dG” for rescoring of the resulting poses.

In silico drug-like properties of amine-based and TIQ-based HDAC inhibitors were calculated in MOE and are listed below in Table S1.

The scores of the top docking poses of all the compounds are listed below in Table S2-S4

Table S1. *In silico* physicochemical properties of amine-based and TIQ-based HDAC inhibitors.

Compound ^a	n	R	h_logS ^b	TPSA ^c	cLogP ^d
1a	6	H	-0.724	68.8	2.84
1b	4	H	-0.167	68.8	1.96
1c	2	H	0.258	68.8	1.08
2a	6	phenyl	-3.20	56.6	4.90
2b	4	phenyl	-2.64	56.6	4.01
2c	2	phenyl	-2.22	56.6	3.13
3a	6	H	-1.61	56.6	3.02
3b	2	H	-0.630	56.6	1.25
3c	4	phenyl	-2.85	56.6	4.04
3d	2	phenyl	-2.43	56.6	3.16
3e	1	phenyl	-2.32	56.6	3.07
3f	2	3-methoxyphenyl	-2.50	65.8	3.15
3g	2	4-methoxyphenyl	-2.50	65.8	3.11
3h	2	4-ethoxyphenyl	-2.74	65.8	3.46
3i	2	3-(trifluoromethyl)phenyl	-3.15	56.6	4.13
3j	2	4-(trifluoromethyl)phenyl	-3.14	56.6	4.09
3k	2	cyclohexyl	-2.21	56.6	3.52
3l	2	4-(<i>tert</i> -butyl)phenyl	-4.36	56.6	4.66
3m	2	naphthalene-2-yl	-3.64	56.6	4.38
3n	2	1,1'-biphenyl-4-yl	-4.67	56.6	5.12

^a All compounds did not violate Lipinski's Rule of Five

^b Log of the aqueous solubility (mol/L) using a 7-parameter model based on Hueckel Theory

^c Topological polar surface area in Å²

^d Log of the octanol/water partition coefficient

Table S2. Scores for top docking poses in closed conformation of HDAC8 (PDB: 1T69).

Compound	S ^a	rmsd_refine ^b	E_conf ^c	E_Place ^d	E_score1 ^e	E_refine ^f	E_score2 ^g
1a	-5.560	2.402	-9.415	-20.873	-13.595	-64.260	-5.560
1b	-5.215	1.278	-16.556	-23.085	-12.252	-60.185	-5.215
1c	-5.030	1.303	-27.241	-14.157	-9.747	-46.741	-5.030
2a	-5.864	1.611	12.607	-21.877	-11.918	-62.146	-5.864
2b	-6.264	2.741	20.477	-30.575	-9.484	-57.403	-6.264
2c	-5.945	3.193	-15.649	-14.668	-10.975	-54.114	-5.945
3a	-5.865	0.936	3.926	-37.504	-12.552	-63.673	-5.865
3b	-5.128	4.915	-11.829	3.314	3.371	-42.592	-5.128
3c	-6.324	3.040	13.430	-19.701	-2.288	-63.199	-6.324
3d	-6.045	3.697	-3.673	-7.891	-2.402	-43.778	-6.045
3e	-6.076	2.242	87.107	-9.145	-4.712	-30.779	-6.076
3f	-6.167	4.079	-9.800	-13.395	4.598	-58.095	-6.167
3g	-6.342	2.573	-8.336	-6.824	-7.224	-48.471	-6.342
3h	-6.564	2.697	-10.822	-7.070	-6.730	-53.962	-6.564
3i	-6.411	2.363	80.013	-8.107	-4.410	-41.598	-6.411
3j	-6.484	1.908	23.083	-4.967	2.981	-60.404	-6.484
3k	-5.845	2.484	17.468	-1.367	8.174	-58.042	-5.845
3l	-6.502	4.150	-24.921	-16.817	-2.869	-52.363	-6.502
3m	-6.729	4.123	-12.043	-4.376	1.303	-37.448	-6.729
3n	-7.002	4.196	25.074	-10.869	11.421	-9.709	-7.002
PCI-34051	-5.772	2.054	71.361	-22.748	-11.464	-59.307	-5.772

^a The final score, which is the score of the last stage that was not set to None.

^b The root mean square deviation between the pose before refinement and the pose after refinement.

^c The energy of the conformer. If there is a refinement stage, this is the energy calculated at the end of the refinement.

^d Score from the placement stage (before refinement stage).

^e Score from rescoring stage 1.

^f Score from the refinement stage, calculated to be the sum of the van der Waals electrostatics and solvation energies, under the Generalized Born solvation model (GB/VI).

^g Score from rescoring stage 2.

Table S3. Scores for top docking poses in open conformation of HDAC8 (PDB: 1VKG).

Compound	S ^a	rmsd_refine ^b	E_conf ^c	E_Place ^d	E_score1 ^e	E_refine ^f	E_score2 ^g
1a	-5.905	3.705	-10.908	-14.963	-9.961	-65.228	-5.905
1b	-5.387	1.711	-11.449	-20.268	-8.437	-57.613	-5.387
1c	-5.177	3.873	-36.476	-8.019	0.811	-22.777	-5.177
2a	-7.187	2.229	23.465	-9.950	-8.576	-59.397	-7.187
2b	-6.077	2.438	9.412	-26.927	-8.802	-64.399	-6.077
2c	-6.054	2.192	-2.989	-29.512	-10.733	-58.398	-6.054
3a	-6.149	1.517	8.436	-22.106	-9.713	-68.064	-6.149
3b	-5.624	4.411	-13.679	-0.277	5.889	-24.759	-5.624
3c	-6.376	4.013	15.760	-13.977	0.758	-33.940	-6.376
3d	-6.079	3.184	-1.263	-4.668	10.300	-61.348	-6.079
3e	-5.990	1.844	94.821	-11.148	1.672	-50.650	-5.990
3f	-6.342	2.587	-8.949	-4.912	1.373	-51.339	-6.342
3g	-6.672	3.984	-11.144	10.845	15.577	-32.980	-6.672
3h	-6.605	5.506	-17.474	-0.318	7.940	-33.516	-6.605
3i	-6.007	2.818	73.663	-11.849	-1.721	-55.738	-6.007
3j	-6.420	2.918	28.376	-23.111	-5.686	-65.009	-6.420
3k	-6.153	2.579	21.479	-5.830	-0.345	-24.228	-6.153
3l	-7.064	3.886	-22.526	-1.707	12.768	-67.128	-7.064
3m	-6.182	3.060	-1.687	-21.098	0.781	-65.287	-6.182
3n	-6.506	4.583	3.537	7.437	14.799	-55.532	-6.506
PCI-34051	-6.220	3.006	70.581	-21.980	-7.474	-33.086	-6.220

^a The final score, which is the score of the last stage that was not set to None.

^b The root mean square deviation between the pose before refinement and the pose after refinement.

^c The energy of the conformer. If there is a refinement stage, this is the energy calculated at the end of the refinement.

^d Score from the placement stage (before refinement stage).

^e Score from rescoring stage 1.

^f Score from the refinement stage, calculated to be the sum of the van der Waals electrostatics and solvation energies, under the Generalized Born solvation model (GB/VI).

^g Score from rescoring stage 2.

Table S4. Scores for top docking poses in HDAC6 (PDB: 5EDU).

Compound	S ^a	rmsd_refine ^b	E_conf ^c	E_Place ^d	E_score1 ^e	E_refine ^f	E_score2 ^g
1a	-6.127	1.609	-9.539	-27.674	-8.725	-64.227	-6.127
1b	-5.917	1.278	-15.998	-22.289	-10.571	-62.278	-5.917
1c	-5.465	1.430	-43.089	-24.494	-8.756	-56.987	-5.465
2a	-7.077	2.454	15.832	-24.608	-6.246	-72.488	-7.077
2b	-6.541	3.387	5.598	-12.421	-3.461	-69.948	-6.541
2c	-5.863	4.444	-18.843	-3.953	-0.469	-32.239	-5.863
3a	-6.730	2.508	4.942	-21.810	-10.166	-69.020	-6.730
3b	-5.967	4.462	-16.435	-6.621	-1.439	-62.085	-5.967
3c	-6.383	3.342	17.243	-13.408	0.398	-70.128	-6.383
3d	-6.170	3.385	-10.035	-13.169	3.298	-61.825	-6.170
3e	-5.647	3.627	95.813	-6.629	0.750	-42.980	-5.647
3f	-6.531	2.617	-12.475	-8.275	3.573	-65.772	-6.531
3g	-6.436	3.851	-12.135	8.727	16.958	-62.201	-6.436
3h	-6.591	4.889	-10.663	2.383	8.127	-54.953	-6.591
3i	-6.054	4.507	69.675	-8.468	0.608	-34.148	-6.054
3j	-6.517	3.468	21.348	-13.480	3.765	-65.814	-6.517
3k	-6.646	1.363	16.597	-25.703	-7.295	-64.698	-6.646
3l	-6.799	2.207	-28.237	-8.056	2.921	-66.737	-6.799
3m	-5.742	3.866	-15.060	-10.344	0.248	-31.432	-5.742
3n	-7.001	2.657	-2.750	-5.799	11.809	-67.528	-7.001
PCI-34051	-6.128	2.154	70.574	-15.983	-1.577	-41.075	-6.128

^a The final score, which is the score of the last stage that was not set to None.

^b The root mean square deviation between the pose before refinement and the pose after refinement.

^c The energy of the conformer. If there is a refinement stage, this is the energy calculated at the end of the refinement.

^d Score from the placement stage (before refinement stage).

^e Score from rescoring stage 1.

^f Score from the refinement stage, calculated to be the sum of the van der Waals electrostatics and solvation energies, under the Generalized Born solvation model (GB/VI).

^g Score from rescoring stage 2.

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