Supporting Information

Structure-Activity Relationship Studies of a Series of Novel δ-Lactam based Histone Deacetylase Inhibitors

Hwan Mook Kim, Dong-Kyu Ryu, Yongseok Choi, Bum Woo Park, Kiho Lee, Sang Bae Han, Chang-Woo Lee, Moo-Rim Kang, Jong Soon Kang, Shanthaveerappa K. Boovanahalli[†] Song-Kyu Park,[*] Jung Whan Han, Tae-Gyu Chun,[¶] Hee-Yoon Lee, Ky-Youb Nam, Eun Hyun Choi, Gyoonhee Han[*]

Experimental Section. All chemicals were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed with silica (Merck EM9385, 230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 300 and at 75 MHz respectively. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane, coupling constants (*J*) are expressed in Hertz. Compound purity was assessed by the reverse phase HPLC (Shimadzu LCMS-2010, using XTerra RP_{18} 4.6x150 mm column) using the following methods, A: 90% MeCN (0.1% TFA)/10 % H_2O (0.1% TFA), 1 mL/min in 20 min, B: 95% MeCN (0.1% TFA)/5 % H_2O (0.1% TFA), 0.2 mL/min in 20 min. Cells were obtained from R&D Systems, Minneapolis, MN, USA.

General Procedures for 7-9. **6a-c** (1.2 equiv) was dissolved in methylene chloride and then **5a** in methylene chloride was added *via* cannular at room temperature under Ar atmosphere. EDC (1.3 equiv) and DMAP (0.3 equiv) were added and the mixture was stirred for 8 h at room temperature. The mixture was diluted with ethyl acetate and washed with 5% HCl, sat. $NaHCO_3$ solutions, brine, and the organic layer was dried over anhydrous $MgSO_4$, **9-11** was obtained by flash chromatography.

3-(Benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (**7a**). **5a** (248 mg, 1.53 mmol) was used and **7a** (170 mg, 38%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.29 (d, *J*= 6.9 Hz, 2H), 7.22 (t, *J*= 6.9 Hz, 3H), 5.69 (br t, 1H), 5.23 (s, 2H), 5.04 (s, 1H), 4.97 (d, *J*= 9.3 Hz,1H), 4.71 (d, *J*= 16.9 Hz, 2H), 3.61 (s, 3H), 3.42 (s, 4H), 2.30 (q, *J*= 7.2 Hz, 2H); ESI (*m/z*) 310.5 (MNa^+).

3-(But-3-enyl-phenethyl-carbamoyl)-but-3-enoic acid methyl ester (**7b**). **5b** (100 mg, 0.57 mmol) was used and **7b** (100 mg, 58%, oil) was obtained by flash chromatography

(ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.28-7.14 (m, 5H), 6.36 (t, *J*= 4.1 Hz, 1H), 3.67 (s, 3H), 3.58 (t, *J*= 7.2 Hz, 2H), 3.26-3.20 (m, 4H), 2.84 (t, *J*= 7.3 Hz, 1H), 2.22 (dd, *J*= 6.7, 5.8 Hz, 2H); ESI (*m/z*) 324.5 (MNa^+).

3-[But-3-enyl-(3-phenyl-propyl)-carbamoyl]-but-3-enoic acid methyl ester (**7c**). **5c** (100 mg, 0.53 mmol) was used and **7c** (100 mg, 58%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.14-7.00 (m, 5H), 5.57 (d, 1H), 4.92-4.84 (m, 2H), 3.49 (s, 3H), 3.29-3.23 (m, 5H), 2.45 (br t, 2H), 2.14 (dd, *J* = 7.1, 7.4 Hz, 2H), 1.88-1.70 (m, 2H); ESI (*m/z*) 338.5 (MNa^+).

3-[But-3-enyl-(4-phenyl-butyl)-carbamoyl]-but-3-enoic acid methyl ester (**7d**). **5d** (130 mg, 0.64 mmol) was used and **7d** (110 mg, 52%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/3). ^{1}H NMR ($CDCl_3$) δ 7.25 (t, *J*= 7.4 Hz, 2H), 7.17-7.13 (m, 3H), 5.74 (br t, 1H), 5.28-5.00 (m, 5H), 3.62 (s, 3H), 3.39 (d, *J*= 9.3 Hz, 5H), 2.61 (s, 2H), 2.29 (q, *J*= 7.2 Hz, 2H), 1.60 (s, 4H); ESI (*m/z*) 352.6 (MNa^+).

4-(Benzyl-but-3-enyl-carbamoyl)-pent-4-enoic acid methyl ester (**8a**). **5a** (600 mg, 3.72 mmol) was used and **8a** (600 mg, 54%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.33-7.12 (m, 5H), 5.10-4.98 (m, 3H), 4.59 (s, 2H), 3.62 (s, 4H), 3.37 (s, 2H), 2.57 (dd, *J*= 5.4 Hz, 5H), 2.26 (s, 2H), 1.47 (q, *J*= 7.8 Hz , 1H); ESI (*m/z*) 324.5 (MNa^+).

4-(But-3-enyl-phenethyl-carbamoyl)-pent-4-enoic acid methyl ester (**8b**). **5b** (500 mg, 2.85 mmol) was used and **8b** (580 mg, 64%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.30-7.11 (m, 5H), 6.72 (br t, 1H), 5.02 (d, *J*= 10.2 Hz, 4H), 3.63 (s, 3H), 3.52 (s, *J*= 7.3 Hz, 3H), 3.23 (s, *J*= 7.3 Hz, 1H), 2.80 (s, 2H), 2.47 (s, 4H), 2.34 (s, 2H); ESI (*m/z*) 338.5 (MNa^+).

4-[But-3-enyl-(3-phenyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (**8c**). **5c**

(200 mg, 1.06 mmol) was used and **8c** (253 mg, 72%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/3). ^{1}H NMR ($CDCl_3$) δ 7.29-7.15 (m, 5H), 5.70 (br t, 1H), 5.01-5.00 (m, 4H), 3.65 (s, 3H), 3.37-3.32 (m, 4H), 2.54 (d, *J*= 7.8 Hz, 6H), 2.27 (s, 2H), 1.87 (s, 1H); ESI (*m/z*) 352.6 (MNa^+).

4-[But-3-enyl-(4-phenyl-butyl)-carbamoyl]-pent-4-enoic acid methyl ester (**8d**). **5d** (150mg, 0.74mmol) was used and **8d** (165mg, 70%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.29-7.13 (m, 5H), 5.10-5.01 (m, 5H), 3.65 (s, 3H), 3.35 (s, 4H), 2.61-2.49 (m, 6H), 2.27 (s, 2H), 1.55 (s, 4H), 1.25 (t, *J*= 3.7 Hz, 2H); ESI (*m/z*) 352.6 (MNa^+).

5-(But-3-enyl-phenethyl-carbamoyl)-hex-5-enoic acid methyl ester (**9b**). **5b** (300 mg, 1.71 mmol) was used and **9b** (553 mg, 98%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.30-7.10 (m, 5H), 6.80-5.60 (m, 1H), 5.09-4.91 (m, 4H), 3.63 (s, 3H), 3.52 (t, *J*= 7.3 Hz, 3H,), 3.22 (s, 1H), 2.83 (d, 2H), 2.33-2.11 (m, 6H) 1.75 (s, 2H); ESI (*m/z*) 352.6 ($M\ Na^+$).

5-[But-3-enyl-(3-phenyl-propyl)-carbamoyl]-hex-5-enoic acid methyl ester (**9c**). **5c** (200 mg, 1.05 mmol) was used and **9c** (172 mg, 48%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.29-7.15 (m, 5H), 5.69 (br t, 1H), 5.06-5.00 (m, 3H), 3.64 (s, 3H), 3.38 (d, *J*= 5.7 Hz, 3H), 2.58 (br t, 2H), 2.37-2.24 (m, 6H), 1.87-1.77 (m, 4H); ESI (*m/z*) 366.6 (MNa^+).

5-[But-3-enyl-(4-phenyl-butyl)-carbamoyl]-hex-5-enoic acid methyl ester (**9d**). **5d** (300 mg, 1.48 mmol) was used and **9d** (419 mg, 79%, oil) was obtained by flash chromatography (ethyl acetate/ hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.27-7.12 (m, 5H), 5.76 (br t, 1H), 5.08 (d, *J*= 7.9 Hz, 2H), 5.06-5.00 (m, 2H), 3.63 (s, 3H), 3.34 (br t, 4H), 2.60 (s, 2H), 2.36-2.25 (m, 6H), 1.82-1.75 (m, 2H), 1.55 (s, 4H); ESI (*m/z*) 380.6

(MNa^+).

General Procedures for 10-12. 7-9 was dissolved in methylene chloride (0.01 M) and the mixture was gased by Ar bubbling for 30 min. After Grubb's catalyst (Type I, 0.02 equiv) was added, the reaction mixture was stirred for 12h in dark. The mixture was concentrated *in vacuo* and **10-12** was obtained by flash chromatography.

(1-Benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid methyl ester (**10a**). **7a** (77 mg, 0.26 mmol) was used and **10a** (50 mg, 74%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.30-7.23 (m, 5H), 6.42 (t, *J*= 4.2 Hz, 1H), 4.61 (s, 2H), 3.69 (s, 3H), 3.32 (t, *J*= 7.2 Hz, 4H), 2.32 (dd, *J*= 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 171.96, 164.46, 137.34, 136.80, 129.34, 128.55, 127.90, 127.32, 51.91, 50.02, 44.68, 36.38, 23.92; ESI (*m/z*) 282.4 (MNa^+).

(2-Oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid methyl ester (**10b**). **7b** (517 mg, 1.72 mmol) was used and **10b** (446 mg, 94%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.21-7.12 (m, 5H), 6.31 (t, *J*= 3.9 Hz, 1H), 3.62(s, 3H), 3.54 (t, *J*= 7.2 Hz, 2H), 3.21-3.15 (m, 4H), 2.80 (t, *J*= 7.3 Hz, 2H), 2.16 (q, *J*= 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 171.93, 164.14, 139.17, 136.65, 129.40, 128.80, 128.37, 126.23, 49.51, 46.34, 36.14, 34.12, 23.87; ESI (*m/z*) 296.4 (MNa^+).

[2-Oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (10c). **7c** (60 mg, 0.19 mmol) was used and **10c** (50 mg, 92%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.19 (t, *J*= 7.7 Hz, 2H), 7.11 (d, *J*= 8.0 Hz, 3H), 6.33 (t, *J*= 3.8 Hz, 1H), 3.61 (s, 3H) 3.38 (t, *J*= 7.5 Hz, 2H), 3.32 (t, *J*= 7.2 Hz, 2H), 3.21(s, 2H), 2.56 (t, *J*= 7.7 Hz, 2H), 2.28 (q, *J*= 6.5Hz, 2H), 1.82-1.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.80, 164.25, 141.69, 136.04, 129.79, ,

128.30, 128.24, 125.80, 51.68, 46.81, 45.43, 36.11, 33.22, 29.23, 24.06; ESI (*m/z*) 310.5 (MNa^+).

[2-Oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (**10d**). **7d** (110 mg, 0.33 mmol) was used and **10d** (90 mg, 90%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.26-7.13 (m, 5H), 6.37 (t, *J*= 4.2 Hz, 1H), 3.64 (s, 3H), 3.42-3.32 (m, 4H), 3.26 (s, 2H) 2.61 (t, *J*= 6.9 Hz, 2H), 2.32 (q, *J*= 6.9 Hz, 2H), 1.64-1.53 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.92, 164.13, 142.17, 136.23, 129.55, 128.32, 128.18, 125.62, 51.79, 46.59, 45.21, 36.25, 28.52, 27.07, 23.93; ESI (*m/z*) 324.5 (MNa^+).

3-(1-Benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (**11a**). **8a** (530 mg, 1.76 mmol) was used and **11a** (389 mg, 81%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.32-7.20 (m, 5H), 6.30 (t, *J*= 4.3 Hz, 1H), 4.59 (s, 2H), 3.62 (s, 3H), 3.24 (t, *J*= 6.9 Hz, 2H), 2.61 (t, *J*= 6.4 Hz, 2H), 2.55-2.50 (m, 2H), 2.24 (q, *J*= 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.52, 164.80, 137.49, 134.31, 133.92, 128.46, 127.85, 127.22, 51.36, 49.89, 44.69, 33.23, 26.65, 23.76; ESI (*m/z*) 296.4 (MNa^+).

3-(2-Oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (**11b**). **8b** (500 mg, 1.74 mmol) was used and **11b** (400 mg, 80%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.28-7.15 (m, 5H), 6.25 (t, *J*= 4.2 Hz, 1H), 3.63 (s, 3H), 3.59 (t, *J*= 7.4 Hz, 2H), 2.84 (t, *J*= 7.2 Hz, 2H), 2.55 (d, *J*= 6.0 Hz, 2H), 2.49 (d, *J*= 6.6 Hz, 2H), 2.15 (q, *J*= 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.46, 164.60, 139.31, 134.42, 133.90, 128.80, 126.24, 51.23, 49.30, 46.36, 34.23, 33.33, 26.54, 23.88; ESI (*m/z*) 310.4 (MNa^+).

3-[2-Oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid

methyl ester (**11c**). **8c** (220 mg, 0.67 mmol) was used and **11c** (160 mg, 79%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.29-7.23 (m, 3H), 7.17 (d, *J*= 7.5 Hz, 2H), 6.28 (t, *J*= 4.5 Hz, 1H), 5.07-5.00 (m, 1H), 3.64 (d, *J*= 5.1 Hz, 2H), 3.47-3.28 (m, 3H), 2.65-2.48 (m, 4H), 2.26 (q, *J*= 6.9 Hz, 1H), 1.92-1.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.13, 133.59, 133.50, 127.77, 127.71, 125.27, 50.76, 46.03, 46.87, 32.74, 32.68, 28.76, 26.09, 23.37; ESI (*m/z*) 324.5 (MNa^+).

3-[2-Oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (**11d**). **8d** (165 mg, 0.54 mmol) was used and **11d** (140 mg, 82%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.28-7.14 (m, 5H), 6.27 (t, *J*= 4.2 Hz, 1H), 3.63 (s, 3H), 3.40 (t, *J*= 6.8 Hz, 2H), 3.28 (t, *J*= 7.4 Hz, 2H), 2.65-2.48 (m, 6H), 2.26 (q, *J*= 6.6 Hz, 2H), 1.60-1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 173.49, 164.52, 142.11, 134.16, 133.72, 128.26, 128.13, 125.57, 51.27, 46.438, 45.22, 35.39, 33.18, 28.50, 27.06, 26.49, 23.80; ESI (*m/z*) 338.5 (MNa^+).

4-(2-Oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-butyric acid methyl ester (**12b**). **9b** (392 mg, 1.19 mmol) was used and **12b** (350 mg, 98%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.24-7.11 (m, 5H), 6.15 (t, *J*= 4.2 Hz, 1H), 3.58 (s, 3H), 3.54 (t, *J*= 7.2 Hz, 2H), 3.11 (t, *J*= 7.0 Hz, 2H), 2.79 (t, *J*= 7.3 Hz, 2H), 2.26-2.20 (m, 4H), 2.09 (dd, *J*= 7.3 Hz, 2H), 1.75-1.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.66, 164.61, 139.02, 134.65, 133.35, 133.21, 128.58, 128.14, 126.00, 51.16, 51.09, 49.11, 46.13, 33.94, 33.22, 29.79, 23.59, 23.55; ESI (*m/z*) 324.5 (MNa^+).

4-[2-Oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (**12c**). **9c** (155 mg, 0.45 mmol) was used and **12c** (137 mg, 97%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.27-7.12 (m,

5H), 6.23 (t, *J*= 4.1 Hz, 1H), 3.62 (s, 3H), 3.42 (t, *J*= 7.3 Hz, 2H), 3.30 (t, *J*= 6.9 Hz, 2H), 2.61 (t, *J*= 7.9 Hz, 2H,), 2.33-2.20 (m, 6H), 1.90-1.74 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 173.85, 164.87, 141.58, 134.92, 133.16, 128.20, 128.14, 125.70, 51.29, 77.00, 76.57, 51.29, 46.56, 45.37, 33.40, 33.12, 29.96, 29.24, 23.81, 23.74; ESI (*m/z*) 338.6 (MNa^+).

4-[2-Oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (**12d**). **9d** (376 mg, 1.05 mmol) was used and **12d** (338 mg, 98%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 7.20-7.05 (m, 5H), 6.16 (t, *J*= 4.1 Hz,1H), 3.56 (s, 3H), 3.34 (t, *J*= 7.1 Hz, 2H), 3.21 (t, *J*= 7.1 Hz, 2H), 2.56 (t, *J*= 7.0 Hz, 2H,), 2.27-2.15 (m, 6H), 1.76-1.69 (m, 2H), 1.58-1.47 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 173.57, 164.55, 141.91, 134.69, 133.00, 132.87, 128.50, 127.91, 125.35, 51.07, 51.01, 46.20, 46.05, 35.17, 33.19, 29.80, 28.31, 26.86, 23.57; ESI (*m/z*) 352.6 (MNa^+).

General Procedures for 13-15. 10-12 was dissolved in methanol (0.5 M solution) and then NH_2OK (1.7 M suspension in methanol, 5.0 equiv) was added at 0□. The mixture was stirred for 20 h at room temperature. 10% HCl was added to pH 2-3 and the mixture was concentrated *in vacuo*. White solid was removed on filter with eluting of methanol/chloroform (1/9). **13-15** was obtained by flash chromatography.

2-(1-Benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-*N*-hydroxy-acetamide (**13a**). **10a** (17 mg, 0.07 mmol) was used and **13a** (10 mg, 55%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.34-7.22 (m, 5H), 6.58 (t, *J*= 4.5 Hz, 1H), 4.60 (s, 2H) 3.39-3.30 (m, 3H) 3.20 (s, 2H), 2.39-2.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 168.44, 165.53, 138.56, 136.73, 128.77, 128.02, 127.88, 127.68, 50.33, 44.81, 36.63, 23.86; ESI (*m/z*) 283.4 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{14}H_{17}N_2O_3$ 261.1234; found 261.1226; Purity > 99% (as determined by RP-HPLC,

Method A: t_R= 2.00 min, Method B: t_R= 8.05 min).

***N*-Hydroxy-2-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetamide** (**13b**). **10b** (20 mg, 0.06 mmol) was used and **13b** (12 mg, 62%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.32-7.12 (m, 5H) 6.47 (br t, 1H) 3.56 (t, *J*= 10.8 Hz, 2H), 3.11 (s, 4H) 2.78 (d, *J*= 6.0 Hz, 2H) 2.14 (d, *J*= 10.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 171.93, 164.15, 139.17, 136.65, 129.40, 128.80, 128.38, 126.23, 51.84, 49.51, 46.34, 36.14, 34.12, 23.87; ESI (*m/z*) 296.4 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{15}H_{19}N_2O_3$ 275.1390; found 275.1382; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.75 min, Method B: t_R= 8.17 min)

***N*-Hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-acetamide** (**13c**). **10c** (30 mg, 0.10 mmol) was used and **13c** (21 mg, 70 %, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J*= 6.5 Hz, 2H) 7.14 (s, 3H) 6.51 (br t, 1H) 3.43-3.32 (m, 5H) 3.11 (s, 1H) 2.59 (s, 2H) 2.29 (s, 2H) 1.84 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.58, 165.21, 141.31, 138.20 128.60, 128.38, 128.23, 125.94, 46.99, 45.41, 36.28, 33.16, 29.11, 23.88; ESI (*m/z*) 311.5 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{16}H_{21}N_2O_3$ 289.1547; found 289.1537; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.84 min, Method B: t_R= 8.35 min)

***N*-Hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-acetamide** (**13d**). **10d** (30 mg, 0.10 mmol) was used and **13d** (16 mg, 53%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.28-7.13 (m, 5H), 6.54 (br t, 1H), 3.44-3.31 (m, 5H), 3.14 (s, 1H) 2.62 (t, *J*= 7.1 Hz, 2H), 2.34 (s, 2H), 1.58 (t, *J*= 3.4 Hz, 4H); ^{13}C NMR($CDCl_3$) δ 165.19, 142.04, 138.02, 128.70,

128.38, 128.35, 128.32, 125.85, 125.80, 47.04, 45.45, 45.38, 35.48, 28.60, 27.10, 26.98, 23.89; ESI (*m/z*) 325.5 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{17}H_{23}N_2O_3$ 303.1703 ; found 303.1705; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 2.23 min, Method B: t_R= 8.54 min)

3-(1-Benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-*N*-hydroxy-propionamide (**14a**). **11a** (50 mg, 0.18 mmol) was used and **14a** (31 mg, 63%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H), 6.44 (t, *J*= 4.3 Hz, 1H), 4.61 (s, 2H), 3.33 (m, 2H), 2.57 (t, *J*= 7.5 Hz, 2H), 2.28 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 172.02, 166.84, 138.69, 137.49, 134.40, 129.68, 128.80, 128.45, 50.94, 46.07, 33.13, 28.17, 24.73; ESI (*m/z*) 297.4 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{15}H_{19}N_2O_3$ 275.1390; found 275.1391; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.96 min, Method B: t_R= 8.38 min)

***N*-Hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide** (**14b**). **11b** (110 mg, 0.38 mmol) was used and **14b** (71 mg, 65%, oil) was obtained by flash chromatography (methanol/chloroform, 1/10). ^{1}H NMR ($CDCl_3$) δ 7.29-7.18 (m, 5H), 6.40 (br t, 1H), 3.62 (t, *J*= 7.2 Hz, 2H), 3.19 (t, *J*= 7.1 Hz, 2H), 2.85 (t, *J*= 7.1 Hz, 2H), 2.54-2.44 (m, 2H), 2.18-2.15 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 169.72, 165.29, 138.95, 136.14, 133.66, 128.89, 128.51, 126.45, 49.29, 46.34, 34.17, 23.70; ESI (*m/z*) 313.5 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{16}H_{21}N_2O_3$ 289.1547; found 289.1539; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.77 min, Method B: t_R= 8.58 min)

***N*-Hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide** (**14c**). **11c** (324 mg, 1.08 mmol) was used and **14c** (235 mg, 72%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.24-7.11 (m, 5H), 6.31 (br t, 1H), 3.35 (br t, 2H), 3.23 (br t, 2H), 2.55 (d, *J*= 6.6 Hz,

4H), 2.33 (s, 2H), 2.18 (s, 2H), 1.80 (br t, 2H); ^{13}C NMR ($CDCl_3$) δ 169.90, 164.78, 141.12, 135.24, 133.09, 127.89, 127.83, 125.40, 46.40, 45.04, 32.72, 28.80, 23.33; ESI (*m/z*) 325.5 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{17}H_{23}N_2O_3$ 303.1703; found 303.1692; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 2.31 min, Method B: t_R= 10.23 min)

***N*-Hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide** (**14d**). **11d** (30 mg, 0.10 mmol) was used and **14d** (10 mg, 30 %, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.28-7.13 (m, 5H), 6.36 (t, *J*= 3.9 Hz, 1H), 3.39 (t, *J*= 6.8 Hz, 2H), 3.29 (t, *J*= 7.1 Hz, 2H), 2.62 (t, *J*= 7.1 Hz, 2H), 2.54 (t, *J*= 6.8 Hz, 2H), 2.40 (t, *J*= 6.8 Hz, 2H), 2.27 (AB q, *J*= 6.0, 5.4 Hz, 2H), 1.58 (t, *J*= 2.7 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 175.60, 165.05, 142.13, 134.39, 128.33, 128.24, 125.70, 48.49, 46.79, 45.41, 35.45, 33.60, 28.49, 27.13, 26.45, 23.87; ESI (*m/z*) 324.5 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{18}H_{25}N_2O_3$ 317.1860; found 317.1857; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.85 min, Method B: t_R= 7.54 min)

***N*-Hydroxy-4-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-butyramide** (**15b**). **12b** (40 mg, 0.13 mmol) was used and **15b** (10 mg, 25%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.29-7.13 (m, 5H), 6.24 (br t, 1H), 3.56 (t, *J*= 7.4 Hz, 2H), 3.31-3.29 (m, 1H), 3.16 (t, *J*= 6.9 Hz, 2H), 2.80 (t, *J*= 7.2 Hz, 2H), 2.14-2.03 (m, 5H), 1.66-1.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.71, 171.26, 143.52, 136.92, 125.68, 115.20, 113.50, 47.81, 43.68, 32.69, 30.51, 28.91, 27.79, 26.27; ESI (*m/z*) 325.5 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{17}H_{23}N_2O_3$ 303.1703; found 303.1712; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.75 min, Method B: t_R= 8.44 min)

***N*-Hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butyramide** (**15c**). **12c** (18 mg, 0.06 mmol) was used and **15c** (18 mg, 57%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.29-7.17 (m, 5H), 6.32 (br t, 1H), 3.46 (t, *J*= 7.3 Hz, 2H), 3.35 (t, *J*= 5.9 Hz, 2H), 2.63 (t, *J*= 7.6 Hz, 2H), 2.37-2.28 (m, 5H), 1.99-1.73 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 169.88, 165.78, 137.09, 134.94, 134.14, 128.41, 128.28, 125.96, 46.93, 45.55, 33.20, 32.30, 29.89, 29.24, 24.77, 23.87; ESI (*m/z*) 339.6 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{18}H_{25}N_2O_3$ 317.1860; found 317.1849; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.83 min, Method B: t_R= 8.54 min)

***N*-Hydroxy-4-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butyramide (15d). 12d** (34 mg, 0.10 mmol) was used and **15d** (10 mg, 30%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.29-7.14 (m, 5H), 6.31(br t, 1H), 3.45 (t, *J*= 6.5 Hz, 2H), 3.32(t, *J*= 7.1 Hz, 2H,), 2.64 (t, *J*= 7.0 Hz, 2H), 2.27 (d, *J*= 7.2 Hz, 5H), 1.60 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 169.59, 165.76, 142.11, 135.00, 134.82, 128.40, 128.32, 125.79, 46.89, 45.47, 35.47, 32.19, 29.86, 28.57, 27.10, 24.76, 23.78; ESI (*m/z*) 353.6 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{19}H_{27}N_2O_3$ 331.2016; found 331.2021; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.96 min, Method B: t_R= 8.67 min)

4-[But-3-enyl-(2,4-dimethoxy-benzyl)-carbamoyl]-pent-4-enoic acid methyl ester (**17**). The same procedures as general procedures for **7a**. But-3-enyl-(2,4-dimethoxy-benzyl)-amine (500 mg, 2.26 mmol) was used and **17** (640mg, 78%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 6.96 (d, *J*= 7.6 Hz, 1H), 6.44-6.42 (m, 2H), 5.72 (t, *J*= 8.3 Hz, 1H,), 5.12-4.97 (m, 4H), 4.47 (s, 2H), 3.76 (s, 6H), 3.63 (s, 3H), 3.33 (br t, 1H), 2.62-2.51 (m, 4H), 2.26 (q, *J*= 6.8 Hz, 2H);

ESI (*m/z*) 384.5 (MNa^+).

3-[1-(2,4-Dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (**18**). The same procedures as general procedures for **10a**. **17** (640 mg, 1.77 mmol) was used and **18** (580 mg, 98%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 7.19 (d, *J*= 3.0 Hz, 1H), 6.45-6.91 (m, 2H), 6.27 (t, *J*= 4.3 Hz, 1H), 4.55 (s, 2H), 3.78 (s, 6H), 3.63 (s, 3H), 3.30 (t, *J*= 7.1 Hz, 2H,), 2.63-2.50 (m, 4H), 2.23 (d, *J*= 6.7 Hz, 2H), 1.57 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 173.6, 164.8, 160.2, 158.5, 134.2, 133.9, 130.4, 118.0, 104.1, 98.3, 55.2, 51.3, 45.0, 44.3, 33.3, 26.6, 23.9; ESI (*m/z*) 356.5 (MNa^+).

3-(2-Oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (**19**). **18** (490 mg, 1.47 mmol) was dissolved in 3mL of TFA and then triethylsilane was added. the reaction mixture was refluxed for 20min at 80□. The solvent was removed *in vacuo* and the residue was diluted in chloroform (50 mL). The organic layer was washed with sat. $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$. **19** (200 mg, 74%, solid) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 6.45 (s, 1H), 6.36 (t, *J*= 4.2 Hz, 2H), 3.61 (s, 3H), 3.31 (dt, *J*= 7.5 Hz, 2H), 2.55-2.45 (m, 4H), 2.27 (dd, *J*= 6.7, 5.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.41, 166.82, 136.09, 133.48, 51.35, 39.52, 33.06, 26.02, 24.01; ESI (*m/z*) 220.4 (MNa^+).

3-(1-Methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (**20a**). To a solution of **19** (100 mg, 0.55 mmol) in THF (1.1mL) was added NaHMDS (0.66 mL, 1.0M in THF, 1.2 equiv) was dropwise at -78□. After stirred at -78□ for 30min, dimethyl sulfate was added dropwise. The reaction mixture was stirred at -78□ for 15min and at 0□ for 2h. The reaction was quenched by sat. NH_4Cl solution. The

organic layer was extracted by ethyl acetate (30 mL x 3) and the combined organic layer was washed with sat. NH_4Cl solution (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. **20a** (80 mg, 74%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/1). ^{1}H NMR ($CDCl_3$) δ 6.28 (t, *J*= 4.2 Hz, 1H), 3.62 (s, 3H), 3.33 (t, *J*= 7.2 Hz, 2H), 2.96 (d, *J*= 3.2 Hz, 3H), 2.58-2.47 (m, 4H), 2.33-2.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.90, 165.53, 134.33, 134.20, 51.65, 47.80, 34.86, 33.53, 26.80, 23.93; ESI (*m/z*) 220.4 (MNa^+).

3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (**20b**). The same procedures as **20a** but used allyl bromide instead of dimethyl sulfate. **19** (100 mg, 0.55 mmol) was used and **20b** (55 mg, 45%, oil) was obtained by flash chromatography (ethyl acetate/hexanes, 1/2). ^{1}H NMR ($CDCl_3$) δ 6.28 (t, *J*= 4.2 Hz, 1H), 5.81-5.68 (m, 1H), 5.14 (t, *J*= 8.7 Hz, 2H), 3.99 (d, *J*= 5.7 Hz, 2H), 3.61 (s, 3H), 3.27 (t, *J*= 7.1 Hz, 2H), 2.56-2.46 (m, 4H), 2.27 (dd, *J*= 6.9 Hz, 5.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.55, 164.57, 134.27, 134.06, 133.27, 117.10, 51.36, 49.01, 44.63, 33.25, 26.55, 23.83; ESI (*m/z*) 246.4 (MNa^+).

General procedures for 21a-c.

***N*-Hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (21a).** The same procedures as **13a**. **20a** (40 mg, 0.20 mmol) was used and **21a** (13.8 mg, 35%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 6.15 (t, *J*= 4.3 Hz, 1H), 3.41 (t, *J*= 7.2 Hz, 2H), 2.97 (s, 3H), 2.51 (t, *J*= 7.5 Hz, 2H), 2.35 (m, 2H), 2.22 (t, *J*= 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 170.56, 136.03, 47.72, 34.77, 31.68, 27.43, 23.61; ESI (*m/z*) 180.3 (M^+-H_2O); HRMS (*m/z*) (MH^+) calc. for $C_9H_{15}N_2O_3$ 199.1077; found 199.1075; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.58 min, Method B: t_R= 8.55 min)

3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-*N*-hydroxy-propionamide (21b). The same procedures as **13a**. **20b** (44 mg, 0.20 mmol) was used and **21b** (20 mg, 45%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 10.08 (br s, 1H), 8.76 (br s, 1H), 6.38 (br t, 1H), 5.75-5.67 (m, 1H), 5.17 (d, *J*= 5.4 Hz, 1H), 5.12 (s, 1H), 3.98 (d, *J*= 5.4 Hz, 2H), 3.30 (t, *J*= 7.0 Hz, 2H), 2.54 (s, 2H), 2.36-2.28 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.17, 165.21, 136.15, 133.46, 132.91, 117.38, 49.25, 44.77, 32.72, 27.12, 23.74; ESI (*m/z*) 247.4 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{11}H_{17}N_2O_3$ 225.1234 ; found 225.1232; Purity > 97% (as determined by RP-HPLC, Method A: t_R= 1.67 min, Method B: t_R= 8.63 min)

3-[1-(2,4-Dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-*N*-hydroxy-propionamide (**21c**). The same procedures as **13a**. **18** (46 mg, 0.14 mmol) were used and **21c** (32 mg, 73%, oil) was obtained by flash chromatography (methanol/chloroform, 1/19). ^{1}H NMR ($CDCl_3$) δ 7.12 (d, *J*= 9.0 Hz, 1H), 6.425-6.33 (m, 3H), 4.51 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.27 (t, *J*= 6.9 Hz, 2H), 2.55 (m, 2H), 2.38 (m, 2H), 2.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.1, 165.4, 160.2, 158.5, 135.8, 133.5, 130.4, 117.5, 104.2, 98.3, 55.3, 44.9, 44.6, 32.8, 27.1, 23.8; ESI (*m/z*) 357.5 (MNa^+); HRMS (*m/z*) (MH^+) calc. for $C_{17}H_{23}N_2O_5$ 335.1602 ; found 335.1609; Purity > 99% (as determined by RP-HPLC, Method A: t_R= 1.65 min, Method B: t_R= 8.42 min)

Molecular Modeling.

The program Insight II[3,4] was used to create a Docking model for human homology HDAC-1 based on the crystal structure of a bacterial HDAC homologue (Figure S1). Both proteins are Class 1 HDACs and share 32% identity. All sequence alignments information were imported from Finnin, M.S. et al paper.[5] The resulting alignments were examined manually. The 3D structure of HDLP (1C3R.pdb) was used as a

template for human HDAC-1 homology modeling. Docking calculations for the analogs were carried out with the program CVFF/DISCOVER.[6] The computational complex model was solvated using a solvent sphere of water extending 23.0 Å around the zinc ion, only residues within 5.0 Å of compound **14d** were allowed to move during the geometry optimizations using 500 steps of steepest decent and 3000 steps of conjugated gradient. The hydroxamic acid coordinates of **14d** were restraint using 10.0 kcal/mol harmonic forces, the zinc ion VDW radius was taken from the work of Store and Karplus.[7]

HDAC Assay.

HDAC fluorescent activity assays using a Fluror de Lys^{TM} Substrate (Biomol, Plymouth Meeting, PA), which contains an acetylated lysine side chain, were performed according to manufacturer's instructions. In brief, HeLa nuclear extracts, which were used as an HDAC enzyme source, were incubated at 25□ with 250 mM of Fluror de Lys^{TM} Substrate and various concentrations of each sample. Reactions were stopped after 20min with Fluror de Lys^{TM} Developer and fluorescence was measured using a microplate spectrofluorometer (LS 50B, PerkinElmer) with excitation at 360 nm and emission at 460 nm.

In vitro **NO assay and TNF-α Immuno assay.** RAW264.7 cells (5 x 10^5 cells/ml) were stimulated with LPS (300 ng/ml) 1 hr before treatment of HDAC inhibitors and then further incubated for 24 hr. NO_2^- accumulation was used as an indicator of NO production in the medium. The isolated supernatants were mixed with an equal volume of Griess reagent (1% sulfanilamide, 0.1% naphthylethylenediamine dihydrochloride, and 2% phosphoric acid) and incubated at room temperature for 10 min. Nitrite production was determined by measuring absorbance at 540 nm versus a $NaNO_2$

standard curve. The concentration of TNF-α secreted in the culture supernatant of RAW264.7 cells was determined by ELISA, according to the manufacture's instruction (R&D Systems, Minneapolis, MN) and expressed as pg/ml. For NO and TNF-α assays HDAC inhibitors were treated in the range between 0.1 μM and 10 μM. IC_{50} values of HDAC inhibitors were calculated to evaluate their ability for suppressing the production of NO and TNF-α.

SRB assay (sulforhodamine B assay)

Cells were harvested from exponential phase cultures by trypsinization, counted and plated in 96-well plates. Optimal seeding densities for the PC-3 cell line were determined to ensure exponential growth during a 5-day assay. The SRB assay was performed according to the method of Skehan et al. and Papazisis et al., with minor modifications.[8,9] The culture medium was aspirated prior to fixation of the cells by the addition of 200 □L 10% cold trichloroacetic acid. After 1-hr incubation at 4 C, cells were washed five times with deionized water. The cells were then stained with 200 □L 0.1% SRB (Sigma-Aldrich) dissolved in 1% acetic acid for at least 15 min and subsequently washed four times with 1% acetic acid to remove unbound stain. The plates were left to dry at room temperature, bound protein stain was solubilized with 200 L 10 mM unbuffered Tris base (tris(hydroxymethyl)a17inomethane), and optical density (OD) was read at 540 nm.

***In vivo* tumor growth inhibition experiment.**

An equal volume of the MDA-MB-231 human breast cancer cells was injected s.c. in the right flank of each BALB/c nude mouse. When the size of the tumors reached to 50-60 mm^3, compounds were intraperitoneally administered daily to the nude mice for 15

days. Tumor length and width were periodically measured until the end of the experiment and tumor volume was calculated using the following formula:

$$\text{Tumor volume} = \text{Length} \times (\text{width})^2 \times \pi/6$$

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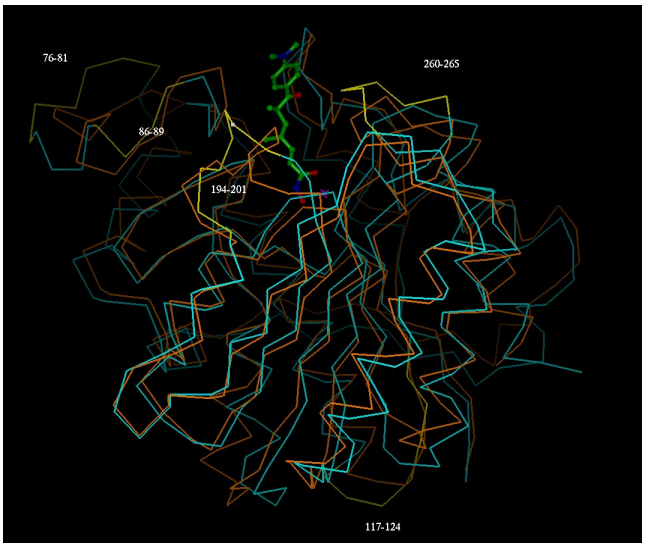

Figure S1. The Ca-carbon trace structures comparison between the homology model (cyan and yellow) and the X-ray structure of HDLP(orange color). Yellow colors reprensented the loop structures of the homology model. TSA is displayed as ball and stick model.

Table S1. HPLC Analysis Data
(Shimadzu LCMS-2010, using XTerra RP_{18} 4.6x150 mm column)

compounds	Purity (t_R)	
	90% MeCN (0.1% TFA)/10 % H_2O (0.1% TFA), 1 mL/min in 20 min	95% MeCN (0.1% TFA)/5 % H_2O (0.1% TFA), 0.2 mL/min in 20 min
13a	>99% (t_R = 2.00 min)	>99% (t_R = 8.05 min)
13b	>99% (t_R = 1.75 min)	>99% (t_R = 8.17 min)
13c	>99% (t_R = 1.84 min)	>99% (t_R = 8.35 min)
13d	>99% (t_R = 2.23 min)	>99% (t_R = 8.54 min)
14a	>99% (t_R = 1.96 min)	>99% (t_R = 8.38 min)
14b	>99% (t_R = 1.77 min)	>99% (t_R = 8.58 min)
14c	>99% (t_R = 2.31 min)	>99% (t_R = 10.23 min)
14d	>99% (t_R = 1.85 min)	>99% (t_R = 7.54 min)
15b	>99% (t_R = 1.75 min)	>99% (t_R = 8.44 min)
15c	>99% (t_R = 1.83 min)	>99% (t_R = 8.54 min)
15d	>99% (t_R = 1.96 min)	>99% (t_R = 8.67 min)
21a	>99% (t_R = 1.58 min)	>99% (t_R = 8.55 min)
21b	>97% (t_R = 1.67 min)	>99% (t_R = 8.63 min)
21c	>99% (t_R = 1.65 min)	>99% (t_R = 8.42 min)