SUPPORTING INFORMATION

Development of *N*-Hydroxycinnamamide-Based Histone Deacetylase Inhibitors with Indole-Containing Cap Group

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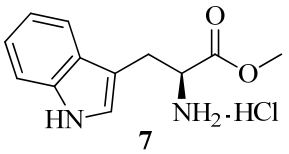
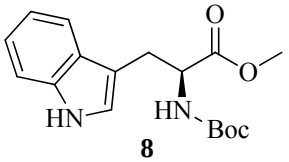
Experiment section

Reagents, instruments and methods. All commercially available starting materials, reagents and solvents were used without further purification unless otherwise stated. All reactions were monitored by TLC with 0.25 mm silica gel plates (60GF-254). UV light, iodine stain and chloride ferric were used to visualize the spots. Silica gel or C18 silica gel was used for column chromatography purification. Melting points were determined uncorrected on an electrothermal melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker AVANCE 300 (300 MHz), Bruker AVANCE 400 (400 MHz) or Varian INOVA 600 (600 MHz) spectrometer, δ in parts per million and *J* in hertz, using TMS as an internal standard. ^{13}C NMR spectra were recorded on an Bruker AVANCE 300 (300 MHz) or Varian INOVA 600 (600 MHz) spectrometer, δ in parts per million relative to the carbon resonance of the deuterated solvent (39.52 in DMSO-d_6). ESI-MS data was recorded on an API 4000 spectrometer. High-resolution mass spectral data and purities of all tested compounds (>95%) were confirmed by LC/MS analysis, performed on a Accela HPLC-LTQ Orbitrap Mass Spectrometer instrument using a Phenomenex Synergi 4μ Hydro-RP 80A column (250 mm × 4.6 mm) according to one of the following methods. Method A: compounds **14a** and **17a-17u** were eluted with 50% acetonitrile / 50% water (containing 0.1 % formic acid) over 20 min, with detection at 254 nm and a flow rate of 1.0 mL/min. Method B: compounds **15** was eluted with 25% acetonitrile / 75% water (containing 0.1 % formic acid) over 20 min, with detection at 254 nm and a flow rate of 1.0 mL/min.



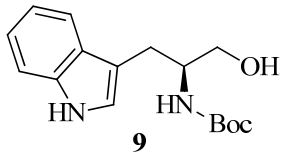
7

(*S*)-Methyl 2-amino-3-(1*H*-indol-3-yl)propanoate hydrochloride (7). Thionyl chloride (3.32 mL, 45.5 mmol) was added dropwise to a stirred solution of tryptophan (**6**, 4.23 g, 20.7 mmol) in 15 mL of MeOH at 0°C. The resulting solution was refluxed at 60°C overnight. The solvent and thionyl chloride in excess were then removed under reduced pressure, to collect compound **7** (5.17 g, 98% yield) as a white solid. This product was used for the following reaction without further purification. ESI-MS *m/z*: 219.1 $[M+H]^+$.



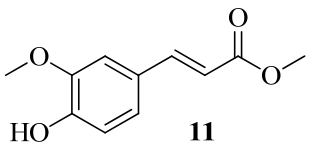
8

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoate (8). At room temperature, to a solution of **7** (5.09 g, 20.0 mmol) in anhydrous CH_2Cl_2 (40 mL), was added Et_3N (4.44 g, 44.0 mmol) followed by $(Boc)_2O$ (4.80 g, 22.0 mmol). After stirring the mixture at room temperature for 8 h, the solution was washed with 1 M aqueous citric acid (3×10 mL) and brine (3×10 mL), dried over $MgSO_4$, and evaporated under vacuum to get the crude product compound **8** (5.09 g, 80% yield) as a white solid. This product was used for the following reaction without further purification. ESI-MS *m/z*: 319.2 $[M+H]^+$.



9

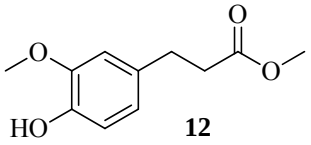
(*S*)-*tert*-Butyl (1-hydroxy-3-(1*H*-indol-3-yl)propan-2-yl)carbamate (9). At 0°C, to a solution of **8** (9.55 g, 30.0 mmol) in anhydrous THF (150 mL) was added $LiAlH_4$ (4.56 g, 120.0 mmol) in batch. After 4 h, the reaction was quenched by adding 1 M aqueous citric acid slowly. Then THF was evaporated with the residue being extracted by EtOAc (3×50 mL). The EtOAc solution was washed with saturated Na_2CO_3 (3×30 mL) and brine (3×30 mL), dried over $MgSO_4$ and evaporated under vacuum. Compound **9** was recrystallized from EtOAc as a light yellow solid (7.51 g, 86% yield). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 4.62-4.63 (m, 1H), 3.64-3.68 (m, 1H), 3.29-3.38 (m, 2H), 2.87 (dd, J = 6.0 Hz, J = 14.4 Hz, 1H), 2.70 (dd, J = 6.0 Hz, J = 14.4 Hz, 1H), 1.35 (s, 9H). ESI-MS *m/z*: 291.2 $[M+H]^+$.



11

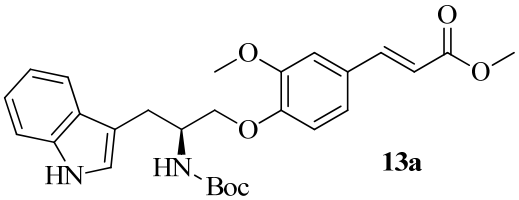
(*E*)-Methyl 3-(4-hydroxy-3-methoxyphenyl)acrylate (11). Ferulic acid (**10**, 29.1 g, 150.0 mmol) was dissolved in dry MeOH (300 mL), then *p*-toluenesulfonic acid (5.17 g, 30.0 mmol) was added. The solution was heated to reflux at 80°C for 6 h, and then concentrated under vacuum with the residue being mixed with water (100 mL) and extracted by EtOAc (3×30 mL). The organic layer was merged, washed with

brine (3×20 mL), dried over $MgSO_4$ and evaporated to give the crude product compound **11** (30.0 g, yield: 96%) as a yellow solid. This product was used for the following reaction without further purification. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 9.61 (s, 1H), 7.56 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.12 (dd, J = 1.8 Hz, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.48 (d, J = 16.2 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 3H). ESI-MS *m/z*: 209.4 $[M+H]^+$.



12

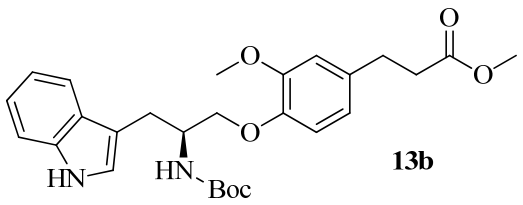
Methyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (12). Compound **11** (25.0 g, 120.0 mmol) was dissolved in MeOH (240 mL), and then 10% Pd-C (0.50 g) was added. After stirring the mixture under hydrogen atmosphere at room temperature for 12 h, the reaction mixture was filtered on Celite and the filtrate was evaporated to get the crude product compound **12** (24.7 g, 98% yield) as diaphanous oil. This product was used for the following reaction without further purification. ESI-MS m/z: 211.3 $[M+H]^+$.



13a

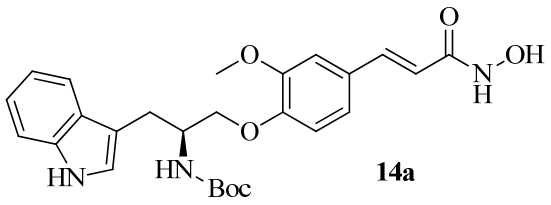
(*S*,*E*)-Methyl 3-(4-(2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propoxy) -3-methoxyphenyl)acrylate (13a). At 0°C, to a solution of **11** (3.96 g, 19.0 mmol) and Ph_3P (4.98 g, 19.0 mmol) in anhydrous THF (40 mL), was added DEAD (3.31 g,

19.0 mmol) dropwise followed by **9** (5.02 g, 17.3 mmol). Stirring was continued for 4 h and then THF was evaporated with the residue being taken up in diethyl ether (40 mL). The mixture was filtered and the filtrate was evaporated to get the crude product compound **13a** (6.24 g, 75% yield) as light yellow oil. This product was used for the following reaction without further purification. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.80 (s, 1H), 7.58 (d, J = 16.2 Hz, 1H), 7.56-7.57 (m, 1H), 7.31-7.37 (m, 2H), 6.90-7.20 (m, 6H), 6.55 (d, J = 16.2 Hz, 1H), 3.93-4.07 (m, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 2.84-3.01 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 166.9, 155.3, 150.2, 149.2, 144.6, 136.1, 127.4, 127.1, 123.3, 122.8, 120.8, 118.2, 115.4, 113.0, 111.3, 111.1, 110.7, 77.7, 69.7, 55.8, 51.3, 50.6, 28.2, 26.6. ESI-MS *m/z*: 481.3 $[M+H]^+$.



13b

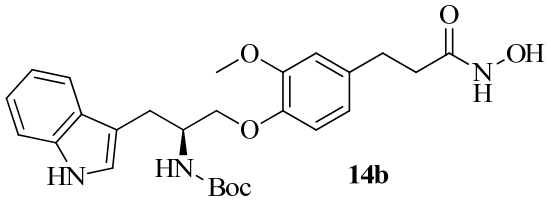
(*S*)-Methyl 3-(4-(2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)propanoate (13b). Using the synthetic method for **13a**, compound **9** and **12** gave **13b** (79% yield) as light yellow oil. ESI-MS *m/z*: 483.3 $[M+H]^+$.



14a

(*S*,*E*)-*tert*-Butyl (1-(4-(3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1H-indol-3-yl)propan-2-yl)carbamate (14a). To a solution of

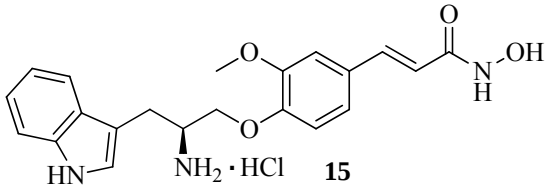
compound **13a** (0.96 g, 2.0 mmol) in 10 mL of anhydrous methanol, was added a solution of NH_2OK (0.14 g, 6 mmol) in 3.5 mL of anhydrous methanol. The mixture was stirred for 0.5 h and the solvent was evaporated under vacuum. The residue was acidified with 2 N HCl until pH 5-6 then extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine (3×10 mL), dried over $MgSO_4$ and evaporated with the residue being purified by C18 reversed-phase column chromatography (H_2O/MeOH 3:7) to give desired compound **14a** (0.99 g, 51% yield) as a white powder. Mp: 104-106°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.55-7.58 (m, 1H), 7.38 (d, J = 16.2 Hz, 1H), 6.89-7.34 (m, 8H), 6.34 (d, J = 16.2 Hz, 1H), 3.91-3.40 (m, 3H), 3.80 (s, 3H), 2.89-3.01 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.2, 155.3, 149.3, 149.2, 138.3, 136.1, 127.9, 127.4, 123.3, 121.2, 120.8, 118.2, 116.8, 113.3, 111.3, 110.7, 77.7, 69.7, 55.7, 50.6, 28.2, 26.9. HRMS (AP-ESI) *m/z* calcd for $C_{26}H_{31}N_3NaO_6$ $[M+Na]^+$ 504.2111found 504.2128.



14b

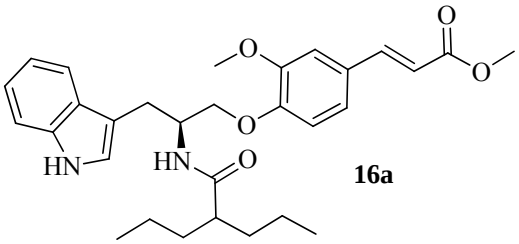
(*S*)-*tert*-Butyl (1-(4-(3-(hydroxyamino)-3-oxopropyl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)carbamate (14b). Using the synthetic method for **14a**, compound **13b** gave **14b** (49% yield) as a white powder. Mp: 80-82°C. ^{1}H-NMR (300MHz, DMSO-d_6) δ 10.79 (s, 1H), 10.34 (s, 1H), 8.68 (s, 1H), 6.62-7.58 (m, 9H), 3.79-3.99 (m, 3H), 3.74 (s, 3H), 2.82-3.01 (m, 2H), 2.73 (t, J = 7.2 Hz, 1H), 2.22 (t, J

= 7.2 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 168.3, 155.2, 149.1, 146.3, 136.1, 134.1, 127.4, 123.3, 120.8, 120.1, 118.3, 118.2, 114.1, 112.8, 111.3, 110.8, 77.6, 70.2, 55.6, 50.7, 34.1, 30.5, 28.2, 27.0. HRMS (AP-ESI) *m/z* calcd for $C_{26}H_{33}N_3NaO_6$ $[M+Na]^+$ 506.2267, found 506.2290.



15

(*S*,*E*)-3-(4-(2-Amino-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)-*N*-hydroxya crylamide (15). To a solution of compound **14a** (0.24 g, 0.5 mmol) in dry EtOAc (8 mL), was added a solution of EtOAc (8 mL) saturated by dry HCl gas. The reaction solution was stirred at room temperature for 3 h when the precipitation appeared. The suspension was filtered with the filter being washed with ether to give desired compound **15** (0.19 g, 90% yield) as a white powder. Mp: 143-145°C. HRMS (AP-ESI) *m/z* calcd for $C_{21}H_{24}N_3O_4$ $[M+H]^+$ 382.1767, found 382.1741.

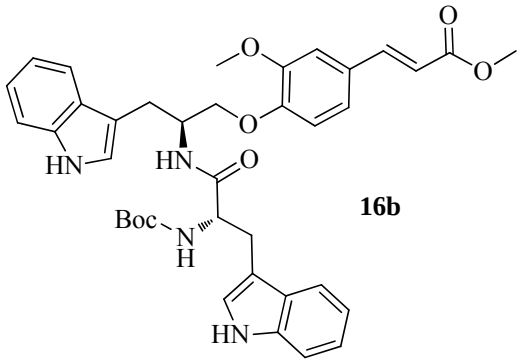


16a

(*S*,*E*)-Methyl 3-(4-(3-(1*H*-indol-3-yl)-2-(2-propylpentanamido)propoxy)-3-methoxyphenyl)acry late (16a). To a solution of **13a** (2.40 g, 5.0 mmol) in anhydrous dichloromethane (20

mL) was added trifluoroacetic acid (7 mL). When the reaction was finished, Et_3N was added to the solution until the pH became weakly basic.

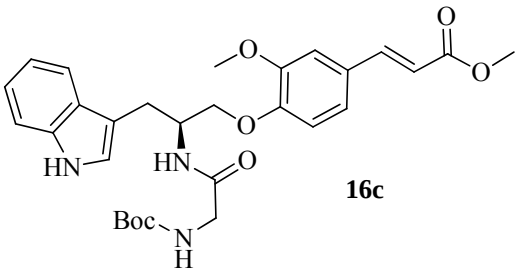
At room temperature, to a solution of valproic acid (0.72 g, 5.0 mmol) in anhydrous THF (20 mL), was added Et_3N (0.56 g, 5.5 mmol) followed by 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU, 1.78 g, 5.5 mmol). After 15 min, aforementioned dichloromethane solution was added. Stirring was continued over night and then the solvent was evaporated with the residue being taken up in EtOAc (40 mL). The EtOAc solution was washed with 1 N HCl (3×10 mL), saturated Na_2CO_3 (3×10 mL) and brine (3×10 mL), dried over $MgSO_4$, and evaporated under vacuum. The crude product was purified by flash column chromatography (petroleum ether/EtOAc 2:1) to give desired compound **16a** (52% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 507.4 $[M+H]^+$.



16b

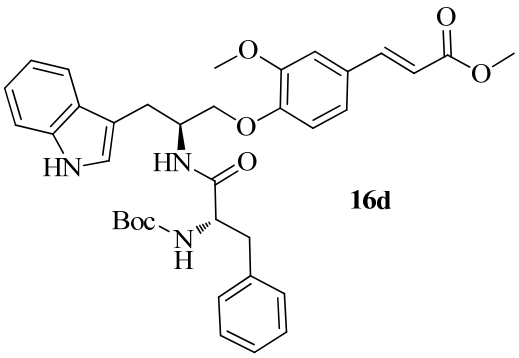
(*E*)-Methyl 3-(4-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16b). Using the synthetic

method for **16a**, compound **13a** and Boc-Trp gave **16b** (71% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 667.5 $[M+H]^+$.



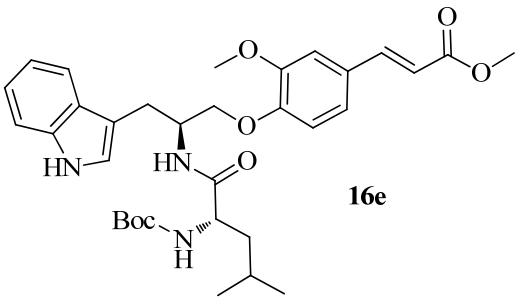
16c

(*S*,*E*)-Methyl 3-(4-(2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16c). Using the synthetic method for **16a**, compound **13a** and Boc-Gly gave **16c** (75% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 538.4 $[M+H]^+$.



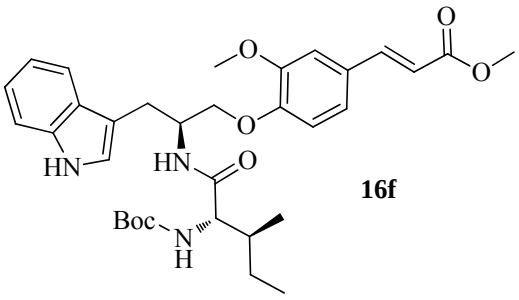
16d

(*E*)-Methyl 3-(4-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16d). Using the synthetic method for **16a**, compound **13a** and Boc-Phe gave **16d** (70% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 628.4 $[M+H]^+$.



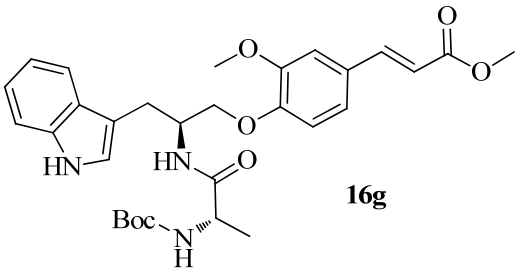
16e

(*E*)-Methyl 3-(4-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16e). Using the synthetic method for **16a**, compound **13a** and Boc-Leu gave **16e** (68% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 594.5 $[M+H]^+$.



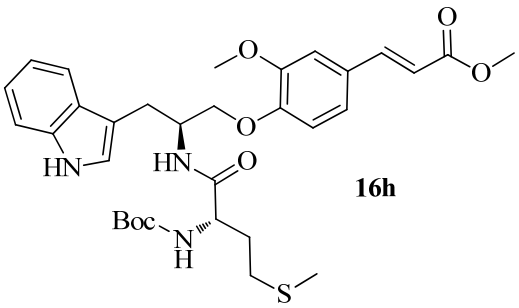
16f

(*E*)-Methyl 3-(4-((*S*)-2-((2*S*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylpentanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16f). Using the synthetic method for **16a**, compound **13a** and Boc-Ile gave **16f** (70% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 594.3 $[M+H]^+$.



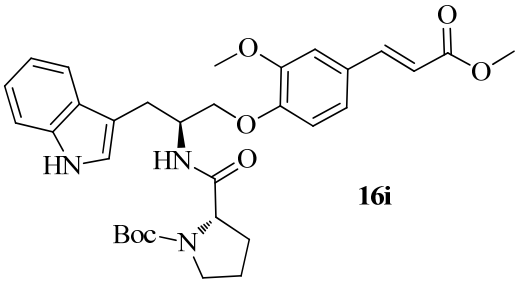
16g

(*E*)-Methyl 3-(4-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16g). Using the synthetic method for **16a**, compound **13a** and Boc-Ala gave **16g** (74% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 552.4 $[M+H]^+$.



16h

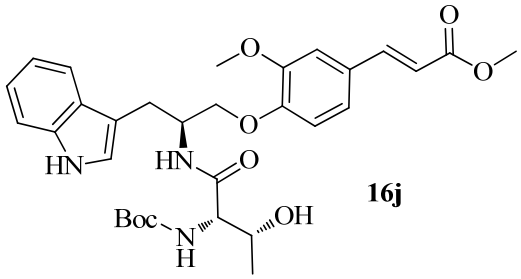
(*E*)-Methyl 3-(4-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-(methylthio)butanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16h). Using the synthetic method for **16a**, compound **13a** and Boc-Met gave **16h** (62% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 612.3 $[M+H]^+$.



16i

(*S*)-*tert*-Butyl

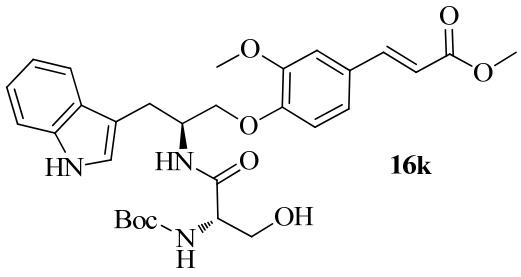
2-(((*S*)-1-(1*H*-indol-3-yl)-3-(2-methoxy-4-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)phenoxy)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (16i). Using the synthetic method for **16a**, compound **13a** and Boc-Pro gave **16i** (60% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 578.5 $[M+H]^+$.



16j

(*E*)-Methyl

3-(4-((*S*)-2-((2*S*,3*R*)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxybutanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16j). Using the synthetic method for **16a**, compound **13a** and Boc-Thr gave **16j** (55% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 582.4 $[M+H]^+$.

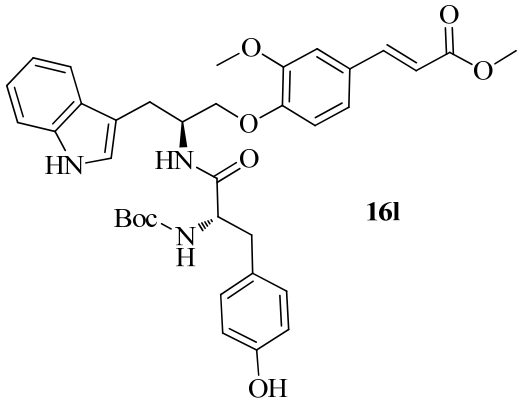


16k

(*E*)-Methyl

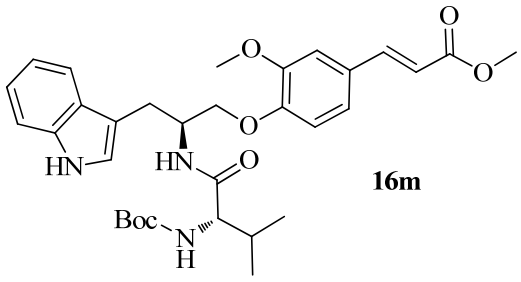
3-(4-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxypropanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16k). Using the synthetic method

for **16a**, compound **13a** and Boc-Ser gave **16k** (57% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 568.4 $[M+H]^+$.



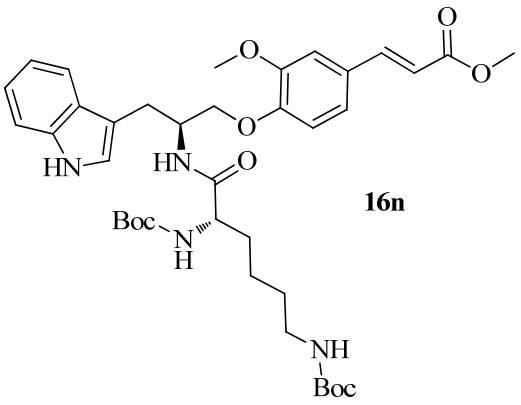
16l

(*E*)-Methyl 3-(4-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16l). Using the synthetic method for **16a**, compound **13a** and Boc-Tyr gave **16l** (63% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 644.3 $[M+H]^+$.



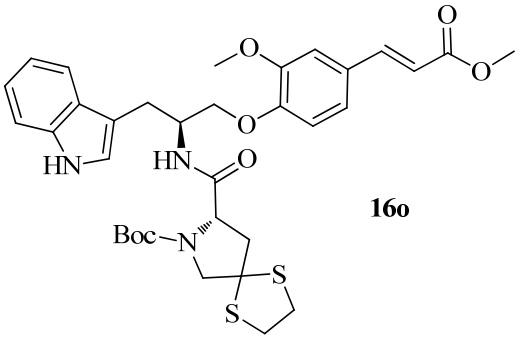
16m

(*E*)-Methyl 3-(4-((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16m). Using the synthetic method for **16a**, compound **13a** and Boc-Val gave **16m** (72% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 580.4 $[M+H]^+$.



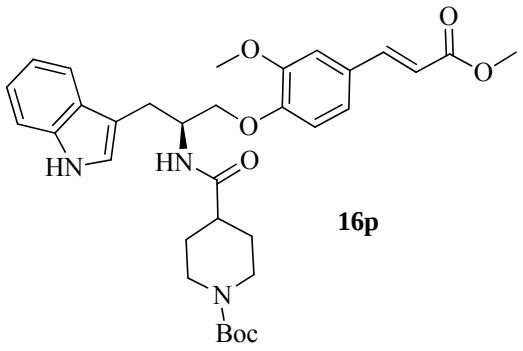
16n

(*E*)-Methyl 3-(4-((*S*)-2-((*S*)-2,6-bis((*tert*-butoxycarbonyl)amino)hexanamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16n). Using the synthetic method for **16a**, compound **13a** and Boc-Lys gave **16n** (75% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 709.5 $[M+H]^+$.



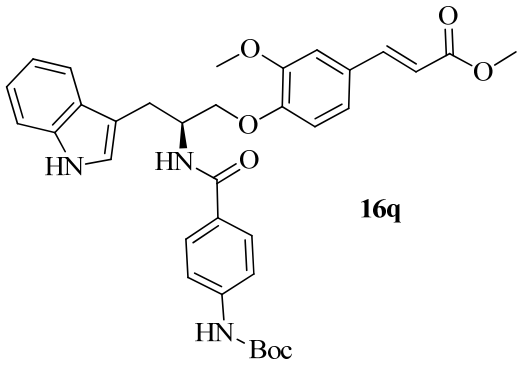
16o

(*S*)-*tert*-Butyl 8-(((*S*)-1-(1*H*-indol-3-yl)-3-(2-methoxy-4-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)phenoxy)propan-2-yl)carbamoyl)-1,4-dithia-7-azaspiro[4.4]nonane-7-carboxylate (16o). Using the synthetic method for **16a**, compound **13a** and (*S*)-7-(*tert*-butoxycarbonyl)-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid gave **16o** (67% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 668.5 $[M+H]^+$.



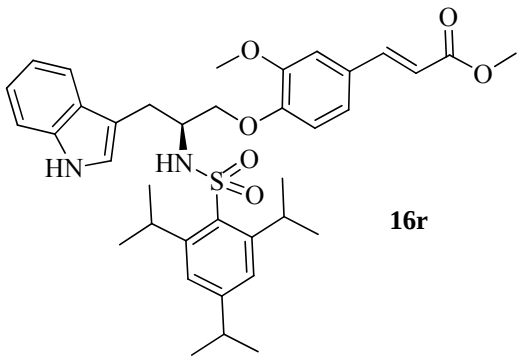
16p

(*S*,*E*)-*tert*-Butyl 4-((1-(1*H*-indol-3-yl)-3-(2-methoxy-4-(3-methoxy-3-oxoprop-1-en-1-yl)phenoxy)propan-2-yl)carbamoyl)piperidine-1-carboxylate (16p). Using the synthetic method for **16a**, compound **13a** and 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid gave **16p** (71% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 592.4 $[M+H]^+$.



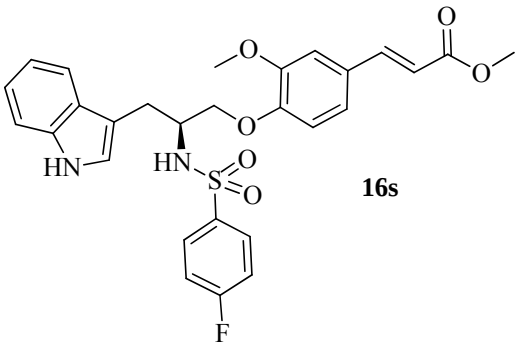
16q

(*S*,*E*)-Methyl 3-(4-(2-(4-((*tert*-butoxycarbonyl)amino)benzamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16q). Using the synthetic method for **16a**, compound **13a** and 4-((*tert*-butoxycarbonyl)amino)benzoic acid gave **16q** (69% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 600.4 $[M+H]^+$.



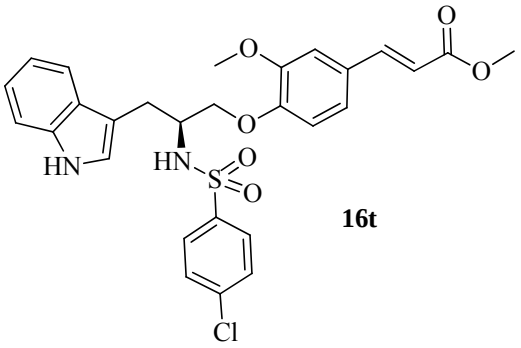
16r

(*S*,*E*)-Methyl 3-(4-(3-(1*H*-indol-3-yl)-2-(2,4,6-triisopropylphenylsulfonamido)propoxy)-3-methoxyphenyl)acrylate (16r). To a solution of **13a** (2.40 g, 5.0 mmol) in anhydrous dichloromethane (20 mL) was added trifluoroacetic acid (7 mL). When the reaction was finished, Et_3N was added to the solution until the pH became weakly basic. Then at 0°C, to this dichloromethane solution was added Et_3N (0.56 g, 5.5 mmol) followed by 2,4,6-triisopropylbenzene-1-sulfonyl chloride (1.51 g, 5.0 mmol). Stirring was continued over night and then the solvent was evaporated with the residue being taken up in EtOAc (50 mL). The EtOAc solution was washed with 1 N HCl (3×10 mL), saturated Na_2CO_3 (3×10 mL) and brine (3×10 mL), dried over $MgSO_4$, and evaporated under vacuum. The crude product was purified by flash column chromatography (petroleum ether/EtOAc 2:1) to give desired compound **16r** (60% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 647.3 $[M+H]^+$.



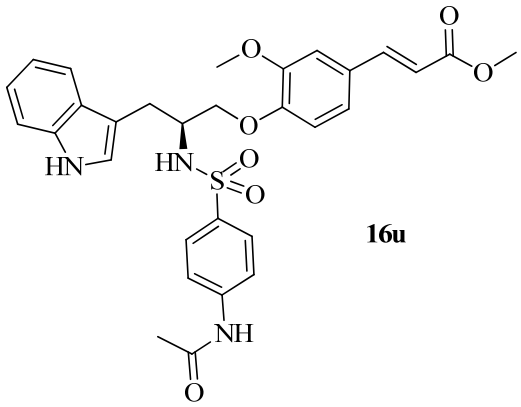
16s

(*S*,*E*)-Methyl 3-(4-(2-(4-fluorophenylsulfonamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxypheny l)acrylate (11s). Using the synthetic method for **16r**, compound **13a** and 4-fluorobenzene-1-sulfonyl chloride gave **16s** (76% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 539.4 $[M+H]^+$.



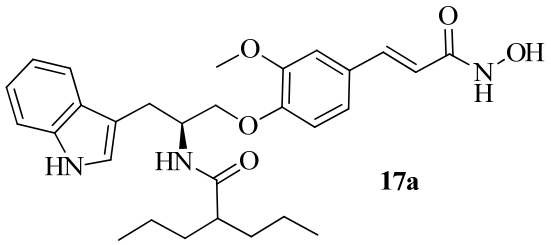
16t

(*S*,*E*)-Methyl 3-(4-(2-(4-chlorophenylsulfonamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxypheny l)acrylate (16t). Using the synthetic method for **16r**, compound **13a** and 4-chlorobenzene-1-sulfonyl chloride gave **16t** (68% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 555.5 $[M+H]^+$.



16u

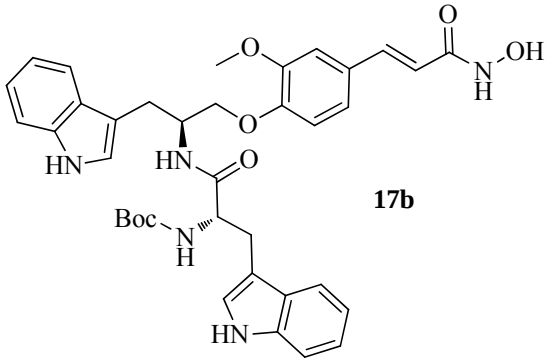
(*S*,*E*)-Methyl 3-(4-(2-(4-acetamidophenylsulfonamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)acrylate (16u). Using the synthetic method for **16r**, compound **13a** and 4-acetamidobenzene-1-sulfonyl chloride gave **16u** (62% yield) as light yellow oil, which crystallized on standing. ESI-MS *m/z*: 578.5 $[M+H]^+$.



17a

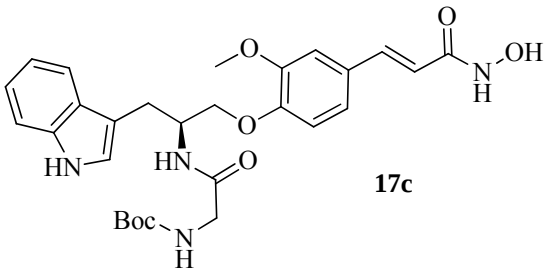
(*S*,*E*)-*N*-(1-(4-(3-(Hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)-2-propylpentanamide (17a). Using the synthetic method for **14a**, compound **16a** gave **17a** (34% yield) as a white powder. Mp: 128-130°C. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.64 (s, 1H), 8.97 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.17 (s, 1H), 7.13 (d, J = 1.8 Hz, 1H), 6.94-7.06 (m, 4H), 6.34 (d, J = 16.2 Hz, 1H), 4.35-4.36 (m, 1H), 3.93-4.00 (m, 2H), 3.81 (s, 3H), 3.01 (dd, J = 6.0 Hz, J = 14.4 Hz, 1H), 2.90 (dd, J = 6.0 Hz, J = 14.4 Hz, 1H), 2.13-2.15 (m, 1H),

1.34-1.42 (m, 2H), 1.14-1.18 (m, 4H), 0.99-1.05 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H), 0.77 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 175.3, 150.6, 149.8, 139.0, 136.7, 127.8, 123.8, 121.6, 121.3, 118.8, 118.7, 117.5, 113.8, 111.7, 111.2, 70.3, 56.2, 49.4, 45.7, 35.4, 35.3, 27.3, 20.6, 20.5, 14.5, 14.4. HRMS (AP-ESI) *m/z* calcd for $C_{29}H_{37}N_3NaO_5$ $[M+Na]^+$ 530.2631, found 530.2614.



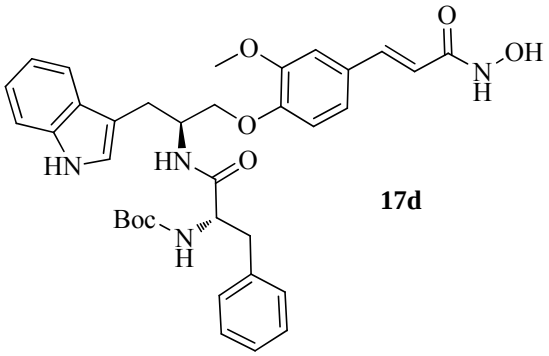
17b

***tert*-Butyl ((*S*)-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (17b).** Using the synthetic method for **14a**, compound **16b** gave **17b** (31% yield) as a white powder. Mp: 122-124°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 10.79 (s, 1H), 10.63 (s, 1H), 8.95 (s, 1H), 7.55-8.03 (m, 3H), 7.38 (d, J = 15.8 Hz, 1H), 6.69-7.34 (m, 12H), 6.34 (d, J = 15.8 Hz, 1H), 4.22-4.24 (m, 1H), 4.30-4.31 (m, 1H), 3.80 (s, 3H), 3.02-3.04 (m, 2H), 2.92-2.94 (m, 2H), 1.31 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 172.3, 163.7, 155.6, 149.8, 138.8, 136.6, 136.5, 128.6, 128.0, 127.9, 124.1, 123.9, 121.6, 121.4, 121.2, 119.0, 118.8, 118.7, 118.6, 117.4, 114.1, 111.8, 111.7, 111.3, 110.9, 110.6, 78.5, 69.8, 56.2, 55.7, 49.7, 28.6, 28.4, 27.0. HRMS (AP-ESI) *m/z* calcd for $C_{37}H_{41}N_5NaO_7$ $[M+Na]^+$ 690.2904, found 690.2972.



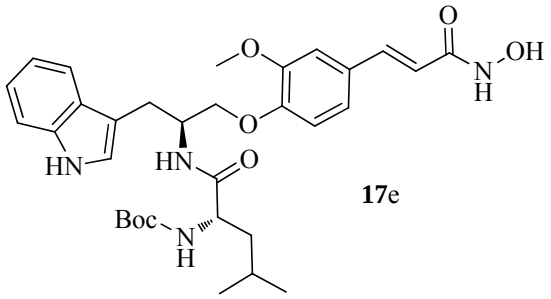
17c

(*S*,*E*)-*tert*-Butyl (2-((1-(4-(3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-2-oxoethyl)carbamate (17c). Using the synthetic method for **14a**, compound **16c** gave **17c** (45% yield) as a white powder. Mp: 101-103°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.82 (s, 1H), 10.63 (s, 1H), 8.96 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.18 (s, 1H), 7.12 (d, J = 1.8 Hz, 1H), 6.90-7.07 (m, 5H), 6.34 (d, J = 16.2 Hz, 1H), 4.28-4.30 (m, 1H), 3.89-3.94 (m, 2H), 3.83 (s, 3H), 3.54-3.55 (m, 2H), 2.90-3.07 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.2, 163.1, 155.7, 149.3, 138.3, 136.1, 128.1, 127.3, 123.4, 121.1, 120.9, 118.3, 118.2, 116.9, 113.5, 111.3, 110.8, 110.4, 78.0, 69.4, 55.7, 49.3, 43.2, 28.1, 26.5. HRMS (AP-ESI) *m/z* calcd for $C_{28}H_{35}N_4O_7$ $[M+H]^+$ 539.2506, found 539.2534.



17d

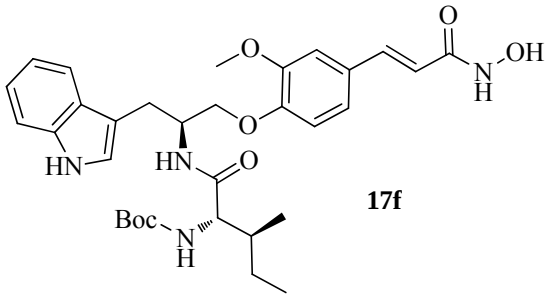
***tert*-Butyl ((*S*)-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (17d).** Using the synthetic method for **14a**, compound **16d** gave **17d** (52% yield) as a white powder. Mp: 115-117°C. ^{1}H-NMR (DMSO-d_6) δ 10.83 (s, 1H), 10.62 (s, 1H), 8.96 (s, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 6.80-7.22 (m, 12H), 6.34 (d, J = 16.2 Hz, 1H), 4.25-4.34 (m, 1H), 4.16-4.23 (m, 1H), 3.87-3.89 (m, 2H), 3.80 (s, 3H), 2.69-3.09 (m, 4H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.5, 163.1, 155.1, 149.3, 138.3, 138.0, 136.1, 129.2, 128.8, 128.1, 127.9, 127.4, 126.1, 123.4, 121.1, 120.9, 118.3, 116.9, 113.4, 111.3, 110.7, 110.4, 78.0, 69.2, 55.7, 49.2, 37.7, 28.07, 26.47. HRMS (AP-ESI) *m/z* calcd for $C_{35}H_{40}N_4NaO_7$ $[M+Na]^+$ 651.2795, found 651.2726.



17e

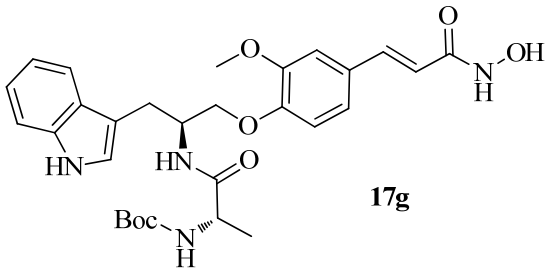
***tert*-Butyl ((*S*)-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (17e).** Using the synthetic method for **14a**, compound **16e** gave **17e** (44% yield) as a white powder. Mp: 107-109°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.82 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.80-7.16 (m, 7H), 6.33 (d, J = 16.2 Hz, 1H), 4.21-4.33 (m, 1H), 3.92-3.94 (m, 3H), 3.81 (s, 3H), 2.95-3.06 (m, 2H),

1.35-1.65 (m, 3H), 1.36 (s, 9H), 0.81-0.85 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.4, 163.1, 155.2, 149.3, 138.3, 136.1, 128.0, 127.3, 123.4, 121.1, 120.9, 118.3, 116.8, 113.5, 111.3, 110.8, 110.4, 77.9, 69.3, 55.7, 52.9, 49.1,41.0, 28.1, 26.6, 24.2, 22.9, 21.6. HRMS (AP-ESI) *m/z* calcd for $C_{32}H_{42}N_4NaO_7$ $[M+Na]^+$ 617.2951, found 617.2908.



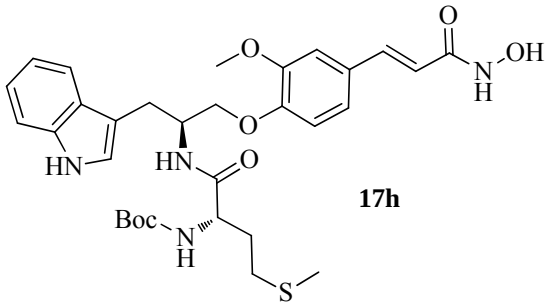
17f

***tert*-Butyl ((2*S*,3*S*)-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-3-methyl-1-oxopentan-2-yl)carbamate (17f).** Using the synthetic method for **14a**, compound **16f** gave **17f** (49% yield) as a white powder. Mp: 116-118°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.10-7.16 (m, 7H), 6.33 (d, J = 16.2 Hz, 1H), 4.32-4.34 (m, 1H), 3.85-3.94 (m, 3H), 3.80 (s, 3H), 2.90-3.06 (m, 2H), 1.35-1.71 (m, 2H), 1.37 (s, 9H), 1.02-1.09 (m, 1H), 0.74-0.78 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.3, 163.2, 155.2, 149.3, 138.3, 136.1, 128.1, 127.3, 123.4, 121.1, 120.9, 118.2, 116.9, 113.4, 111.3, 110.8, 110.5, 78.0, 69.3, 58.8, 55.7, 49.2, 36.6, 28.1, 26.7, 24.3, 15.2, 10.9. HRMS (AP-ESI) *m/z* calcd for $C_{32}H_{42}N_4NaO_7$ $[M+Na]^+$ 617.2951, found 617.2956.



17g

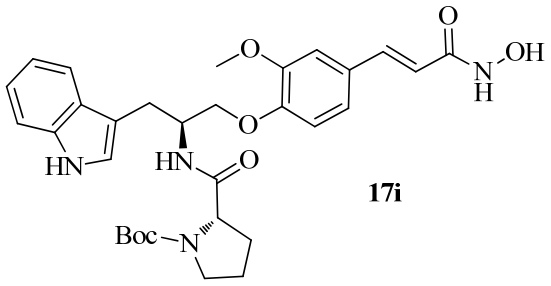
***tert*-Butyl ((*S*)-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-1-oxopropan-2-yl)carbamate (17g).** Using the synthetic method for **14a**, compound **16g** gave **17g** (43% yield) as a white powder. Mp: 120-122°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.82 (s, 1H), 10.62 (s, 1H), 8.96 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.83-7.17 (m, 7H), 6.34 (d, J = 16.2 Hz, 1H), 4.28-4.30 (m, 1H), 3.92-3.98 (m, 3H), 3.81 (s, 3H), 2.93-3.06 (m, 2H), 1.36 (s, 9H), 1.16 (d, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.6, 163.2, 154.9, 149.3, 138.3, 136.1, 128.1, 127.4, 123.4, 121.1, 120.9, 118.3, 116.9, 113.6, 111.3, 110.9, 110.4, 78.0, 69.4, 55.7, 49.8, 49.2, 28.1, 26.5, 18.3. HRMS (AP-ESI) *m/z* calcd for $C_{29}H_{36}N_4NaO_7$ $[M+Na]^+$ 575.2482, found 575.2451.



17h

***tert*-Butyl ((*S*)-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (17h).** Using the synthetic method for **14a**, compound **16h** gave

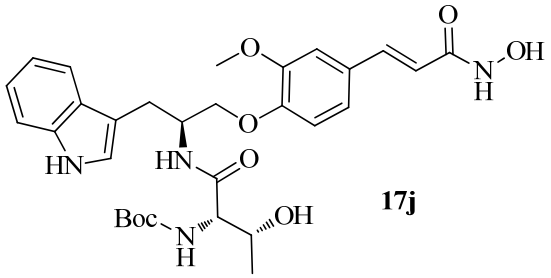
17h (36% yield) as a white powder. Mp: 104-106°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.82 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.87-7.16 (m, 7H), 6.33 (d, J = 16.2 Hz, 1H), 4.31-4.33 (m, 1H), 3.92-4.10 (m, 3H), 3.81 (s, 3H), 2.91-3.06 (m, 2H), 2.38-2.42 (m, 2H), 1.97 (s, 3H), 1.71-1.87 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.5, 163.2, 155.3, 149.3, 138.3, 136.1, 128.1, 127.3, 123.4, 121.0, 120.9, 118.3, 116.9, 113.4, 111.3, 110.7, 110.4, 78.1, 69.3, 55.7, 53.7, 49.2, 31.9, 29.6, 28.1, 26.6, 14.5. HRMS (AP-ESI) *m/z* calcd for $C_{31}H_{40}N_4NaO_7S$ $[M+Na]^+$ 635.2515, found 635.2591.



17i

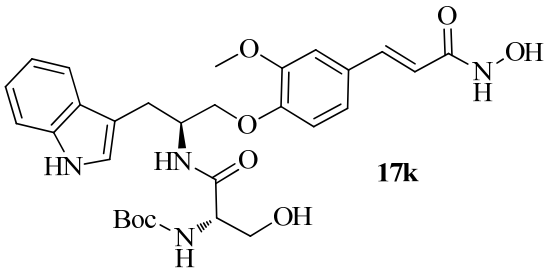
(*S*)-*tert*-Butyl 2-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (17i). Using the synthetic method for **14a**, compound **16i** gave **17i** (40% yield) as a white powder. Mp: 112-114°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.82 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.87-7.16 (m, 7H), 6.33 (d, J = 16.2 Hz, 1H), 4.32-4.37 (m, 1H), 3.92-4.14 (m, 3H), 3.79 (s, 3H), 3.32-3.37 (m, 2H), 2.98-3.00 (m, 2H), 1.65-2.07 (m, 4H), 1.38 + 1.26 (s, 9H, cis/trans). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.4, 163.1, 153.4, 149.2, 138.3, 136.2, 128.0, 127.4, 127.3, 123.3,

121.1, 120.9, 118.3, 116.9, 113.3, 111.3, 110.6, 78.3, 69.4, 55.6, 49.1, 46.5, 31.0, 30.0, 28.1, 27.9, 26.9, 23.8, 23.0. HRMS (AP-ESI) *m/z* calcd for $C_{31}H_{38}N_4NaO_7$ $[M+Na]^+$ 601.2638, found 601.2613.



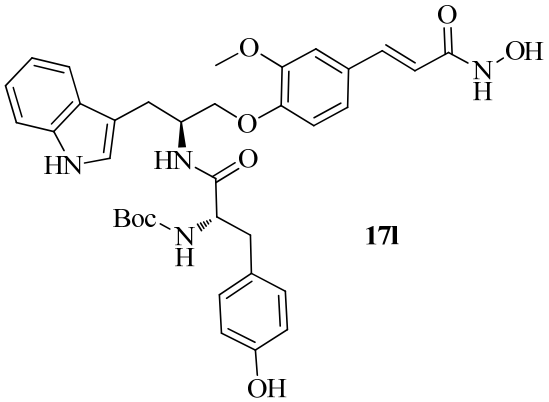
17j

***tert*-Butyl ((2*S*,3*R*)-3-hydroxy-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-1-oxobutan-2-yl)carbamate (17j).** Using the synthetic method for **14a**, compound **16j** gave **17j** (49% yield) as a white powder. Mp: 112-114°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.63 (s, 1H), 8.96 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.88-7.17 (m, 6H), 6.31-6.36 (m, 2H), 4.73 (d, J = 5.7 Hz, 1H), 4.28-4.35 (m, 1H), 3.86-3.92 (m, 4H), 3.82 (s, 3H), 2.92-3.07 (m, 2H), 1.38 (s, 9H), 1.01 (d, J = 5.7 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.4, 163.1, 155.3, 149.3, 138.3, 136.1, 128.1, 127.3, 123.5, 121.1, 120.9, 118.3, 116.9, 113.5, 111.3, 110.7, 110.4, 78.2, 69.2, 66.9, 60.2, 55.7, 49.2, 28.1, 26.5, 19.9. HRMS (AP-ESI) *m/z* calcd for $C_{30}H_{38}N_4NaO_8$ $[M+Na]^+$ 605.2587, found 605.2580.



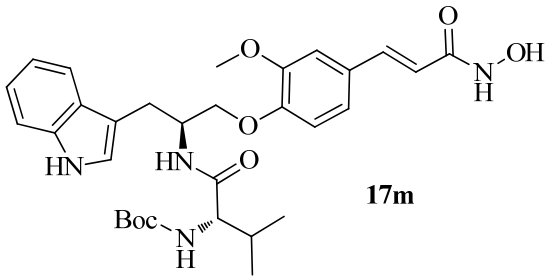
17k

***tert*-Butyl ((*S*)-3-hydroxy-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-1-oxopropan-2-yl) carbamate (17k).** Using the synthetic method for **14a**, compound **16k** gave **17k** (49% yield) as a white powder. Mp: 104-106°C. ^{1}H-NMR (DMSO-d_6) δ 10.82 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.89-7.18 (m, 6H), 6.63 (d, J = 7.8 Hz, 1H), 6.34 (d, J = 16.2 Hz, 1H), 4.78 (t, J = 5.7 Hz, 1H), 4.26-4.32 (m, 1H), 3.86-4.12 (m, 3H), 3.83 (s, 3H), 3.46-3.59 (m, 2H), 2.96-3.07 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.2, 163.1, 155.1, 149.3, 138.3, 136.1, 128.1, 127.4, 123.4, 121.1, 120.9, 118.2, 116.9, 113.7, 111.3, 110.9, 110.4, 78.1, 69.3, 61.9, 56.9, 55.8, 49.2, 28.1, 26.4. HRMS (AP-ESI) *m/z* calcd for $C_{29}H_{36}N_4NaO_8$ $[M+Na]^+$ 591.2431, found 591.2478.



17l

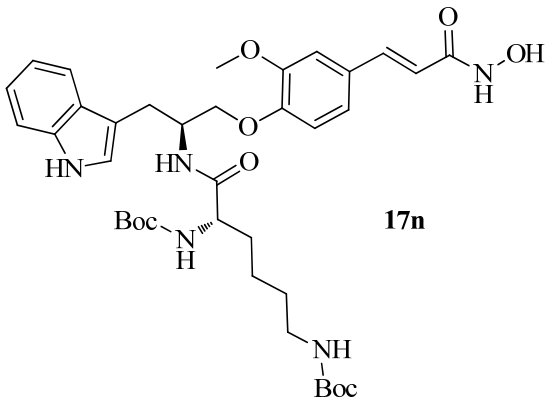
***tert*-Butyl ((*S*)-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (17l).** Using the synthetic method for **14a**, compound **16l** gave **17l** (36% yield) as a white powder. Mp: 118-120°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.82 (s, 1H), 10.63 (s, 1H), 9.13 (s, 1H), 8.96 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 6.88-7.16 (m, 8H), 6.71 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 2H), 6.34 (d, J = 16.2 Hz, 1H), 4.25-4.32 (m, 1H), 4.1.-4.15 (m, 1H), 3.85-3.95 (m, 2H), 3.81 (s, 3H), 2.90-3.09 (m, 2H), 2.78-2.84 (m, 1H), 2.61-2.68 (m, 1H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.6, 163.2, 155.7, 155.1, 149.3, 138.3, 136.1, 130.1, 128.1, 128.0, 127.4, 123.4, 121.1, 120.9, 118.3, 118.2, 116.9, 114.7, 113.5, 111.3, 110.8, 110.4, 78.0, 69.3, 55.9, 55.7, 49.2, 36.9, 28.1, 26.5. HRMS (AP-ESI) *m/z* calcd for $C_{35}H_{40}N_4NaO_8$ $[M+Na]^+$ 667.2744, found 667.2756.



17m

***tert*-Butyl ((*S*)-1-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (17m).** Using the synthetic method for **14a**, compound **16m** gave **17m** (44% yield) as a white powder. Mp: 107-109°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz,

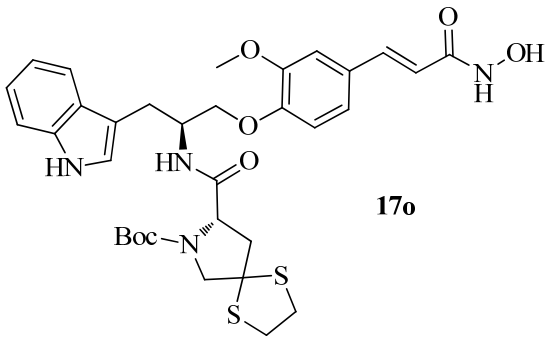
1H), 7.37 (d, *J* = 16.2 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 6.57-7.16 (m, 7H), 6.33 (d, *J* = 16.2 Hz, 1H), 4.30-4.37 (m, 1H), 3.93-3.94 (m, 2H), 3.78-3.83 (m, 1H), 3.81 (s, 3H), 2.90-3.06 (m, 2H), 1.84-1.95 (m, 1H), 1.38 (s, 9H), 0.78-0.81 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.2, 163.1, 155.3, 149.3, 138.3, 136.1, 128.0, 127.3, 123.4, 121.1, 120.9, 118.3, 116.8, 113.4, 111.3, 110.7, 110.5, 77.9, 69.3, 55.6, 49.2, 30.5, 28.1, 26.7, 19.1, 18.1. HRMS (AP-ESI) *m/z* calcd for $C_{31}H_{40}N_4NaO_7$ $[M+Na]^+$ 603.2795, found 603.2715.



17n

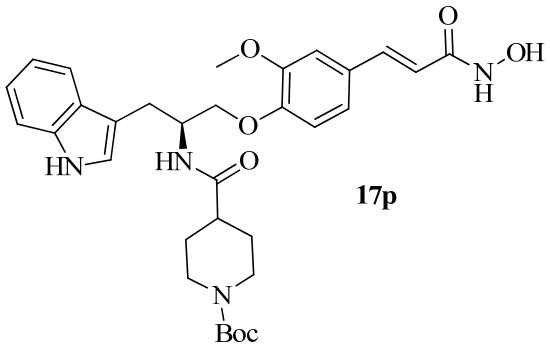
***di-tert*-Butyl ((*S*)-6-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)amino)-6-oxohexane-1,5-diyl)dicarbamate (17n).** Using the synthetic method for **14a**, compound **16n** gave **17n** (37% yield) as a white powder. Mp: 107-109°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), δ 10.62 (s, 1H), 8.95 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 15.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 6.70-7.16 (m, 8H), 6.33 (d, *J* = 15.9 Hz, 1H), 4.26-4.33 (m, 1H), 3.83-3.93 (m, 3H), 3.81 (s, 3H), 2.83-3.06 (m, 4H), 1.15-1.57 (m, 6H), 1.36 (s, 18H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.1, 163.0, 155.5, 155.2, 149.3, 138.3, 136.1, 128.1, 127.4, 123.4, 121.1, 120.9, 118.3, 116.9, 113.6, 111.3, 110.9, 110.4, 78.0, 77.3, 69.4, 55.7, 54.4, 49.1, 31.8, 29.2, 28.2, 28.1,

26.5, 22.7. HRMS (AP-ESI) *m/z* calcd for $C_{37}H_{51}N_5NaO_9$ $[M+Na]^+$ 732.3584, found 732.3523.



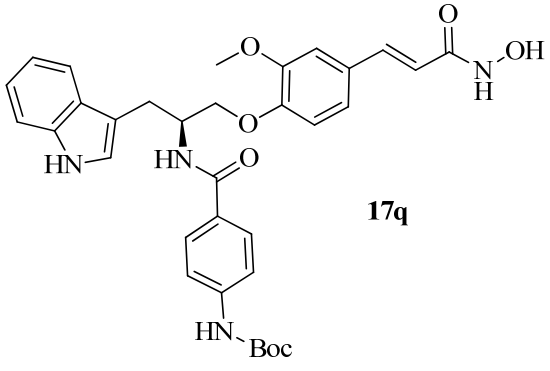
17o

(*S*)-*tert*-Butyl 8-(((*S*)-1-(4-((*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)carbamoyl)-1,4-dithia-7-azaspiro[4.4]nonane-7-carboxylate (17o). Using the synthetic method for **14a**, compound **16o** gave **17o** (38% yield) as a white powder. Mp: 114-116°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 10.63 (s, 1H), 8.96 (s, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 15.6 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.87-7.18 (m, 6H), 6.33 (d, J = 15.6 Hz, 1H), 4.16-4.33 (m, 2H), 3.53-3.98 (m, 4H), 3.81 (s, 3H), 3.28-3.40 (m, 4H), 2.99-3.00 (m, 2H), 2.15-2.55 (m, 2H), 1.39 +1.25 (s, 9H, cis/trans). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 171.4, 170.8, 163.7, 153.5, 149.8, 138.8, 136.7, 128.6, 127.8, 123.9, 121.5, 121.4, 118.8, 118.7, 117.4, 113.9, 111.8, 111.2, 111.0, 79.9, 69.8, 66.6, 62.1, 60.6, 56.2, 49.9, 46.7, 39.1, 28.5, 28.3, 27.3. HRMS (AP-ESI) *m/z* calcd for $C_{33}H_{40}N_4NaO_7S_2$ $[M+Na]^+$ 691.2236, found 691.2285.



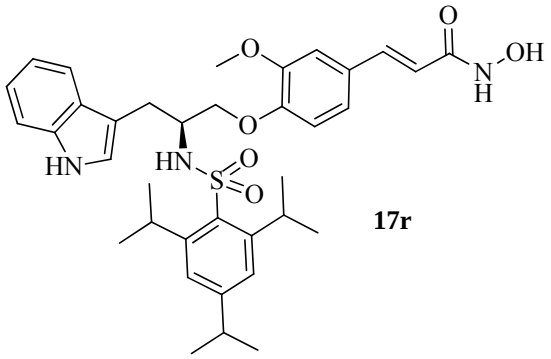
17p

(*S*,*E*)-*tert*-Butyl 4-((1-(4-(3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)carbamoyl)piperidine-1-carboxylate (17p). Using the synthetic method for **14a**, compound **16p** gave **17p** (40% yield) as a white powder. Mp: 122-124°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.78 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 15.6 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.92-7.17 (m, 6H), 6.34 (d, J = 15.6 Hz, 1H), 4.23-4.34 (m, 1H), 3.82-3.97 (m, 4H), 3.81 (s, 3H), 2.86-3.06 (m, 2H), 2.56-2.78 (m, 2H), 2.26-2.35 (m, 1H), 1.35-1.63 (m, 4H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.9, 163.1, 153.8, 149.3, 138.3, 136.1, 128.0, 127.4, 123.3, 121.1, 120.8, 118.3, 118.2, 116.9, 113.5, 111.3, 110.9, 110.7, 78.5, 69.7, 55.7, 49.0, 41.6, 28.2, 28.1, 26.6. HRMS (AP-ESI) *m/z* calcd for $C_{32}H_{40}N_4NaO_7$ $[M+Na]^+$ 615.2795, found 615.2706.



17q

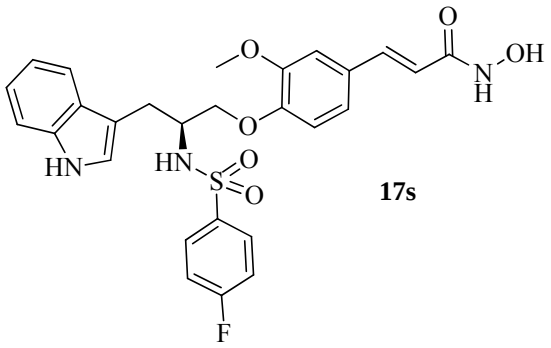
(*S*,*E*)-*tert*-Butyl (4-((1-(4-(3-(hydroxyamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)-3-(1*H*-indol-3-yl)propan-2-yl)carbamoyl)phenyl)carbamate (17q). Using the synthetic method for **14a**, compound **16q** gave **17q** (38% yield) as a white powder. Mp: 138-140°C. ^{1}H-NMR (DMSO-d_6) δ 10.79 (s, 1H), 10.62 (s, 1H), 9.60 (s, 1H), 8.95 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.38 (d, J = 16.2 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.93-7.17 (m, 6H), 6.33 (d, J = 16.2 Hz, 1H), 4.49-4.60 (m, 1H), 4.15-4.25 (m, 1H), 4.00-4.06 (m, 1H), 3.78 (s, 3H), 3.03-3.16 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.8, 163.2, 152.6, 149.3, 149.2, 142.2, 138.3, 136.1, 128.1, 128.0, 127.8, 127.4, 123.3, 121.2, 120.9, 118.3, 118.2, 117.0, 116.9, 113.5, 111.3, 110.8, 79.4, 69.7, 55.7, 49.8, 28.0, 26.7. HRMS (AP-ESI) *m/z* calcd for $C_{33}H_{36}N_4NaO_7$ $[M+Na]^+$ 623.2482, found 623.2477.



17r

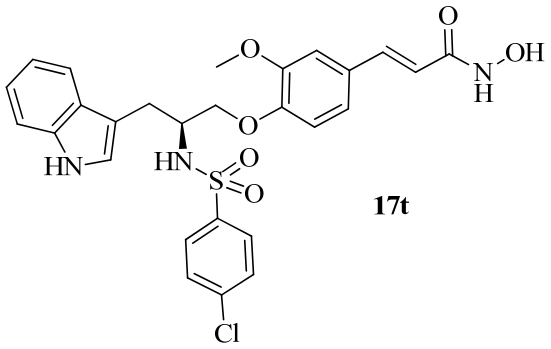
(*S*,*E*)-3-(4-(3-(1*H*-Indol-3-yl)-2-(2,4,6-triisopropylphenylsulfonamido)propoxy)-3-methoxyphenyl)-*N*-hydroxyacrylamide (17r). Using the synthetic method for **14a**, compound **16r** gave **17r** (51% yield) as a white powder. Mp: 100-102°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 10.62 (s, 1H), 8.95 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 15.6 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 6.83-7.23 (m, 8H),

6.57 (d, J = 7.8 Hz, 1H), 6.31 (d, J = 15.6 Hz, 1H), 4.14-4.22 (m, 2H), 3.65-3.85 (m, 3H), 3.72 (s, 3H), 3.02-3.10 (m, 1H), 2.82-2.98 (m, 2H), 1.13-1.23 (m, 18H) . ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.1, 151.9, 149.4, 149.3, 149.1, 138.2, 136.1, 134.3, 128.2, 127.0, 123.6, 123.4, 120.9, 118.2, 117.8, 116.9, 113.8, 111.3, 111.0, 109.8, 69.5, 55.7, 52.6, 33.3, 28.9, 27.7, 24.7, 24.6, 23.4. HRMS (AP-ESI) *m/z* calcd for $C_{36}H_{45}N_3NaO_6S$ $[M+Na]^+$ 670.2927, found 670.2996.



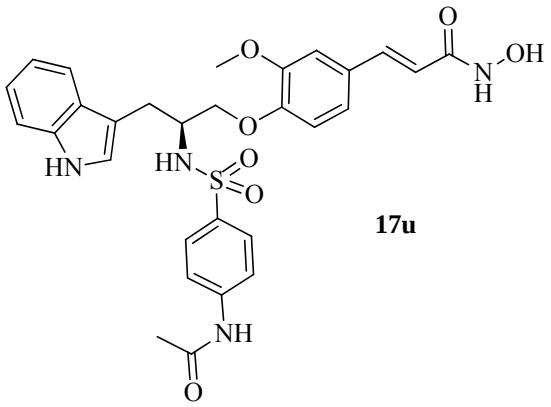
17s

(*S*,*E*)-3-(4-(2-(4-Fluorophenylsulfonamido)-3-(1*H*-indol-3-yl)propoxy)-3-methoxyphenyl)-*N*-hydroxyacrylamide (17s). Using the synthetic method for **14a**, compound **16s** gave **17s** (54% yield) as a white powder. Mp: 92-94°C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.71 (s, 1H), 10.63 (s, 1H), 8.96 (s, 1H), 8.05 (d, J = 7.8, 1H), 7.60-7.65 (m, 2H), 7.39 (d, J = 15.6 Hz, 1H), 7.26 (d, J = 8.7 Hz, 2H), 6.81-7.17 (m, 8H), 6.34 (d, J = 15.6 Hz, 1H), 3.75-3.98 (m, 3H), 3.81 (s, 3H), 3.03 (dd, J = 6.6 Hz, J = 14.4 Hz, 1H), 2.80 (dd, J = 6.6 Hz, J = 14.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.3, 163.1, 161.9, 149.2, 148.9, 138.3, 137.1, 136.1, 128.9, 128.8, 128.1, 126.8, 123.9, 121.0, 120.7, 118.2, 117.7, 116.9, 115.7, 115.4, 113.3, 111.3, 110.7, 109.5, 70.2, 55.7, 53.4, 27.4. HRMS (AP-ESI) *m/z* calcd for $C_{27}H_{26}FN_3NaO_6S$ $[M+Na]^+$ 562.1424, found 562.1397.



17t

(*S*,*E*)-3-(4-(2-(4-Chlorophenylsulfonamido)-3-(1*H*-indol-3-yl)propoxy)-3-metho xyphenyl)-*N*-hydroxyacrylamide (17t). Using the synthetic method for **14a**, compound **16t** gave **17t** (42% yield) as a white powder. Mp: 96-98°C. ^{1}H-NMR (300MHz, DMSO-d_6) δ 10.71 (s, 1H), 10.63 (s, 1H), 8.96 (s, 1H), 8.13 (d, J = 6.9 Hz, 1H), 7.53-7.58 (m, 2H), 7.39 (d, J = 15.6 Hz, 1H), 6.80-7.31 (m, 10H), 6.34 (d, J = 15.6 Hz, 1H), 3.75-3.99 (m, 3H), 3.81 (s, 3H), 3.03 (dd, J = 6.6 Hz, J = 14.4 Hz, 1H), 2.81 (dd, J = 6.6 Hz, J = 14.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.1, 149.2, 148.9, 139.6, 138.3, 136.6, 136.1, 128.5, 125.2, 127.8, 126.9, 123.9, 121.0, 120.7, 118.2, 117.7, 117.0, 113.4, 111.4, 110.8, 109.5, 70.2, 55.7, 53.5, 27.5. HRMS (AP-ESI) *m/z* calcd for $C_{27}H_{26}ClN_3NaO_6S$ $[M+Na]^+$ 578.1129, found 578.1197.



17u

(*S*,*E*)-3-(4-(2-(4-Acetamidophenylsulfonamido)-3-(1*H*-indol-3-yl)propoxy)-3-m ethoxyphenyl)-*N*-hydroxyacrylamide (17u). Using the synthetic method for **14a**,

compound **16u** gave **17u** (39% yield) as a white powder. Mp: 98-100°C. ^{1}H-NMR (300, MHz, DMSO-d_6) δ 10.76 (s, 1H), 10.63 (s, 1H), 10.18 (s, 1H), 8.96 (s, 1H), 7.87 (d, J = 6.9 Hz, 1H), 7.59-7.71 (m, 4H), 7.37 (d, J = 15.6 Hz, 1H), 6.70-7.29 (m, 8H), 6.33 (d, J = 15.6 Hz, 1H), 3.75-3.90 (m, 3H), 3.82 (s, 3H), 3.01 (dd, J = 6.6 Hz, J = 14.4 Hz, 1H), 2.82 (dd, J = 6.6 Hz, J = 14.4 Hz, 1H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 168.8, 163.1, 149.1, 149.0, 142.5, 138.3, 136.1, 134.7, 131.5, 128.0, 127.4, 127.0, 123.8, 121.0, 120.8, 118.9, 118.2, 117.9, 116.8, 113.1, 111.4, 110.6, 109.6, 106.9, 69.4, 55.6, 53.3, 27.5, 24.1. HRMS (AP-ESI) *m/z* calcd for $C_{29}H_{30}N_4NaO_7S$ $[M+Na]^+$ 601.1733, found 601.1784.

***In vitro* HDACs inhibition fluorescence assay.** *In vitro* HDACs inhibition assays were conducted as previously described.[1-3] Boc-Lys (acetyl)-AMC substrate was used in inhibition assays against HeLa cell nuclear extract, class I (HDAC1, HDAC2, HDAC3) and class IIb (HDAC6), while Boc-Lys (triflouroacetyl)-AMC substrate for class IIa (MDA-MB-231 cell lysate). In brief, 10 μL of enzyme solution was mixed with various concentrations of tested compound (50 μL). Five minutes later, 40 μL of fluorogenic substrate was added, and the mixture was incubated at 37 °C for 30 min and then stopped by addition of 100 μL of developer containing trypsin and TSA. After incubation at 37 °C for 20 min, fluorescence intensity was measured using a microplate reader at excitation and emission wavelengths of 390 nm and 460 nm, respectively. The inhibition ratios were calculated from the fluorescence intensity readings of tested wells relative to those of control wells, and the IC_{50} values were calculated using a regression analysis of the concentration/inhibition data.

***In vitro* antiproliferative assay.** *In vitro* antiproliferative assays were determined by the MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2*H*-tetrazolium bromide) method as previously described.[2,3] Briefly, U937 (human leukemic monocyte lymphoma), PC-3 (human prostate cancer), A549 (human lung cancer), ES-2 (human ovarian cancer), MDA-MB-231 (human breast cancer) and HCT116 (human colon cancer) cell lines were maintained in RPMI1640 medium containing 10% FBS at 37 ^{o}C in 5% CO_2 humidified incubator. Cells were passaged the day before dosing into a 96-well cell plate, allowed to grow for a minimum of 4 h prior to addition of compounds. After compounds addition, the plates were incubated for an additional 48 h, and then 0.5% MTT solution was added to each well. After further incubation for 4 h, formazan formed from MTT was extracted by adding 200 μL of DMSO for 15 min. Absorbance was then determined using an ELISA reader at 570 nm and the IC_{50} values were calculated according to the inhibition ratios.

Western blot analysis. For western blot analysis, total protein extracts were separated on a polyacrylamide gel, transferred onto PVDF membranes and blotted as previously described.[4] Briefly, MDA-MB-231 cells with different treatment were collected and lysed with lysis buffer (20 mM Tris-HCl [pH 7.5], 1% NP-40, 1 mM sodium vanadate, 1 mM EDTA, 1 mM EGTA, 50 mM NaF, 1 mM phenylmethyl sulfonylfluoride [PMSF]) for 30 min, then centrifuged for 15 min at 14000 rpm at 4°C, the supernatant was the whole-cell extracts. Total protein extracts (30 μg per lane) were separated by 12% SDS polyacrylamide gel electrophoresis and transferred onto PVDF membranes (Cat. IPVH00010, Millipore). Membrane was blocked with 5%

milk in TBS-T (10 mM Tris [pH 7.4], 150 mM NaCl and 0.1% Tween 20) for 1 h at room temperature, then incubated with a 1:1000 or 1:2000 dilution of primary antibody overnight at 4°C including acetylated tubulin (Sigma), acetylated histone H3 (Sigma), acetylated histone H4 (Sigma), p21 (Cell Signaling) and β-Actin (Sigma). Then the membrane was washed three times and incubated at 1:2000 dilution of anti-mouse or anti-rabbit goat-HRP-conjugated secondary antibodies for 2 h at room temperature. Finally the membrane was washed another three times and developed by enhanced chemiluminescence (ECL, Cat. WBKLS0050, Millipore).

***In vivo* antitumor assay against U937 xenograft.** For *in vivo* antitumor efficacy research, 1×10^7 human histiocytic lymphoma cells (U937) were inoculated subcutaneously in the right flank of male athymic nude mice (5-6 weeks old, SLAC LABORATORY ANIMAL, Shanghai). Ten days after injection, tumors were palpable and mice were randomized into treatment and control groups (7 mice per group). The treatment groups received compound **17a** (60 mg/kg/d) or Tamibarotene (20 mg/kg/d) by oral administration, and the blank control group received equal volume of PBS solution containing 40 % DMSO. During treatment, subcutaneous tumors were measured with vernier caliper every three days, and body weight was monitored regularly. After treatment, mice were sacrificed and dissected to weigh the tumor tissues and to examine the internal organ injury. Tumor growth inhibition (TGI) and relative increment ratio (T/C) were used as the evaluation indicators to reveal the antitumor effects in tumor weight and tumor volume, respectively. Data were

analyzed by Student's two-tailed *t* test. A *P* level < 0.05 was considered statistically significant.

TGI = (the mean tumor weight of control group – the mean tumor weight of treated group) / the mean tumor weight of control group.

Tumor volumes (V) were estimated using the equation ($V = ab^2 / 2$, where a and b stand for the longest and shortest diameter, respectively). T/C was calculated according to the following formula:

T/C = the mean RTV of treated group / the mean RTV of control group.

RTV, namely relative tumor volume = V_t / V_0 (V_t: the tumor volume measured at the end of treatment; V_0: the tumor volume measured at the beginning of treatment).

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