TIMP3 expression associates with prognosis in colorectal cancer and its novel arylsulfonamide inducer, MPT0B390, inhibits tumor growth, metastasis and angiogenesis

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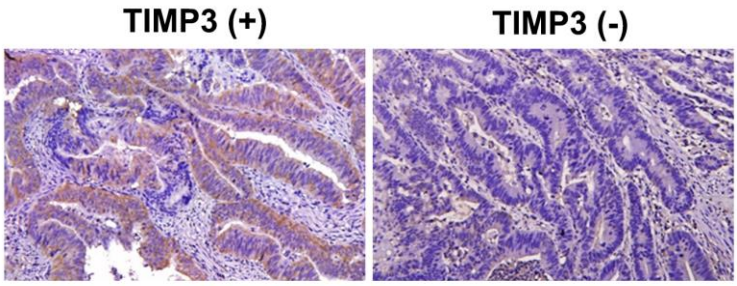
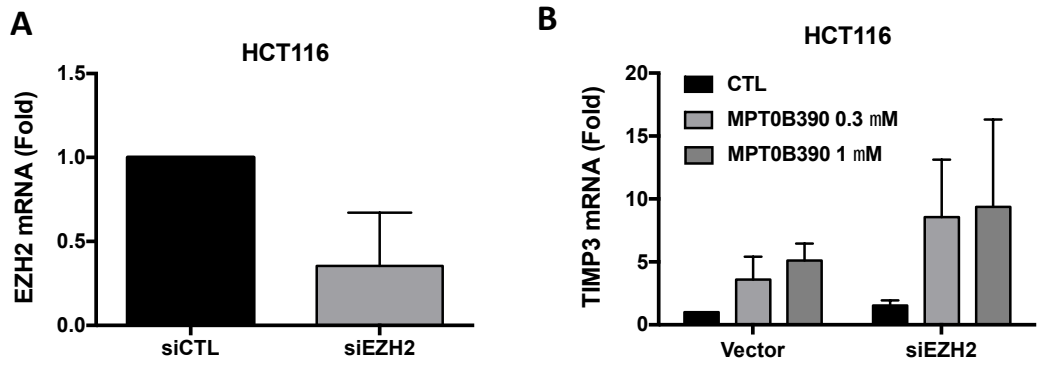


Supplementary Figure S1. Representative TIMP3 expression in colon cancer patients (Patients' information and Kaplan-Meier analysis please see Table 2, and Figure 2A and B, respectively).



Supplementary Figure S2. Effect of MPT0B390 on *TIMP3* induction in EZH2 knockdown HCT116 cell. (A) Knockdown efficiency of siEZH2 in HCT116 cells. HCT116 cells were transfected with siEZH2 for 24 h and then collected for mRNA detection using real-time PCR. (B) MPT0B390 further induced *TIMP3* expression in EZH2 knockdown HCT116 cells. HCT116 cells were transfected with siEZH2 for 24 h and treated with MPT0B390 for an additional 24h. Cells were then collected for mRNA detection using real-time PCR.

Supplementary Table S1. Inhibition of HeLa nuclear extract HDAC activity by compounds **7-18**

Compd	Alternative name	HeLa nuclear HDACs
	IC_{50} (μM)	
14	MPT0B369	0.078
7	MPT0B390	0.004
9	MPT0B515	0.050
8	MPT0B517	0.060
10	MPT0B519	0.030
11	MPT0B522	0.008
12	MPT0B524	0.003
13	MPT0B534	0.170
15	MPT0B553	0.032
16	MPT0B554	0.007
17	MPT0B555	0.008
18	MPT0B556	0.1

Supplementary Table S2. Activities of MPT0B390 and reference Trichostatin A against HDAC isoforms 1, 2, 3, 4, 5, 6, 7, 8, 9 and 11

	IC_{50} (nM)	
Isoenzyme	MPT0B390	Trichostatin A
HDAC1	17.2	14.5
HDAC2	10.1	11.8
HDAC3	4.16	17.9
HDAC4	-	5870.0
HDAC5	-	1440.0
HDAC6	20.9	3.96
HDAC7	-	1490.0
HDAC8	72.2	148.0
HDAC9	-	8860.0
HDAC11	19.9	30.7

Supplementary Table S3. Primer sequences for qRT-PCR and chromatin immunoprecipitation assays.

A. qRT-PCR	
TIMP3	5’-TGCTCTCTGTCTCTTTTTTCAGCTT-3’ (Foward) 5’-CTACAGTGTGTTGTCTGCTGCTTTT-3’ (Reverse)
uPA	5’-CCACAACGACATTGCCTTGCTGAA-3’ (Foward) 5’-ATCGTTATACATCGAGGGCAGGCA-3’ (Reverse)
uPAR	5’-AAGATCACCAGCCTTACCGAGGTT-3’ (Foward) 5’-ATTCGAGGTAACGGCTTCGGGAAT-3’ (Reverse)
c-Met	5’-ATCAACATGGCTCTAGTTGTC-3’ (Foward) 5’-GGGAGAATATGCAGTGAACC-3’ (Reverse)
E-cadherin	5’-ATTCTGATTCTGCTGCTCTTG-3’ (Foward) 5’-AGTCCTGGTCCTCTTCTCC-3’ (Reverse)
GAPDH	5’-TGGGATTTCCATTGATGACAAG-3’ (Foward) 5’-ATTCCACCCATGGCAAATTC-3’ (Reverse)
18S rRNA	5’-AACCCGTTGAACCCCATT-3’ (Foward) 5’-CCATCCAATCGGTAGTAGC-3’ (Reverse)
B. qRT-PCR primers for ChIP assay	
TIMP3 Set a	5’-GTTAGAGTGAAGGCAGGGAAG-3’ (Foward) 5’-TTTGAGCACTTTAGCCATAGGA-3’ (Reverse)
TIMP3 Set b	5’-TGGAAGATCCCAGCTGCAAAT-3’ (Foward) 5’-GAGACATGCATTTCCCTGAACG-3’ (Reverse)
TIMP3 Set c	5’-GTGAGAGCTATAATACGGTGAGATAC-3’ (Foward) 5’-CAGGATCCTAGACGACTAGCTATAA-3’ (Reverse)
TIMP3 Set d	5’-CAGCAGATGGCTTCCCATATC-3’ (Foward) 5’-CACAGAGGAGAAAGACCCAAAC-3’ (Reverse)

Supporting information

N-(5-Bromopyridin-2-yl)-4-methoxybenzenesulfonamide (**20**). A mixture of 2-amino-5-bromopyridine (**19**, 1.05 g, 6.07 mmol), DMAP (0.07 g, 0.55 mmol), ACN (14 mL) and pyridine (3.6 mL) was added 4-methoxybenzensulfonyl chloride (1.27 g, 6.13 mmol) under nitrogen and stirred at rt. Overnight. The reaction was quenched with water and extracted with ethyl acetate (30 mL x 3). The organic layer was collected and dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a dark brown product. The residue was purified by flash column over silica gel (ethyl acetate: n-hexane = 1:1) to afford **20** (1.08 g, 51.84%) as a yellow solid. ^{1}H-NMR (300MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.93(d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 1H), 7.73-7.81 (m, 3H), 8.40 (s, 1H).

(*E*)-3-(6-(4-Methoxyphenylsulfonamido)7xpressi-3-yl)acrylic acid (**21**). A mixture of **20** (0.14 g, 0.41 mmol), palladium acetate (0.01 g, 0.04 mmol), triphenylphosphine (0.02 g, 0.08 mmol), triethylamine (0.06 mL, 0.41 mmol), sodium bicarbonate (0.07 g, 0.82 mmol) and DMF (1.5 mL) was stirred for a while then added the *t*-butyl acrylate (0.07 mL, 0.49 mmol) at 120 ^{o}C and stirred overnight. The residue was purified by flash column over silica gel (ethyl acetate: n-hexane = 1:2) to give the *t*-butyl acrylate compound as a yellow solid. To the ester compound was added trifluoroacetic acid (1.5 mL) and stirred at room temperature for 1 hour. The reaction

was quenched with water and filtered by gravity filtration to yield a as a white solid **21** without further purification (0.21g, 61.55%). ^{1}H-NMR (300 MHz, CD_3OD + DMSO-d_6): δ 3.90 (s, 3H), 6.51 (d, *J* = 15.9 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 9.0 Hz, 1H), 8.35 (s, 1H).

(*E*)-N-Hydroxy-3-(6-(4-methoxyphenylsulfonamido)pyridin-3-yl)acrylamide (**6**)**.** A mixture of **21** (0.30 g, 0.90 mmol), EDC•HCl (0.26 g, 1.35 mmol), HOBt (0.15 g, 1.08 mmol), NMM (0.24 mL, 2.16 mmol) and DMF (2 mL) was stirred for a while then added the NH_2OTHP (0.13 g, 1.08 mmol) at room temperature and was stirred overnight. The residue was purified by flash column over silica gel (ethyl acetate: n-hexane = 4:1) to afford the oily product. The resulting oily product was dissolved in MeOH (5 mL) and added the 10% $TFA_{(aq.)}$ (5 mL) at room temperature and stirred for overnight. The reaction was added H_2O to produce the precipitant. The residue was without more purification to afford **6** (0.17g, 54.16%) as a white solid with m.p. 180.0-181.0 ^{o}C. ^{1}H-NMR (300MHz, DMSO-d_6): δ 3.79 (s, 3H), 6.33 (d, *J* = 15.9 Hz, 1H), 7.06 (d, *J*= 9.0 Hz, 2H), 7.12 (d, *J*= 9.0 Hz, 1H), 7.35 (d, *J*=15.9 Hz, 1H), 7.82 (t, *J*= 9.0 Hz, 2H), 7.89 (d, *J*= 9.0 Hz, 1H), 8.25 (s, 1H), 9.01 (s, 1H), 10.72 (s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 55.61, 112.78, 114.17, 118.76, 128.98, 132.69,

134.22, 136.69, 152.70, 162.30, 162.52. HRMS (ESI) for $C_{15}H_{15}N_3O_5S$ ($[M+H]^+$): calcd, 349.0730; found, 350.0803.

5-bromo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (**23**). To a mixture of 7-azaindoline (**22**, 4.0 g, 33.29 mmol), pyridine (4 mL) and CH_2Cl_2 (40 mL) was slowly added Br_2 (1.72 mL, 33.29 mmol) in CH_2Cl_2 (24 mL) under ice bath and was allowed to stir for 2 h under nitrogen. The reaction was quenched with water and extracted with ethyl acetate (30 mL x 3). The organic layer was collected and dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a dark brown product. The residue was purified by flash column over silica gel (ethyl acetate: n-hexane = 2:1) to afford **23** (4.88 g, 73.65%) as a yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.06 (t, *J* = 8.5 Hz, 2H), 3.64 (t, *J* = 8.5 Hz, 2H), 7.31 (s, 1H), 7.85 (s, 1H).

5-Bromo-1-(4-methoxyphenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (24a). A mixture of **23** (0.35 g, 1.76mmol), 4-methoxybenzenesulfonyl chloride (0.55 g, 2.64 mmol) and pyridine (3 mL) was refluxed overnight. The reaction was quenched with water and extracted with ethyl acetate (30 mL x 3). The organic layer was collected and dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield a brown product. The residue was purified by flash column over silica gel (ethyl acetate: n-hexane = 1:1) to afford **24a** (0.34 g, 52.31%) as a yellow solid. ^{1}H-NMR

(500 MHz, $CDCl_3$): δ 3.02 (t, *J* = 8.5 Hz, 2H), 3.84 (s, 3H), 4.05 (t, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 9.5 Hz, 2H), 7.45 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 8.18 (s, 1H).

5-Bromo-1-(phenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (24b). The title compound was obtained in 78.73% overall yield from compound **23** and benzenesulfonyl chloride in a similar manner as described for the preparation of **24b**. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.04 (t, *J* = 8.5 Hz, 2H), 4.08 (t, *J* = 8.5 Hz, 2H), 7.46 (s, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 8.08 (t, *J* = 8.0 Hz, 2H), 8.18 (s, 1H).

5-Bromo-1-(3-methoxyphenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (24c). The title compound was obtained in 86.17% overall yield from compound **23** and 3-methoxybenzenesulfonyl chloride in a similar manner as described for the preparation of **24c**. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.04 (t, *J* = 8.5 Hz, 2H), 3.84 (s, 3H), 4.07 (t, *J* = 8.5 Hz, 2H), 7.11 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 7.62 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.65 (s, 1H), 8.19 (s, 1H).

5-Bromo-1-(3-nitrophenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (24d). The title compound was obtained in 53.24% overall yield from compound **23** and 3-nitrobenzenesulfonyl chloride in a similar manner as described for the preparation of **24d**. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.11 (t, *J* = 8.5 Hz, 2H), 4.16 (t, *J* = 8.5 Hz,

2H), 7.51 (s, 1H), 7.72 (t, *J* = 9.0 Hz, 1H), 8.18 (s, 1H), 8.42-8.44 (m, 1H), 8.46-8.49 (m, 1H), 8.96 (t, *J* = 9.0 Hz, 1H).

5-Bromo-1-(4-bromophenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (24e). The title compound was obtained in 77.46% overall yield from compound **23** and 4-bromobenzenesulfonyl chloride in a similar manner as described for the preparation of **24e**. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.05 (t, *J* = 8.5 Hz, 2H), 4.06 (t, *J* = 8.5 Hz, 2H), 7.47 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H), 8.16 (s, 1H).

5-Bromo-1-(3-bromophenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (24f). The title compound was obtained in 76.10% overall yield from compound **23** and 3-bromobenzenesulfonyl chloride in a similar manner as described for the preparation of **24f**. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.07 (t, *J* = 8.5 Hz, 2H), 4.09 (t, *J* = 8.5 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.48-7.49 (m, 1H), 7.69-7.71 (m, 1H), 8.03-8.05 (m, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H).

5-Bromo-1-(2-bromophenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (24g). The title compound was obtained in 40.77% overall yield from compound **23** and 2-bromobenzenesulfonyl chloride in a similar manner as described for the preparation of **24g**. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.18 (t, *J* = 8.5 Hz, 2H), 4.49 (t, *J*

= 8.5 Hz, 2H), 7.38-7.42 (m, 1H), 7.48-7.52 (m, 2H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H).

(*E*)-3-(1-(4-Methoxyphenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl) acrylic acid (24a). The title compound was obtained in 43.43% overall yield from compound **25a** in a similar manner as described for the preparation of **21.** ^{1}H-NMR (500 MHz, CD_3OD): δ 3.09 (t, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 4.07 (t, *J* = 8.5 Hz, 2H), 6.42 (d, *J* =16.0 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H),7.58 (d, *J* =16.0 Hz, 1H), 7.86 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 2H), 8.16 (s, 1H).

(*E*)-3-(1-(Phenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)acrylic acid (25b). A mixture of **24b** (0.47 g, 1.39 mmol), palladium acetate (0.03 g, 0.14 mmol), triphenylphosphine (0.07 g, 0.28 mmol), triethylamine (0.19 mL, 1.39mmol), sodium bicarbonate (0.23 g, 2.78 mmol) and DMF (3 mL) was stirred for a while then added the methyl acrylate (0.15 mL, 1.67 mmol) at 120 ^{o}C and stirred for overnight. The residue was purified by flash column over silica gel (ethyl acetate: n-hexane = 1:1) to give the methyl acrylate compound as a yellow solid. A mixture of ester compound and dioxane (5 mL) was added 1M $LiOH_{(aq.)}$ (2.22 mL, 2.22 mmol) and stirred overnight at 40 ^{o}C. The reaction was removed out solvent and dissolved in water. The water layer was added the 3N $HCl_{(aq.)}$ and filtered by gravity filtration to yield a white product **25b** (0.36 g, 98.17%). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.08 (t, *J* = 8.5 Hz,

2H), 4.08 (t, *J* = 8.5 Hz, 2H), 6.44 (d, *J* =16.0 Hz, 1H), 7.50 (d, *J* =16.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.94 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 8.26 (s, 1H).

(*E*)-3-(1-(3-Methoxyphenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl) acrylic acid (25c). The title compound was obtained in 93.32% overall yield from compound **24c** in a similar manner as described for the preparation of **21**. ^{1}H-NMR (500 MHz, CD_3OD): δ 3.09 (t, *J* = 8.5 Hz, 2H), 3.82 (s, 3H), 4.08 (t, *J* = 8.5 Hz, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 7.18 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.44 (t, *J* = 8.5 Hz, 2H), 7.57-7.61 (m, 3H), 7.83 (s, 1H), 8.19 (s, 1H).

(*E*)-3-(1-(3-Nitrophenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-acr ylic acid (25d). The title compound was obtained in 45.05% overall yield from compound **24d** in a similar manner as described for the preparation of **21**. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.10 (t, *J* = 8.5 Hz, 2H), 4.15 (t, *J* = 8.5 Hz, 2H), 6.46 (d, *J* = 16.0 Hz, 1H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.90 (t, *J* = 8.0 Hz, 1H), 7.97 (s, 1H), 8.29 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.74 (s, 1H).

(*E*)-4-(4-(5-((*E*)-2-Carboxyvinyl)-2,3-dihydro-1H-pyrrolo[2,3-b]13xpressi-1-ylsulf onyl)-phenyl)but-2-enoic acid (25e). The title compound was obtained in 42.33% overall yield from compound **24e** in a similar manner as described for the preparation of **21**. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.09 (t, *J* = 8.5 Hz, 2H), 4.10 (t, *J* = 8.5 Hz,

2H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 16.0 Hz, 1H), 7.59 (d, *J* = 16.5 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.95 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 8.27 (s, 1H).

(*E*)-3-(3-(5-((*E*)-2-Carboxyvinyl)-2,3-dihydro-1H-pyrrolo[2,3-b]14xpressi-1-ylsulfonyl)-phenyl)but-2-enoic acid (25f). The title compound was obtained in 35.35% overall yield from compound **24f** in a similar manner as described for the preparation of **21**. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.09 (t, *J* = 8.5 Hz, 2H), 4.15 (t, *J* = 8.5 Hz, 2H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 7.49 (d, *J* = 16.0 Hz, 1H), 7.61-7.66 (m, 2H), 7.95 (s, 1H), 8.02 (t, *J* = 9.0 Hz, 2H), 8.21 (s, 1H), 8.26 (s, 1H).

(*E*)-3-(2-(5-((*E*)-2-Carboxyvinyl)-2,3-dihydro-1H-pyrrolo[2,3-b]14xpressi-1-ylsulfonyl)phenyl)acrylic acid (25g). The title compound was obtained in 33.42% overall yield from compound **24g** in a similar manner as described for the preparation of **25b**. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.11 (t, *J* = 8.5 Hz, 2H), 4.32 (t, *J* = 8.5 Hz, 2H), 6.39-6.43 (m, 2H), 7.45 (d, *J* = 16.0 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.95 (s, 1H), 8.07 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 16.0 Hz, 1H).

(*E*)-*N*-Hydroxy-3-(1-(4-methoxyphenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)acrylamide (7). The title compound was obtained in 88.79% overall yield from compound **25a** in a similar manner as described for the preparation of **6** with

m.p. 201.6-202.6 ^{o}C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.06 (t, *J* = 8.5 Hz, 2H), 3.80 (s, 3H), 4.01 (t, *J* = 8.5 Hz, 2H), 6.34 (d, *J* =16.0 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* =16.0 Hz, 1H), 7.72 (s, 1H), 7.93 (t, *J* = 9.0 Hz, 2H), 8.19 (s, 1H), 8.99 (br, 1H), 10.70 (s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 24.44, 48.72, 55.68, 114.28, 118.48, 125.49, 125.54, 128.89, 129.97, 130.59, 134.88, 147.10, 156.32, 162.58, 163.21. MS (ESI) *m*/*z*: 376.0 ([M+H]$^{+}$). HRMS (ESI) for $C_{17}H_{17}N_3O_5S$ ([M-H]$^{-}$): calcd, 374.0816; found, 374.0823.

(*E*)-N-hydroxy-3-(1-(phenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl) acrylamide (8). The title compound was obtained in 89.09% overall yield from compound **25b** in a similar manner as described for the preparation of **6** with m.p. 198.1-199.0 ^{o}C. ^{1}H-NMR (500MHz, DMSO-d_6): δ 3.08 (t, *J* = 8.5 Hz, 2H), 4.06 (t, *J* = 8.5 Hz, 2H), 6.35 (d, *J* =16.0 Hz, 1H), 7.36 (d, *J* =16.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.74 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 2H), 8.19 (s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 24.47, 48.79, 118.60, 125.57, 125.64, 127.59, 129.16, 130.70, 133.76, 134.85, 137.49, 147.10, 156.13, 162.56. MS (ESI) *m*/*z*: 368.0 ([M+Na] $^{+}$). HRMS (ESI) for $C_{16}H_{15}N_3O_4S$ ([M-H]$^{-}$): calcd, 344.0705; found, 344.0686.

(*E*)-*N*-Hydroxy-3-(1-(3-methoxyphenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]py ridin-5-yl)acrylamide (9). The title compound was obtained in 40.80% overall yield

from compound **25c** in a similar manner as described for the preparation of **6** with m.p. 219.1-220.4 ^{o}C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.07 (t, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 4.03 (t, *J* = 8.5 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 7.22-7.24 (m, 1H), 7.37 (d, *J* = 16.0 Hz, 1H), 7.47-7.56 (m, 3H), 7.74 (s, 1H), 8.23 (s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 24.47, 48.82, 55.61, 112.51, 118.67, 119.57, 119.75, 125.66, 125.78, 130.38, 130.76, 134.84, 138.45, 147.11, 156.12, 159.22, 162.55. MS (ESI) *m*/*z*: 398.0 ($[M+Na]^+$). HRMS (ESI) for $C_{17}H_{16}N_3O_5S$ ($[M-H]^-$): calcd, 374.0816; found, 374.0825.

(*E*)-N-Hydroxy-3-(1-(3-nitrophenylsulfonyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)acrylamide (10). The title compound was obtained in 71.16% overall yield from compound **25d** in a similar manner as described for the preparation of **6** with m.p. 158.8-160.3 ^{o}C. ^{1}H-NMR (500 MHz, CD_3OD+ DMSO-d_6): δ 3.14 (t, *J* = 8.5 Hz, 2H), 4.17 (t, *J* = 8.5 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 15.5 Hz, 1H), 7.75 (s, 1H), 7.84 (t, *J* = 8.0 Hz, 1H), 8.20 (s, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.48-8.50 (m, 1H), 8.90 (t, *J* = 9.0 Hz, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 24.56, 48.94, 118.92, 122.69, 125.74, 126.07, 128.35, 131.06, 131.21, 133.56, 134.72, 138.79, 146.92, 147.71, 155.64, 162.48. MS (ESI) *m*/*z*: 413.0 ($[M+Na]^+$). HRMS (ESI) for $C_{16}H_{13}N_4O_6S$ ($[M-H]^-$): calcd, 389.0561; found, 389.0543.

(*E*)-N-Hydroxy-4-(4-(5-((*E*)-3-(hydroxyamino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-ylsulfonyl)phenyl)but-2-enamide (11). The title compound was obtained in 15.49% overall yield from compound **25e** in a similar manner as described for the preparation of **6** with m.p. 194.9-196.0 ^{o}C (decomp.). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.07 (t, *J* = 8.5 Hz, 2H), 4.07 (t, *J* = 8.5 Hz, 2H), 6.34 (d, *J* = 16.0 Hz, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 7.36 (d, *J* = 16.0 Hz, 1H), 7.45 (d, *J* = 16.0 Hz, 1H), 7.72-7.84 (m, 3H), 8.00 (d, *J* = 8.5 Hz, 2H), 8.18 (s, 1H), 10.70 (s, 1H), 10.83 (s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 24.50, 48.82, 118.65, 122.64, 125.63, 125.72, 127.94, 128.26, 130.74, 134.84, 136.38, 137.52, 139.92, 147.11, 156.05, 161.95, 162.55. MS (ESI) *m*/*z*: 453.0 ([M+Na]$^{+}$). HRMS (ESI) for $C_{19}H_{17}N_4O_6S$ ([M-H]$^{-}$): calcd, 429.0874; found, 429.0882.

(*E*)-N-Hydroxy-3-(3-(5-((*E*)-3-(hydroxyamino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-ylsulfonyl)phenyl)acrylamide (12). The title compound was obtained in 37.17% overall yield from compound **25f** in a similar manner as described for the preparation of **6** with m.p. 219.6-220.7 ^{o}C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.09 (t, *J* = 8.5 Hz, 2H), 4.10 (t, *J* = 8.5 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 7.36 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 16.0 Hz, 1H), 7.61 (t, *J* = 8.5 Hz, 1H), 7.75 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 10.0 Hz, 2H), 10.71 (s, 1H), 10.84 (s, 1H). ^{13}C-NMR (125MHz,

DMSO-d_6): δ 24.51, 48.86, 118.69, 121.42, 125.67, 125.76, 125.81, 128.01, 129.89, 130.74, 132.86, 134.82, 135.83, 136.52, 138.13, 147.10, 156.04, 162.03, 162.55. MS (ESI) *m*/*z*: 453.0 ($[M+Na]^+$). HRMS (ESI) for $C_{19}H_{17}N_4O_6S$ ($[M-H]^-$): calcd, 429.0874; found, 429.0891.

(*E*)-*N*-Hydroxy-3-(2-(5-((*E*)-3-(hydroxyamino)-3-oxoprop-1-enyl)-2,3-dihydro-1 H-pyrrolo[2,3-b]pyridin-1-ylsulfonyl)phenyl)acrylamide (13). The title compound was obtained in 33.19% overall yield from compound **25g** in a similar manner as described for the preparation of **6** with m.p. 220.2-221.4 ^oC. ^1H-NMR (500 MHz, DMSO-d_6): δ 3.10 (t, *J* = 8.5 Hz, 2H), 4.28 (t, *J* = 8.5 Hz, 2H), 6.26-6.33 (m, 2H), 7.31 (d, *J* = 16.0 Hz, 1H), 7.60-7.71 (m, 3H), 7.74 (s, 1H), 7.96 (s, 1H), 8.14-8.17 (m, 2H), 8.99 (br, 1H), 9.17 (br, 1H), 10.69 (s, 1H), 10.83 (s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 24.37, 47.89, 118.40, 123.64, 125.12, 125.39, 128.04, 129.10, 130.45, 130.72, 133.86, 134.08, 134.30, 134.79, 137.08, 146.94, 155.65, 161.69, 162.49. MS (ESI) *m*/*z*: 453.0 ($[M+Na]^+$). HRMS (ESI) for $C_{19}H_{17}N_4O_6S$ ($[M-H]^-$): calcd, 429.0874; found, 429.0882.

5-Bromo-1-(4-methoxyphenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (27a). A mixture of 5-bromo-7-azaindole (**26**, 0.35 g, 1.78mmol) was dissolved in DMF (2mL) and added the 60% NaH (0.06 g, 2.67mmol) and stirred for a while. Then added the 4-methoxybenzenesulfonyl chloride (0.55 g, 2.67mmol) and stirred for overnight at

room temperature. The reaction was added H_2O to produce the precipitant. The residue was without more purification to afford **27a** (0.57 g, 87.20%) as a white solid. ^{1}H-NMR (500MHz, $CDCl_3$): δ 3.83 (s, 3H), 6.52 (d, *J* = 4.0 Hz, 1H), 6.93 (t, *J* = 9.0 Hz, 2H), 7.73 (t, *J* = 4.0 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 8.11 (d, *J* = 9.0Hz, 2H), 8.44 (d, *J* = 2.5 Hz, 1H).

5-Bromo-1-(4-fluorophenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (27b). The title compound was obtained in 93.32% overall yield from compound **26** in a similar manner as described for the preparation of **27a**. ^{1}H-NMR (500MHz, $CDCl_3$): δ 6.55 (d, *J* = 4.0 Hz, 1H), 7.17 (t, *J* = 9.0 Hz, 2H), 7.72 (t, *J* = 4.0 Hz, 1H), 7.99 (d, *J* = 2.5 Hz, 1H), 8.21-8.23 (m, 2H), 8.44 (d, *J* = 2.0 Hz, 1H).

5-bromo-1-(4-bromophenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (27c). The title compound was obtained in 81.20% overall yield from compound **26** in a similar manner as described for the preparation of **27a**. ^{1}H-NMR (500MHz, $CDCl_3$): δ 6.56 (d, *J* = 4.0 Hz, 1H), 7.64 (t, *J* = 9.0 Hz, 2H), 7.71 (t, *J* = 4.0 Hz, 1H), 7.99 (s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 8.44 (d, *J* = 2.0 Hz, 1H).

5-Bromo-1-(3-bromophenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (27d). The title compound was obtained in 85.26% overall yield from compound **26** in a similar manner as described for the preparation of **27a**. ^{1}H-NMR (500MHz, $CDCl_3$): δ 6.57

(d, *J* = 3.5 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 4.5 Hz, 2H), 7.99 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.33 (s, 1H), 8.46 (d, *J* = 2.0 Hz, 1H).

5-Bromo-1-(2-bromophenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (27e). The title compound was obtained in 89.32% overall yield from compound **26** in a similar manner as described for the preparation of **27a**. ^{1}H-NMR (500MHz, $CDCl_3$): δ 6.57 (d, *J* = 4.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0, 1H), 7.96 (d, *J* = 4.0 Hz, 1H), 7.99 (d, *J* = 2.0 Hz, 1H), 8.25 (d, *J* = 1.5 Hz, 1H), 8.61 (d, *J* = 8.0 Hz, 1H).

(*E*)-3-(1-(4-Methoxyphenylsulfonyl)-1H-pyrrolo[2,3-b]20xpressi-5-yl)acrylic acid (28a). The title compound was obtained in 88.17% overall yield from compound **27a** in a similar manner as described for the preparation of **21**. ^{1}H-NMR (500MHz, CD_3OD): δ 3.82 (s, 3H), 6.57 (d, *J* = 16.0 Hz, 1H), 6.73 (d, *J* = 4.0 Hz, 1H), 7.03 (t, *J* = 9.0 Hz, 2H), 7.76 (d, *J* = 16.0 Hz, 1H), 7.83 (t, *J* = 4.0 Hz, 1H), 8.08 (d, *J* = 9.0Hz, 2H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.52 (d, *J* = 2 Hz, 1H).

(*E*)-3-(1-(4-Fluorophenylsulfonyl)-1H-pyrrolo[2,3-b] 20 xpressi-5-yl)acrylic acid (28b). The title compound was obtained in 63.12% overall yield from compound **27b** in a similar manner as described for the preparation of **21**. ^{1}H-NMR (500MHz, CD_3OD): δ 6.58 (d, *J* = 16.0 Hz, 1H), 6.77 (d, *J* = 3.5 Hz, 1H), 7.29 (t, *J* = 8.5 Hz,

2H), 7.76 (d, *J* = 16.0 Hz, 1H), 7.85 (t, *J* = 4.0 Hz, 1H), 8.22-8.25 (m, 2H), 8.26 (s, 1H), 8.53 (d, *J* = 2.0 Hz, 1H).

(*E*)-3-(4-(5-((*E*)-2-Carboxyvinyl)-1H-pyrrolo[2,3-b] 21 xpressi-1-ylsulfonyl)phenyl) acrylic acid (28c). The title compound was obtained in 88.31% overall yield from compound **27c** in a similar manner as described for the preparation of **21**. ^{1}H-NMR (500MHz, DMSO-d_6): δ 6.63 (d, *J* = 16.0 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.85 (d, *J* = 4.0 Hz, 1H), 7.57 (d, *J* = 15.5 Hz, 1H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.96 (d, *J* = 4.0 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 8.41 (d, *J* = 2.0 Hz, 1H), 8.67 (d, *J* = 1.5 Hz, 1H).

(*E*)-3-(3-(5-((*E*)-2-Carboxyvinyl)-1H-pyrrolo[2,3-b] 21 xpressi-1-ylsulfonyl)phenyl) acrylic acid (28d). The title compound was obtained in 87.57% overall yield from compound **27d** in a similar manner as described for the preparation of **21**. ^{1}H-NMR (500MHz, CD_3OD+ DMSO-d_6): δ 6.62 (d, *J* = 16.0 Hz, 2H), 6.83 (d, *J* = 4.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 16.0 Hz, 1H), 7.77 (d, *J* = 16.0 Hz, 1H), 7.94 (d, *J* = 4.0 Hz, 2H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 8.42 (s, 1H), 8.60 (d, *J* = 2.0 Hz, 1H).

(*E*)-3-(2-(5-((*E*)-2-Carboxyvinyl)-1H-pyrrolo[2,3-b] 21 xpressi-1-ylsulfonyl)phenyl) acrylic acid (28e). The title compound was obtained in 81.24% overall yield from compound **27e** in a similar manner as described for the preparation of **21**. ^{1}H-NMR

(500MHz, CD_3OD+DMSO-d_6): δ 6.15 (d, *J* = 16.0 Hz, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.76 (d, *J* = 4.0 Hz, 1H), 7.66-7.74 (m, 4H), 7.91 (d, *J* = 4.0 Hz, 1H), 8.26 (s, 1H), 8.39-8.42 (m, 2H), 8.45 (d, *J* = 16.0 Hz, 1H).

(*E*)-N-Hydroxy-3-(1-(4-methoxyphenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl) acrylamide (14). The title compound was obtained in 90.91% overall yield from compound **28a** in a similar manner as described for the preparation of **6** with m.p. 192.5-193.3. ^{1}H-NMR (500MHz, DMSO-d_6): δ 3.78 (s, 3H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.81 (d, *J* = 4.0 Hz, 1H), 7.10 (t, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 16.0 Hz, 1H), 7.89 (t, *J* = 4.0 Hz, 1H), 8.03 (d, *J* = 9.0Hz, 2H), 8.23 (d, *J* = 1.5 Hz, 1H), 8.55 (d, *J* = 1.5 Hz, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 55.85, 105.88, 114.77, 119.78, 122.57, 126.54, 127.82, 127.91, 128.64, 130.01, 135.45, 144.75, 146.67, 162.44, 163.93. HRMS (ESI) for $C_{17}H_{16}N_3O_5S$ ($[M+H]^+$): calcd, 374.0811; found, 374.0822.

(*E*)-3-(1-(4-Fluorophenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-hydroxy-acrylamide (15). The title compound was obtained in 86.69% overall yield from compound **28b** in a similar manner as described for the preparation of **6** with m.p. 213.6-214.5. ^{1}H-NMR (500MHz, DMSO-d_6): δ 6.52 (d, *J* = 15.5 Hz, 1H), 6.86 (d, *J* = 4.0 Hz, 1H), 7.47 (t, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 15.5 Hz, 1H), 7.93(d, *J* = 4.0 Hz, 1H), 8.18-8.21 (m, 2H), 8.25 (s, 1H), 8.56 (s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 106.42, 116.92, 117.11, 119.98, 122.68, 126.82, 127.88, 128.03, 130.91, 130.99,

133.63, 135.37, 144.88, 146.70, 162.41, 164.44, 166.46. HRMS (ESI) for $C_{16}H_{13}FN_3O_4S$ ($[M+H]^+$): calcd, 362.0611; found, 362.0618.

(*E*)-N-Hydroxy-3-(4-(5-((*E*)-3-(hydroxyamino)-3-oxoprop-1-enyl)-1H-pyrrolo[2,3-b]pyridin-1-ylsulfonyl)phenyl)acrylamide (16). The title compound was obtained in 38.90% overall yield from compound **28c** in a similar manner as described for the preparation of **6** with m.p. 188.7-190.5 (decomp.). ^{1}H-NMR (500MHz, DMSO-d_6): δ 6.54 (t, *J* = 16.0 Hz, 2H), 6.86 (d, *J* = 4.0 Hz, 1H), 7.44 (d, *J* = 15.5 Hz, 1H), 7.54 (d, *J* = 15.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 4.0 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 8.25(s, 1H), 8.56(s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 106.43, 119.96, 122.67, 123.36, 126.80, 127.94, 128.15, 128.35, 135.34, 136.06, 137.17, 140.95, 144.91, 146.76, 162.38. HRMS (ESI) for $C_{19}H_{17}N_4O_6S$ ($[M+H]^+$): calcd, 429.0869; found, 429.0876.

(*E*)-N-Hydroxy-3-(3-(5-((*E*)-3-(hydroxyamino)-3-oxoprop-1-enyl)-1H-pyrrolo[2,3-b]pyridin-1-ylsulfonyl)phenyl)acrylamide (17). The title compound was obtained in 67.43% overall yield from compound **28d** in a similar manner as described for the preparation of **6** with m.p. 219.4-221.3 (decomp.). ^{1}H-NMR (500MHz, DMSO-d_6): δ 6.52 (t, *J* = 15.5 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.87 (d, *J* = 4.0 Hz, 1H), 7.50 (d, *J* = 16.0 Hz, 1H), 7.55 (d, *J* = 15.5 Hz, 1H), 7.64 (t, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 4.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.25(s, 1H), 8.34 (s, 1H),

8.59(s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 106.44, 119.99, 121.98, 122.68, 125.67, 126.84, 127.76, 127.92, 128.03, 130.39, 133.74, 135.34, 136.10, 136.30, 138.08, 144.89, 146.72, 161.93, 162.39. HRMS (ESI) for $C_{19}H_{17}N_4O_6S$ ([M+H]$^+$): calcd, 429.0869; found, 429.0884.

(*E*)-N-Hydroxy-3-(2-(5-((*E*)-3-(hydroxyamino)-3-oxoprop-1-enyl)-1H-pyrrolo[2,3-b]pyridin-1-ylsulfonyl)phenyl)acrylamide (18). The title compound was obtained in 67.20% overall yield from compound **28e** in a similar manner as described for the preparation of **6** with m.p. 159.6-161.9 (decomp.). ^{1}H-NMR (500MHz, DMSO-d_6): δ 6.19 (d, *J* = 15.5 Hz, 1H), 6.49 (d, *J* = 5.5 Hz, 1H), 6.84 (d, *J* = 4.0 Hz, 1H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.65-7.70 (m, 2H), 7.76 (t, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 4.0 Hz, 1H), 8.10 (d, *J* = 15.5 Hz, 1H), 8.24 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.41 (s, 1H). ^{13}C-NMR (125MHz, DMSO-d_6): δ 105.63, 119.94, 122.46, 124.86, 126.80, 127.68, 127.94, 128.68, 129.48, 130.91, 133.08, 134.56, 135.25, 135.33, 144.84, 146.55, 161.34, 162.40. HRMS (ESI) for $C_{19}H_{16}NaN_4O_6S$ ([M+Na]$^+$): calcd, 451.0688; found, 451.0683.